PEAR Clinical Study Protocol

Study Title:	**PEAR:** Phase I dose Escalation of pAlliative Radiotherapy with anti-PD1 antibody pembrolizumab in thoracic tumours
Protocol number:	CCR 4282
Sponsor:	Royal Marsden NHS Foundation Trust
EudraCT number:	2014-005673-36
ClinicalTrials.gov Identifier:	NCT02587455
Product:	MK-3475/pembrolizumab (KEYTRUDA®)
Development phase:	I
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3 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.

Chief Investigator Name:

Signature:

Date:

Statistician Signature:

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

Sponsor Representative Name:

Signature:

Date:

4 TRIAL SUMMARY

Title	**PEAR:** Phase I dose Escalation of pAlliative Radiotherapy with anti-PD1 antibody pembrolizumab in thoracic tumours
Abbreviated Title	Pembrolizumab and palliative radiotherapy in lung
Trial Phase	Phase I
Clinical Indication	The treatment of patients with non-small cell carcinoma (NSCLC) of lung requiring palliative radiotherapy (RT) to the chest for which no curative therapy exists
Trial Type	Interventional

Type of control	No treatment control
Route of administration	Intravenous pembrolizumab and external radiotherapy
Trial Blinding	Unblinded, open label, dose escalation phase I study, with a subsequent expansion phase

Treatment Groups	**Part A – Dose escalation stage:**
	• **DOSE LEVEL 1:**
	  ○ **Low Dose RT Arm:** 100mg every 2 weeks at Week 0 and Week 2 then followed by maintenance dose of 200mg every 3 weeks starting at week 5.
	  ○ **High Dose RT Arm:** 100mg every 2 weeks at Week 0, Week 2 and Week 4 then followed by maintenance dose of 200mg every 3 weeks starting at week 6.
	• **DOSE LEVEL 2:**
	  ○ **Low Dose RT Arm:** 200mg every 2 weeks at Week 0 and Week 2 then followed by maintenance dose of 200mg every 3 weeks starting at week 5.
	  ○ **High Dose RT Arm:** 200mg every 2 weeks at Week 0, Week 2 and Week 4 then followed by maintenance dose of 200mg every 3 weeks starting at week 6.
	• **DOSE LEVEL -1 (If DLTs are seen at dose level 1):**
	  ○ **Low Dose RT Arm:** 50mg every 2 weeks at Week 0 and Week 2 then followed by maintenance dose of 200mg every 3 weeks starting at week 5.
	  ○ **High Dose RT Arm:** 50mg every 2 weeks at Week 0, Week 2 and Week 4 then followed by maintenance dose of 200mg every 3 weeks starting at week 6.
	
	Part B – Expansion cohort:
	An additional 12 patients will be recruited and will receive High Dose RT and the recommended dose determined in part A.

Number of trial patients	Approximately 36 patients may be recruited depending on the dose levels tolerated – up to 24 patients will be recruited to the dose escalation phase in a 3+3 design, and the dose expansion phase will recruit up to 12 patients in total.
Estimated duration of trial	24months.
Duration of Participation	Until disease progression, unacceptable toxicity or withdrawal from the trial.
Study Objectives	*Primary* • To determine the safety and tolerability of pembrolizumab in combination with RT to the lung. *Secondary* • To assess overall progression free survival (PFS) and overall survival (OS). • To evaluate PFS in a PD-L1 strong population. • To assess overall responses rates as per RECIST v1.1 and differential responses rates in squamous versus non-squamous histological subtypes. • To assess oesophagitis rates in this population. *Exploratory* • To assess for evidence of abscopal response.

	• Identification of biomarkers that correlate with immunological response to therapy.
Study Endpoints	*Primary* • To establish the maximum tolerated dose (MTD) that can be safely combined with RT in the absence of dose limiting toxicity (DLT). • To measure the toxicity rate of pneumonitis at grade ≥2 assessed two months after the last fraction of RT has been administered. *Secondary* • To measure the PFS and OS at 6 months and 1 year. • To measure PFS in PD-L1 strong population at 6 months and 1 year. • To measure the duration of clinical benefit using RECIST v1.1 including the different response rate between squamous versus non-squamous histological sub-types at 6 months and 1 year. • To measure the oesophagitis rates assessed at two months after the last fraction of RT has been administered. *Exploratory* • To evaluate the abscopal effect when pembrolizumab and RT are combined. • Characterisation of TILs and tumour antigens in the tumour biopsies. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2. • Analysis of research blood samples for ctDNA.
Summary of Main Inclusion Criteria	• Patients ≥18 years of age with measurable (RECIST v1.1) NSCLC; requiring palliative RT for which no curative therapy exists will be recruited into the trial. Patients are permitted to have extra-thoracic disease which will not be encompassed in the RT field. This disease will be assessed for abscopal response. • ECOG between 0-1 and the ability to tolerate a week or 2.5 week course of palliative RT. • Demonstrate adequate organ function and a baseline lung function of FEV1 > 0.8L or > 30%. • Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion. • Female patients of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to confirmation of study eligibility. • 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 6 months after the last dose of study medication.
Summary of Main Exclusion Criteria	• Taking any IMP or using an Investigational device within 4 weeks of the first dose. • Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose. • Prior monoclonal antibody within 4 weeks prior to the first dose or who has not recovered from adverse events due to agents administered more than 4 weeks earlier. • Previous RT to the lung

	• Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 4 weeks prior to the first dose or who has not recovered from adverse events due to a previously administered agent. • Additional malignancy that is progressing or requires active treatment. • Active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable, have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. • 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. • 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). • 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. • Psychiatric or substance abuse disorders that would interfere with patients participation. • Pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 6 months after the last dose. • Has 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). • History of HIV. HIV 1/2 antibodies, Hepatitis B or Hepatitis C. • Has received a live vaccine within 30 days prior to the first dose of trial treatment.
Treatment / Main Study Procedures	Patients will be registered to receive pembrolizumab at one of the above dosing levels in combination with low or high dose RT. Pembrolizumab will be given 2 weekly at the dose level currently under evaluation during RT and then the patient will move into a maintenance phase where they will receive 200mg of pembrolizumab alone 3 weekly thereafter. Additionally, an expansion phase will take place using the dose administered at the achieved MTD. Patients will undergo clinical assessment on the day of each administration of pembrolizumab and will continue on this regimen 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 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 Additional information on study procedures can be found in the study schedule of assessment (Table 3)

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1.0 BACKGROUND & RATIONALE

1.1 Background

1.1.1 Immune evasion in cancer

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for many years (1). Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies (2-6). 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 (7, 8). The immune system may then develop an adaptive immune response requiring competent cytotoxic T cells. This is mediated through the major histocompatibility complex (MHC) system. Antigen presenting cells (APC) capture tumour antigens priming them to T cells in regional lymph nodes. NSCLC display reduced 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 that induce aberrant expansion of CD4+ FoxP3+ regulatory T cells, thus inhibiting cytotoxic T cell and NK cell activity (9).

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 (CTLA-4) 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 (10).

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 (10).

1.1.2 Pharmaceutical and Therapeutic Background

PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 and has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (7, 8). The structure of murine PD-1 has been resolved (11). 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 signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling 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 CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade (7, 12-14). 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 signaling proteins (15, 16). PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T cells, B-cells, T regs and NK cells (17, 18). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells, as well as subsets of macrophages and dendritic cells (18). 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-haematopoietic tissues, as well as in various tumours (15, 19-21). 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 signaling 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-haematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on APCs 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 (15). 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 (22-25) although the figure is more likely to around the 50% mark (23, 26). 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 (22, 23). TILs seem to be absent in PD-L1 positive regions of tumours (23). 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 (27).

PD-L1 expression may be directly regulated by 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 (10).

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

The role of T cells in response to radiation was suggested in 1979 when reduced therapeutic efficacy was noted in mice that lacked an adequate T cell response (28). Now it is known that ionising radiation (IR) induced cell death can generate tumour cell antigens for dendritic cell presentation. IR in fact 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 ATP. Tumour cells that receive sub-lethal doses of radiation undergo phenotypic changes that enhance their susceptibility to immune effectors (29-31). Enhanced expression of death receptors (32, 33), MHC class 1 molecules (29, 34, 35), co-stimulatory molecules (36), adhesion molecules (37-39), and stress-induced ligands (40-42) 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 RT can engage both the innate and adaptive arms of the immune system, with the potential to convert the irradiated cancer 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, anti-CTLA-4, anti-CD137 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 RT were cured. $CD8^+$ T cells were essential for curative responses to this combinatorial regimen. CD137 expression on tumour-associated $CD8^+$ T cells was largely restricted to a subset that highly expressed PD-1. PD-1 signaling within the AT-3 tumours was a critical limiting factor to the therapeutic efficacy of anti-CD137 therapy, alone and in combination with RT (43).

Recently with the advent of large radiation fraction sizes in the form of stereotactic body radiotherapy (SBRT), the concept of combining SBRT with immune check point inhibitors has been explored with some groups suggesting that combined modality treatment with SBRT may be more efficacious than low dose RT. In a mouse orthotropic cell line glioma model, SBRT with 10Gy 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 (44). 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 15Gy, given in various size fraction. 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 7.5Gy/fraction seemed to produce the best tumour control and tumour specific T cell response while still maintaining low regulatory T cell numbers (43). 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 20Gy × 1, 8Gy × 3, or 6Gy × 5 fractions in combination with monoclonal antibody against CTLA-4. Authors found that fractionated but not single-dose RT induces an abscopal effect when used with anti-CTLA-4 antibody (45). However, another preclinical study comparing ablative radiation doses against fractionated radiation noted that ablative radiation, such as a single dose of 20–25Gy, dramatically increased T cell activity and tumour control. When 5Gy × 4 fractions given over 2 weeks were compared against a single 20Gy dose, radiation-initiated immune responses and tumour reduction appeared to be abrogated by the fractionated radiation (46). As is evident the relationship between RT dose, fraction size and immune interplay is a complex one. This study therefore in part will begin to explore the effects of dose fractionation on T cell response in the clinical setting. This will aid design of future RT trials help determine if conventionally fractionated RT provides the ideal tumour micro-environment for anti-PD-1 therapy or if combination with SBRT should be explored in concept. However prior to designing such trials the tolerability and safety of drug with IR needs to be established which is the primary objective of this trial.

1.1.4 Preclinical and Clinical Trial Data on Pembrolizumab

1.1.4.1 Clinical trial data on Pembrolizumab

At ASCO 2015, pooled results from KEYNOTE-001 were presented. 495 patients with NSCLC showed an objective response rate as assessed by RECIST v1.1 of 19.4% (95% confidence interval 16.0 – 23.2), which included a response rate of 18.0% (95% confidence interval 14.4 – 22.2) in the 394 treatment naïve patients and 24.8% (95% confidence interval 16.7 – 34.3) in the 101 previously treated patients. The response rates were similar regardless of dose, schedule, and histological diagnosis. The median duration of response of 12.5 months (range 1.0 – 23.3) in all patients, 23.3 months (range 1.0 – 23.3) in treatment naïve patients and 10.4 months (range 1.0 – 10.4) in previously treated patients. The median PFS was 3.7 months (95%CI: 2.9 – 4.1) for all patients, with 6.0 months (95%CI: 4.1 – 8.6) in treatment naïve patients and 3.0 months (95%CI: 2.2 – 4.0) in previously treated patients. The median OS was 12.0 months (95%CI: 9.3 – 14.7) for all patients, with 16.2 months (95%CI: 16.2 – not reached) in treatment naïve patients and 9.3 months (95%CI: 8.4 – 12.4) in previously treated patients (47).

Treatment related adverse events (AEs) occurred in 351 patients (70.9%), with no clear difference according to dose or schedule. The most common AEs attributed to pembrolizumab were fatigue (any grade: 19.4%; grade 3 – 5: 0.8%), pruritus (any grade: 10.7; grade 3 – 5: 0%), and decreased appetite (any grade: 10.5%; grade 3 – 5: 1.0%), with no clear difference according to dose or schedule. AEs of grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion related reactions (in 15 patients [3%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). All patients with hypothyroidism were successfully treated with medical therapy. Pneumonitis of grade 3 or greater was observed in 9 patients (1.8%), including 1 (0.2%) who died. At the time of data analysis, 2 cases of pneumonitis (both grade 1 or 2) were on going (47).

This data has 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 (47). Actively recruiting studies include KEYNOTE-024, is a phase III randomised controlled trial looking at pembrolizumab in first line NSCLC (48), and KEYNOTE-021, a phase 1 study looking at the combination of ipilimumab and pembrolizumab (49).

KEYNOTE-001 also validated the PD-L1 biomarker using the anti-PD-L1 antibody clone 22C3 (Merck) and immunohistochemistry. Tumour slides were stained and scored for neoplastic membranous staining and intercalated mononuclear inflammatory cells, as with <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) (47).

Similarly in melanoma, he immunotherapeutic effect of pembrolizumab is now established. The phase I study presented at ASCO 2014 consisted of 411 patients with advanced melanoma on pembrolizumab yielded long-term responses in a high percentage of patients. One-year overall survival was 69% across all patient subgroups, and responses were on going in 88% of patients at analysis, after a median follow-up of 12 months. The study enrolled 221 patients with prior ipilimumab treatment and 190 patients who had not previously received ipilimumab. Overall, 34% of patients experienced tumour response, as assessed by Independent Review Committee, including 40% of patients not previously treated with ipilimumab and 28 % of patients whose disease progressed on prior ipilimumab.

Responses were durable with 88% on going at the time of analysis. Activity was observed across all dose levels and patient subgroups, irrespective of prior ipilimumab therapy, performance status, LDH levels, *BRAF* mutation status, tumour stage, and number and type of prior therapies. Daud *et al* presented biomarker data for 135 of these patients at the American Association for Cancer Research 2 months prior to the ASCO presentation. Tumour PD-L1 expression was assessed by IHC. A preliminary cut-off of 1% of stained cells was used to define PD-L1 Median PFS was 36 weeks, 6-month OS rate was 89%, and 12-month OS rate was 81%. Median duration of response and OS were not reached. In the 116 patients with measurable disease, ORR was 41%. PFS and response rate were significantly associated with tumour PD-L1 expression. Median PFS for PD-L1 positive tumours was 10.6 months versus 2.9 months for PD-L1 negative patients (HR 0.54, *P*-value=0.034). The drug has been granted FDA priority review designation under its accelerated Approval program.

1.1.4.2 Preclinical data on Pembrolizumab

Preclinical data for anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumour responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T cell infiltration into the tumour and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T cell function *in vivo* (30-36). Experiments have confirmed the *in vivo* efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumour models (see the Investigator's Brochure [IB]).

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

1.2 Rationale for the Trial and Selected Patient Population

There is an increasing body of evidence of the efficacy of anti-PD-1 therapy in several tumour types notably melanoma and lung cancer, both of which highly express tumour PD-L1. Biomarker data suggests that tumours expressing PD-L1 will be particularly susceptible to pembrolizumab. This drug is therefore being explored in a number of phase II and phase III trials in differing tumour types known to express PD-L1. In addition a phase 1 trial is assessing pembrolizumab activity in PD-L1 positive patients with advanced cancers in 20 solid tumour types not previously assessed. Pembrolizumab-0028 is a multicentre non-randomised, trial recruiting patients with colon/rectal adenocarcinoma, anal canal squamous cell carcinoma, pancreas adenocarcinoma, oesophageal squamous cell carcinoma/adenocarcinoma, biliary tract adenocarcinoma, carcinoid tumours, neuroendocrine carcinomas, ER positive Her2 negative breast cancer, ovarian epithelial, fallopian tube or primary peritoneal carcinoma, endometrial

carcinoma, cervical squamous cell cancer, vulvar squamous cell carcinoma, small cell lung cancer, mesothelioma, head and neck tumours, glioblastoma multiforme, leiomyosarcoma, and prostate adenocarcinoma. This trial prohibits radiation prior to trial entry and during trial participation. Similarly other on-going trials with pembrolizumab have prohibited concomitant radiation. This is due to two reasons; firstly to maintain the scientific integrity of the trials but secondly due to lack of knowledge of the effects of pembrolizumab on radiation and its radiosensitising potential.

A reported adverse event (AE) of this class of drug is pneumonitis. Table 1 describes the incidence of pneumonitis in the melanoma patients. Pneumonitis/interstitial lung disease was observed in 1.9% of patients treated with 2 mg/kg Q2W, 1.6% of patients treated with 10 mg/kg Q3W, and 10.5% of patients treated with 10 mg/kg Q2W. The incidence seems similar in patients treated at the every 3 week schedule, but is more prevalent in patients treated at the every 2 week schedule. These cases are grade 1-2 in severity. Most cases are considered drug-related by investigators. No drug-related deaths have resulted from pneumonitis; however a 96-year old man with melanoma suffered a fatal myocardial infarction after a bronchoscopy to evaluate grade 2 interstitial lung disease.

	PEMBROLIZUMAB 2 mg/kg Q3W		**PEMBROLIZUMAB 10 mg/kg Q3W**		**PEMBROLIZUMAB 10 mg/kg Q2W**		**Total**	
	n	%	n	%	n	%	n	%
Patients in population	162	-	192	-	57	-		411
Respiratory thoracic mediastinal disorders	3	1.9	3	1.6	6	10.5	12	2.9
Interstitial lung disease	0	0	0	0	1	1.8	1	0.2
Pneumonitis	3	1.9	3	1.6	5	8.8	11	2.7

Table 1: Patients with Pneumonitis (Incidence > 0%) in One or More Treatment Groups for melanoma patients

From the 38 patients with previously-treated NSCLC treated with Pembrolizumab 10 mg/kg every 3 weeks, 2 patients (5.3%) have been reported with pneumonitis and one patient (2.6%) has been reported with steroid-responsive pulmonary oedema. Two cases were grade 2; the case of pulmonary oedema was grade 3. These cases began as early as four days after the first dose to several cycles (Week 18) after the first dose. It is not clear the role of prior thoracic radiation to the development of this adverse event. The grade 3 episode responded to steroids, whereas the grade 2 cases did not. The grade 3 pulmonary oedema and a case of grade 2 pneumonitis were considered drug-related; the third case was considered not drug-related. All three patients died from malignant neoplasm progression. In the case of the two drug-related cases, the patients died within 3 weeks of the start of pneumonitis or pulmonary oedema from malignant neoplasm progression

This study has been designed to assess that pembrolizumab can be safely administered in patients receiving palliative courses of RT to the lung. Patients with NSCLC are eligible for the study. If this is proven, patients receiving pembrolizumab in the future as long term therapy will not require treatment interruptions whilst receiving palliative RT to the lung. Secondly the trial will explore dose scheduling. This will help design future studies looking at concomitant pembrolizumab and RT and help establish whether conventionally fractionated RT or SBRT protocols should be considered. It is not a prerequisite of the study to be PD-L1 strong since the main objective of the study is to assess safety. However biomarker data will be collected and exploratory analyses will be performed to assess if PD-L1 status influences drug-RT responses.

1.3 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (KEYNOTE-001) was conducted to evaluate the safety and clinical activity of single agent Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1mg/kg, 3mg/kg, and 10mg/kg, administered every 2 weeks (Q2W) in patients with advanced solid tumours. All 3 dose levels were well tolerated and no DLTs were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumour size reduction at all dose levels (1mg/kg, 3mg/kg and 10mg/kg Q2W). No MTD was been identified, with 10 mg/kg Q2W being the highest dose tested. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

Pharmacokinetic data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early pharmacokinetic and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population pharmacokinetic model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalised dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200mg fixed dose regimen relative to a 2mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10mg/kg Q3W vs the proposed dose regimen of 2mg/kg Q3W (i.e. 5-fold higher dose and

exposure). The population pharmacokinetic evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications.

For this study maintenance treatment will be given as 200mg Q3W. Dosing during RT is given on a Q2W schedule to maximise the radiosensitising potential. The starting dose (dose level 1) will be 100mg Q2W, decreasing to dose level -1 i.e. 50mg Q2W, if MTD in dose level 1 is achieved. Dose level 2 is 200mg Q2W. Pneumonitis levels were >10% for monotherapy in melanoma patients at dose level 10mg/kg Q3W but for this study only 3 doses at dose level 2 will be given concomitant with RT followed by the maintenance dose of 200mg Q3W. Dose level 2 is expected to be the MTD. In the expansion cohort the dose of pembrolizumab administered with RT will be the MTD dose.

1.4 Rationale for Endpoints

1.4.1 Efficacy, Safety and Tolerability Endpoints

The primary objective of this study is to determine the safety and tolerability of combining pembrolizumab with RT. For this objective there will be 1 condition that will be regarded as DLT, and 2 conditions that will be criteria for the termination of the study. For this study a DLT would be regarded as any event of pneumonitis at ≥ grade 2.

- Pneumonitis:
    - Pneumonitis rates for palliative RT to the lung are consistently below 10%. It has been shown for high dose pembrolizumab pneumonitis rates can go up to 10%. As this study is combining these two treatments pneumonitis of ≥ grade 2 will be considered a DLT. A 25% rate of ≥ grade 2 pneumonitis or more will be considered unacceptable.

In addition, if 1 patient with oesophagitis of ≥ grade 4 or 2 patients of myelitis of ≥ grade 2 occurred at dose levels -1 and/or 1 these would be considered events on which the study would be terminated. However, if these adverse events occurred at dose levels 2 and/or 3, they would lead to dose de-escalation and cohort expansion as defined in Section 3.2.1 of the protocol.

Tolerability will be assessed by documenting all AEs and serious adverse events (SAEs). This is part of the safety endpoint to ensure that the combination regimen is tolerable and that there are no unexpected AEs when combining pembrolizumab with RT. Events of clinical interest (ECI) as per Table 13 will also be assessed.

1.4.2 Progression free survival and overall survival

Median OS for lung tumours is <12 months and median PFS < 6months in patients receiving low dose RT. It is anticipated that with the addition of pembrolizumab during the RT period and continuation of the drug into the

maintenance phase, PFS and OS will be potentially prolonged. With the duration of PFS and OS being significantly more prolonged in PD-L1 strong patients.

1.4.3 Response rates

Response rates will be assessed locally at site using RECIST v1.1 (50) that will be adapted to account for the unique tumour response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab 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 (e.g., cord compression) 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 PD, 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 PD) 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. Differential response rates will be assessed for tumours that are squamous versus non-squamous histological subtypes. RECIST v1.1 states that tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded).

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. The details of the clinical decision must be recorded in full in the patients' medical notes.

1.4.4 Abscopal effect

The abscopal effect refers to a rare phenomenon of tumour regression at a site distant from the primary site of RT (51). Localised RT has been shown to induce abscopal effects in several types of cancer, including melanoma, lymphoma, renal-cell carcinoma and NSCLC (52-55). 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 (56). This effect may be more pronounced in response to ablative rather than conventional dosage or fractionation schedules (46). More recently, the abscopal effect has been described in the context of patients receiving immunotherapy concurrently with RT. Formenti *et al* described a case of abscopal response in a patient with advanced NSCLC who received palliative hepatic RT while on ipilimumab. The response was seen 2.5 months following RT (57). Experimental data from multiple cancer models have provided sufficient evidence to propose a paradigm shift, whereby some of the effects of IR are recognised as contributing to systemic antitumor immunity. Therefore, the traditional palliative role of RT 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 pre-treated cancer patients (58).

For this study this phenomenon can only be assessed in those patients who have disease present outside of the irradiated field and will be an exploratory analysis only. For patients with assessable disease outside the RT field; individual lesion response (Completed Response [CR]/ Partial Response [PR]/ PD/ Stable disease [SD]) will be determined by RECIST v1.1.

1.4.5 Biomarker Research

Archived tissue, newly collected biopsies and correlative blood studies will be assessed for characterisation of TILs and tumour antigens. However any archived slides used must have been generated within 6 months prior to assay due to sample stability limitations. Blood samples will be obtained before the first dose of pembrolizumab (week 0), then again at week 4, at cycle 2 and on disease progression for the analysis of ctDNA, but not necessarily limited to this.

This tumour analysis will allow assessment for PD-L1 status, which could in turn be used to assess differential responses rates according to PD-L1 status. This trial will not be enriched for PD-L1 strong patients, however PD-L1 testing will be batched and performed retrospectively. Furthermore, it will assess for possible effects of immune priming with RT.

2.0 STUDY OBJECTIVES & ENDPOINTS

2.1 Study Objectives & Hypothesis

2.1.1 Primary

Objective: To determine the safety and tolerability of pembrolizumab in combination with RT to the lung.

Hypothesis: Pembrolizumab can be safely administered in combination with both high and low dose RT to the lung.

Objective: To describe the safety profile of pembrolizumab in combination with RT to the lung.

Hypothesis: Pembrolizumab can be safely administered in combination with RT to the lung.

2.1.2 Secondary

Objective: To assess overall PFS and OS.

Hypothesis: Combining pembrolizumab with RT and with maintenance treatment leads to prolonged responses following palliative RT.

Objective: To evaluate PFS against PD-L1 expression.

Hypothesis: Prolonged responses following palliative RT are expected in patients with greater in PD-L1 expression.

Objective: To assess overall responses rates as per RECIST v1.1 and differential responses rates in squamous versus non-squamous histological subtypes.

Hypothesis: High levels of PD-L1 expression predict for poor prognosis in squamous carcinoma.

Objective: To assess oesophagitis rates in this population

Hypothesis: Pembrolizumab can be safely administered in combination with RT for lung irradiation.

2.1.3 Exploratory

Objective: To assess for evidence of abscopal response by individual lesion response (CR/PR/PD/SD) determined by RECIST v1.1.

Hypothesis: Combination RT with pembrolizumab leads to abscopal responses

Objective: Identification of biomarkers that correlate with immunological response to therapy

2.2 Study Endpoints

2.2.1 Primary

1. **A:** To establish the MTD that can be safely combined with RT to the lung in the absence of DLT

   B: To measure the toxicity rate of DLTs assessed two months after the last fraction of RT has been administered

2.2.2 Secondary

1. To measure the PFS and OS at 6 months and 1 year.
2. To measure PFS and OS in PD-L1 strong population at 6 months and 1 year.
3. To measure the duration of clinical benefit using RECIST v1.1 including the different response rates between squamous and non-squamous histological sub-types at 6 months and 1 year.
4. To measure the oesophagitis rates assessed at two months after the last fraction of RT has been administered.

2.2.3 Exploratory

1. To evaluate the abscopal effect between pembrolizumab and RT.
2. Characterisation of TILs and tumour antigens in the tumour biopsies. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.
3. Analysis of research blood samples for ctDNA.

3.0 STUDY DESIGN

3.1 Summary of study design

This is a single centre non-randomised phase 1b open label trial of pembrolizumab given in combination with RT and will recruit up to 36 patients with lung cancer undergoing palliative RT to the lung. The study will be conducted in two parts; initially as a dose escalation trial (Part A), followed by an expansion stage (Part B) wherein patients will be treated at the administered dose below the achieved MTD. Patients will be allocated to either low or high dose RT as standard of care and will be registered to receive pembrolizumab, in combination with their treatment. Patients will continue on the treatment regimen described in the study flow chart (section 3.3) unless they have PD, unacceptable toxicities, discontinuation for other reasons or withdrawal from the study.

3.2 Treatment Regimen

Each patient will receive either high or low dose external beam RT as per standard protocol (Appendix 1). All patients will commence with a pre-loading dose of pembrolizumab (at the dose level under current evaluation –100/200mg) administered 14 days prior to RT (week 0), another dose at day 1 of RT (week 2) and then for high dose patients only another dose 14 days after the commencement of RT (week 4). Both the low dose and high dose RT arms will run simultaneously. Two weeks after the completion of RT; if the patient is to continue on treatment they will enter the maintenance phase and will receive 200mg of pembrolizumab alone every 3 weeks until PD, unacceptable toxicities, discontinuation for other reasons or withdrawal from the study. Patients receiving low dose RT with begin this phase on week 5 and patients receiving high dose RT will begin on week 6.

A minimum of 3 patients will be required per RT cohort at each dose level. A minimum gap of 1 week should be left between the treatment of the first and second patient with the combination of RT and pembrolizumab during the dose escalation phase to mitigate against multiple patients suffering from any acute toxicity. The second and third patient need to be started at least 24 hours apart during the dose escalation phase. If no DLTs are observed in the first 3 patients at a dose level, pembrolizumab will be escalated to the next dosing level. If 1 in 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 previous dosing level, the MTD, should be used for the expansion phase. If the MAD is reached at dose level 1 the study will de-escalate to dose level -1. If the MTD is seen at dose level -1 in both arms then the study will be stopped. Once the MTD has been determined the trial enters the expansion cohort whereby a further 12 patients are treated with the determined dosage of pembrolizumab in combination with high dose RT only (see section 3.2.1).

3.2.1 Dose Levels

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. The DLT will be for a period of 2 months following the final fraction of RT (at the beginning of cycle 4; see Table 3), using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 for acute toxicity by the Pembrolizumab Project Safety Review Committee (PPSRC) before recruitment to the next dose level can begin.

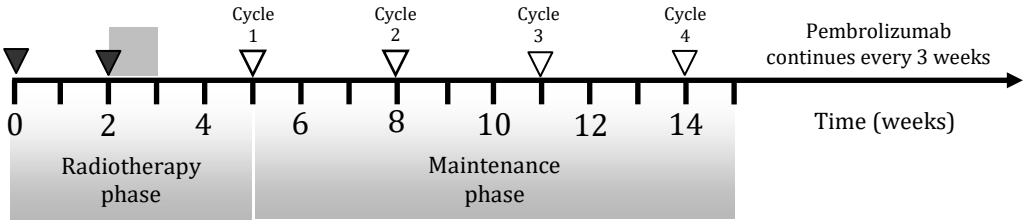
For this study DLTs will be assessed by the presence of pneumonitis of ≥ grade 2. Pneumonitis will be assessed at screening, start of RT (week 2) and cycle 1, 2 and 3 of the maintenance phase. At these visits all patients must be assessed on the basis of clinical symptoms combined with findings from previous CXR and CT scans. Dose escalation to the next dose level will not proceed until the following criteria are satisfied:

- If 0/3 patients experience a DLT escalation to the next dose level can proceed.
- If 1/3 patients experiences a DLT a further 3 patients will be assessed at that dose level.
    - If 1/6 patients experience a DLT pneumonitis then escalation to the next dose level can proceed.
    - If ≥ 2/6 patients in a specific dose level experience a DLT, the MAD will have been reached and all patients in the expansion cohort will be recruited at the previous dose level, the MTD.
- 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, the MTD, unless this occurs at dose level 1 wherein the study will de-escalate to dose level -1.
- If the MTD occurs at dose level -1 the expansion cohort will go ahead at dose level -1.

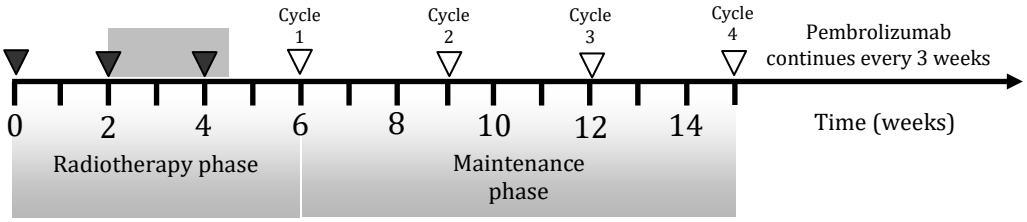
All dose escalation and stopping rules used will be identical in both the low dose and high dose cohorts, respectively. However, the low and high dose RT arms are independent of each other running in parallel, the outcome from one is not expected to affect the decision-making process in the other. Dose expansion will be in the high dose RT arm, as the clinical data reviewed here supports a higher dose being more immunogenic. However, the dose per fraction is higher in the low dose RT arm (4Gy/fraction) versus high dose RT arm (3Gy/fraction), and therefore the response rates during the dose escalation phase will have to be carefully considered by the PPSRC before confirming dose expansion. If in the event the high dose RT arm proves to be too toxic during dose escalation i.e. 2 or more DLTs in dose level -1, the dose expansion will occur, at the MTD defined, in the low dose RT arm only assuming it has not occurred at dose level -1 too.

3.3 Study Flow chart

Low dose radiotherapy group



High dose radiotherapy group



Radiotherapy administration
Radiotherapy dose of Pembrolizumab
Maintenance dose of Pembrolizumab

3.4 Follow-Up

3.4.1 30 Days Safety Follow-Up

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 AEs and 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 Post-Safety Follow-Up

Patients who discontinue trial treatment 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, PD, 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 Follow-Up

Once a patient experiences confirmed PD 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 and/or General Practitioner 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 the study is defined when the last patient has completed or discontinued the study for other reasons.

3.5.1 Clinical 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 MTD is seen at dose level -1.
6. If the incidence of ≥ grade 2 pneumonitis is ≥25% in the study.
7. The occurrence of 1 patient with oesophagitis ≥ grade 4, at dose levels -1 and/or 1.
8. The occurrence of 2 patients with myelitis ≥ grade 2, at dose levels -1 and/or 1.

In accordance with the conditions of supply agreement with MSD, ample notification will be provided to the sponsor 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 Study Termination

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

4.0 SELECTION OF PATIENTS

4.1 Screening and Enrolment

The Investigator at site should keep a record of all patients screened for entry into this study. Copies of the screening logs should be filed in the Site File. For each patient the primary reason for exclusion should be recorded. Diagnostic data obtained as part of the patient's standard care can 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 that patient a trial ID that will be used to identify the patient for all future assessments. 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 3 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 PI's responsibility to maintain a confidential record of the identity i.e. full name and hospital number for the patients enrolled in this study along with their date of birth and 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. This includes patients that discontinue the trial for progressive disease within the DLT reporting period. A patient who 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 the day of their loading dose or day 1 of RT will be removed from the trial and can be replaced in that dose level cohort. Also patients who do not reach follow-up at cycle 3 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. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Histologically verified NSCLC including squamous cell carcinoma, adenocarcinoma, adenosquamous or large cell anaplastic carcinoma.
5. Primary tumour in the thorax, where palliative RT is considered appropriate. Patients are permitted to have extra-thoracic disease that will not be encompassed in the RT field. This disease will be assessed for abscopal response
6. Ability to tolerate a course of palliative RT to the lung.
7. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion.
8. Have a performance status of 0-1 on the ECOG Performance Scale.
9. Demonstrate adequate organ function as defined in Table 2, all screening labs should be performed within 10 days of confirmation of eligibility.

System	Laboratory Value
Haematological	
• Absolute neutrophil count (ANC)	≥1,500 /mcL
• Platelets	≥100,000 / mcL
• Haemoglobin	≥9 g/dL 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 X ULN **OR** **≤** 5 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

Table 2: Adequate Organ Function Laboratory Values

10. Female patient of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to confirmation of study eligibility. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. 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 6 months after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilised or have not been free from menses for > 1 year.
12. Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy through 6 months after the last dose of study therapy.
13. Patient's lung function tests at baseline should have an FEV1 > 0.8L or > 30%.

4.4.2 Exclusion Criteria

The patient must be excluded from participating in the trial if the patient:

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
4. Previous RT to the lung
5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or to baseline) from AEs due to a previously administered agent.
   - Note: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
   - Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer that has undergone potentially curative therapy.
7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of

progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

8. Has an active automimmune 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. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require the use of bronchodilators or local steroid injections are not excluded from this study. Patients with hypothyroidism stable on hormone replacement or Sjörgen's syndrome will not be excluded from the study.
9. 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).
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 6 months after the last dose of trial treatment.
13. Has 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).
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.0 STUDY PLAN AND PROCEDURES

5.1 Study Schedule

Whilst on this treatment patients will be assessed 14 days (week 0) before RT, day 1 (week 2), day 8 (week 3), day 15 (week 4) and day 22 (week 5) (high dose arm only) of RT and then every 3 weeks at the administration of their next dose of pembrolizumab until they have disease progression, unacceptable toxicities, discontinuation for other reasons or withdrawal from the study. Patients will also 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 will be reviewed every 12 weeks to assess for disease status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The schedule of study assessment (Table 3) summarises the trial procedures to be performed at each visit. Individual trial procedures are described in detail below.

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 C, etc.). Such evaluations/testing will be performed in accordance with local regulations.

LOW DOSE RADIOTHERAPY ARM																		
Trial Period:	**Screening Phase**	**Pembrolizumab administration 2 weekly during Radiotherapy**				**Pembrolizumab administration 3 weekly during Maintenance** *(Can be repeated beyond 8 cycles)*										**End of Treatment** *(If applicable)* [8]	**Post-Treatment**		
																	Safety Follow-up (SFU)	**Post Safety Follow-up**	**Survival Follow-up**
Treatment Cycle/Week Title:	**Screening**					**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	*Discontinuation of IMP*	*30 days after last dose* [9]	*Every 9 wks from SFU*	*Every 12 wks from SFU*
		Wk	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**				
		0	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**14**	**17**	**20**	**23**	**26**				
Visit Window (Days):	*-28 to -1*	*- 14 RT*	*D1 RT*	*D8*	*D15*	*±3*			*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*
Administrative Procedures																			
Informed Consent [1]	X																		
Inclusion/Exclusion Criteria	X																		
Demographics, Medical & Treatment History	X																		
New Anti-Cancer Therapy Review																		X	
Survival Status																			X
Clinical Procedures / Assessments																			
Adverse Events Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Radiation Toxicity Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X^4	X^4		
MRC Dyspnoea Score	X		X			X			X	X						X			
Pneumonitis Assessment	X^3		X^3			X^3			X^3	X^3						X^4			
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X	X				X										X	X		
Directed Physical Examination			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	X		
Height	X																		
ECOG Performance Status	X	X	X	X		X			X	X	X	X	X	X	X	X	X		
Pulmonary Function Tests	X					X				X		X		X^7					
Haematology and Biochemistry	X	X	X	X		X			X	X	X	X	X	X	X	X	X		
FT3, FT4 and TSH	X	X				X			X	X	X	X	X	X	X	X	X		
PT and aPTT	X																		
Urinalysis	X																		
Pregnancy Test - Urine/Serum	X					X													
Pembrolizumab Administration		X	X			X			X	X	X	X	X	X	X^{10}				
Radiotherapy			X																
Tumour Imaging - MRI/CT	CT/CXR		CXR			CXR			CT	CXR		CT			CT^5	CT^6			
Archival/New Tumour Biopsies	X																		
PD-1 Assessment[2]	X																		
Research Blood Collection		X			X				X							X			
OPTIONAL Research Biopsies (Part B only)		X							X										

1. Patients that do not have archival tissue must sign the study consent prior to undergoing a newly obtained biopsy
2. 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
3. Pneumonitis should be assessed by a combination of clinical assessment and CXR or CT results. CXR shoul be used at screening, week2, cycle 1 and cycle 3. CT results should be used at cycle 2
4. Only applicable if SFU is before cycle 4 of the maintenance period
5. MRI/CT Imaging should occur at screening, cycle 2 and every 3 cycles (every 9 weeks) for the first 6 months then every 12 weeks after 6 months (regardless of treatment delays) Images can be up to 7 days before visit to ensure results at the visit. The same imaging technique should be used throught the trial
6. Only applicable if the patient comes off for other reason than disease progression and no measurement had been taken within the last 4 weeks
7. Pulmonary function tests at screening, cycle 1 and then every other cycle
8. This visit is only applicable if the patient comes off the study between treatment cycles
9. Or before the initiation of a new anti-cancer therapy
10. Maintenance Pembrolizumab will continue until disease progression, withdrawal of consent or unacceptable toxicity. Patients obtaining CR or completing 35 cycles of treatment may discontinue treatment, with the option of restarting on progression

Table 3.1: Study Schedule of Assessment (Low Dose Radiotherapy Arm)

HIGH DOSE RADIOTHERAPY ARM																		
Trial Period:	**Screening Phase**	**Pembrolizumab administration 2 weekly during Radiotherapy**					**Pembrolizumab administration 3 weekly during Maintenance** *(Can be repeated beyond 8 cycles)*									**End of Treatment** *(If applicable)* [8]	**Post-Treatment**		
																	Safety Follow-up (SFU)	**Post Safety Follow-up**	**Survival Follow-up**
							C1		**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**				
Treatment Cycle/Week Title:	**Screening**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	**Wk**	*Discontinuation of IMP*	*30 days after last dose* [9]	*Every 9 wks from SFU*	*Every 12 wks from SFU*
		0	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**12**	**15**	**18**	**21**	**24**	**27**				
Visit Window (Days):	*-28 to -1*	*-14 RT*	*D1 RT*	*D8*	*D15*	*±3*			*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*
Administrative Procedures																			
Informed Consent [1]	X																		
Inclusion/Exclusion Criteria	X																		
Demographics, Medical & Treatment History	X																		
New Anti-Cancer Therapy Review																		X	
Survival Status																			X
Clinical Procedures / Assessments																			
Adverse Events Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Radiation Toxicity Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	X[4]		
MRC Dyspnoea Score	X		X				X		X	X						X			
Pneumonitis Assessment	X[3]		X[3]				X[3]		X[3]	X[3]						X[4]			
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X	X					X									X	X		
Directed Physical Examination			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	X	X		
Height	X																		
ECOG Performance Status	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X		
Pulmonary Function Tests	X						X			X		X		X[7]					
Haematology and Biochemistry	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X		
FT3, FT4 and TSH	X	X					X		X	X	X	X	X	X	X	X	X		
PT and aPTT	X																		
Urinalysis	X																		
Pregnancy Test - Urine/Serum	X						X												
Pembrolizumab Administration		X	X		X		X		X	X	X	X	X	X	X[10]				
Radiotherapy			X	X	X														
Tumour Imaging - MRI/CT	CT/CXR		CXR				CXR		CT	CXR		CT			CT[5]	CT[6]			
Archival/New Tumour Biopsies	X																		
PD-1 Assessment[2]	X																		
Research Blood Collection		X			X				X							X			
OPTIONAL Research Biopsies (Part B only)		X							X										

1. Patients that do not have archival tissue must sign the study consent prior to undergoing a newly obtained biopsy
2. 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
3. Pneumonitis should be assessed by a combination of clinical assessment and CXR or CT results. CXR shoul be used at screening, week2, cycle 1 and cycle 3. CT results should be used at cycle 2
4. Only applicable if SFU is before cycle 4 of the maintenance period
5. MRI/CT Imaging should occur at screening, cycle 2 and every 3 cycles (every 9 weeks) for the first 6 months then every 12 weeks after 6 months (regardless of treatment delays) Images can be up to 7 days before visit to ensure results at the visit. The same imaging technique should be used throught the trial
6. Only applicable if the patient comes off for other reason than disease progression and no measurement had been taken within the last 4 weeks
7. Pulmonary function tests at screening, cycle 1 and then every other cycle
8. This visit is only applicable if the patient comes off the study between treatment cycles
9. Or before the initiation of a new anti-cancer therapy
10. Maintenance Pembrolizumab will continue until disease progression, withdrawal of consent or unacceptable toxicity. Patients obtaining CR or completing 35 cycles of treatment may discontinue treatment, with the option of restarting on progression

Table 3.2: Study Schedule of Assessment (High Dose Radiotherapy Arm)

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 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 Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, 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.

Patients who achieve a CR or complete 35 cycles of maintenance pembrolizumab may discontinue treatment. They may restart maintenance pembrolizumab on disease progression. Provided their consent is on the current version of the PIS, patients are not required to re-consent to the trial on reinitiating maintenance pembrolizumab.

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 /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. In addition any abnormal and clinically significant results seen during the screening period should be recorded in the medical history form. 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
- Review all prior cancer treatments including systemic treatments, radiation and surgeries

5.2.4 Anti-Cancer Therapy Review

Patients that discontinue from pembrolizumab for any other reason than 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 trial treatment. If a patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 days 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 at specified visits as defined in the schedule of study assessment (Table 3). The assessment will include the patient status and if applicable details of patient death or details if patient has been lost to follow up.

5.2.6 Prior and Concomitant Medications Review

5.2.6.1 Prior Medications

The investigator / 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 / designee will record all medication, if any, taken by the patient during the trial. All medications related to reportable SAEs and overdose and liver toxicity ECIs should be recorded as defined in Section 7.

5.3 Clinical Procedures/Assessments

5.3.1 PD-1 Assessment

To participate in the trial patients must have archived tissue of a tumour lesion not previously irradiated (tumours progressing in a prior site of radiation are allowed) for PD-L1 characterisation. Neither the dose escalation nor the dose expansion cohorts will be enriched for PD-L1 strong patients. This specimen will be batched and analysed retrospectively at a central laboratory for expression status of PD-L1 by immunohistochemistry (IHC). If no tissue is available then following informed consent they should undergo a biopsy of a tumour lesion for biomarker analysis.

5.3.2 Adverse Event (AE) Monitoring

The investigator / designee will assess each patient for potential new or worsening AEs as specified in the schedule of study assessment (Table 3) and more frequently if clinically indicated. AEs will be graded and recorded from first dose of pembrolizumab until the patients 30 days safety follow-up visit according to NCI CTCAE Version 4.0 (see Appendix 2). 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 immunologic aetiology (irAE). See Section 7 and Appendix 5 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 Radiation Toxicity Assessment

RT toxicity will be documented using the LENT SOMA radiation toxicity grading system (Appendix 3). Assessments will take place weekly for 6 weeks beginning at week 2 and ending at week 7. Additional assessments of RT toxicity will be documented at each cycle of the maintenance phase.

5.3.4 Full Physical Exam

The investigator / designee will perform a complete physical exam at screening period and the time points defined in the study schedule of assessment (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 assessment (Table 3), the investigator / designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

5.3.6 Vital Signs

The investigator /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 assessment (Table 3). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

5.3.7 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator / designee will assess ECOG status (Table 4)at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the study schedule of assessment (table 3).

Grade	Description
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 in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J ClinOncol 5:649-655, 1982.*The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Table 4: ECOG Performance Status

5.3.8 Pulmonary Function Tests

Spirometry assessments will be performed at screening and cycle 1, 3, 5 and 7 only of the maintenance period.

5.3.9 MRC Dyspnea Scale

The investigator or qualified designee will assess the patient's dyspnoea using the MRC Dyspnoea Score (Appendix 6) at screening period and the time points defined in the study schedule of assessments (Table 3).

5.3.10 Pregnancy Tests

Female patients of childbearing potential should have a negative urine or serum pregnancy during screening and within 72 hours prior to confirmation of study eligibility. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Patients will be required to undergo an additional pregnancy test before commencing cycle 1 of the maintenance phase.

5.3.11 Haematology, Clinical Biochemistry and Urinalysis (including FT3, FT4, TSH, PT, aPTT and β-hCG†)

All Laboratory tests will be performed at screening and then certain assessments at every visit as defined in the schedule of study assessment (Table 3). Sample will be analysed by the local study site laboratory using standard methods for routine tests. The following variables (Table 5) will be measured:

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.			

Table 5: Required Laboratory Assessments

Laboratory tests for screening can be performed within 10 days prior to confirmation of eligibility. 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.

5.3.12 Pneumonitis Assessment

A screening pneumonitis score should be documented on the basis of clinical symptoms and screening CXR and CT scan. If there is evidence of active pneumonitis at that visit, the patient will not be permitted to continue in the study. Patients will then be re-assessed at week 2 (day 1 of RT) and cycle 1, 2 and 3 of the maintenance period.

5.3.13 Tumour Imaging and Assessment of Disease

5.3.13.1 Baseline tumour imaging

Imaging should be undertaken to confirm that the patient has a primary tumour in the thorax, where palliative RT is considered appropriate and the lesion is measurable using RECIST v1.1. The scan will also be assessed for an extra-thoracic disease; if present these lesions will be used to assess for abscopal response

5.3.13.2 Timing and Assessment of Disease

Tumour imaging may be performed by CT or magnetic resonance imaging (MRI), but the same imaging technique should be used in a patient throughout the trial. 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 then at cycle 2 to assess RT response. After cycle 2 imaging will be performed every 3 cycles (every 9 weeks) for the first 6 months (± 7 days) then every 12 weeks after 6 months, and should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies.

Local investigator assessment will be used to determine eligibility and for patient management. Tumour imaging and assessment per local standard of care should be performed for patient management, and may include additional imaging (e.g. bone scan for lung cancer patients).

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.

5.3.13.3 Confirmation of Disease Response

Per RECIST v1.1 (Appendix 4), 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.

5.3.13.4 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

5.3.14 Tumour Tissue Collection and Correlative Studies Blood Sampling

5.3.14.1 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.

5.3.15 Tumour Biopsies and Research Blood Samples

For patients without archived samples tumour biopsies will be obtained during the screening period and if the patient consents optional research blood samples will be obtained at week 0, week 4, cycle 2 and end of study visit (Disease Progression).

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 RT. Assays may include, but are not limited to:

- **Characterisation 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 markers: CD4, CD8, FOXp3, PD-1, PDL1, and PD-L2.

- **ctDNA**

  Research blood samples will be analysed for ctDNA.

5.3.16 Optional Fresh Tumour Biopsies and Processing/Storage

The collection of fresh tumour tissue is entirely OPTIONAL and will only be considered in consenting patients during the dose expansion phase ONLY. At least 6 paired biopsies will be collected, with a minimum of 2 patients with squamous cell histology and 2 patients with non-squamous histology.

All potentially biopsiable patients will have their most recent computerised tomography (CT) (preferably within the last 4 weeks) discussed with a Consultant Radiologist (tumour stream radiologist or interventional radiologist) will decide if 2 paired core biopsies can be safely performed in potential patients. If 2 paired core biopsies can safely be considered, the site to be biopsied (e.g. hepatic biopsy, lung biopsy, or percutaneous biopsy of subcutaneous lesion) and the modality of imaging to be used (e.g. CT guidance, ultrasound scan (USS) guidance) will be advised on. These will only be performed if they are felt safe in the opinion of the Consultant Radiologist. All CT guided liver and lung biopsies, will be performed by the Interventional Radiologist at the Chelsea site. Ultrasound guided liver and percutaneous biopsies can be performed at either site by a Consultant Radiologist.

If a bronchoscopy guided biopsy is required, this will need to be discussed further with the Honorary Respiratory Consultant at the Sutton site. If the Honorary Respiratory Consultant feels that paired biopsies can be performed safely, then this will need to be organised through the Sutton site.

Consenting patients will have biopsies considered at 2 time points:

A. Baseline
B. At 8 – 9 weeks (around cycle 2 ± 3 days)

The biopsy will be performed under sterile conditions with a trucut biopsy device (under radiological guidance, if indicated) using standard biopsy procedures. The specimen will be immediately transferred to the recommended storage solution and processed to either fresh frozen sample or paraffin wax. All FFPE tissue will be stored at room temperature and all frozen tumour samples will be stored at -80^{o}C.

All standard operating procedures for organising ultrasound guided biopsies, CT guided biopsies and bronchoscopy guided biopsies at the Royal Marsden NHS Foundation Trust must be adhered to. This includes performing a full blood count, biochemistry and coagulation studies within the specified trust guidelines. Further, the lead medical team should ensure the patients are given appropriate advice about anti-platelets drugs (e.g. aspirin and clopidogrel), oral anticoagulants (e.g. warfarin, dabigatran, rivaroxaban and apixaban) and low molecular weight heparins (e.g. enoxaparin, dalteparin, and tinzaparin). Where possible, the biopsy should be performed before 1 pm to allow for routine post-procedure observations during working hours. In addition to having signed the consent for this clinical trial protocol, all patients undergoing a biopsy must sign the appropriate Royal Marsden NHS Foundation Trust imaging-guided biopsy consent form. This consent must be taken by the doctor performing the biopsy. A new consent must be done for each paired biopsy performed.

Risks associated with research biopsies:

A. Hepatic biopsies have a mortality rate of 0.13-0.33% and a complication rate of 5.9% (including all major and minor events - the majority of these comprising of post-procedure pain or non-significant haematomas (*Gut* 1999;**45**:IV1-IV11 doi:10.1136/gut.45.2008.iv1).
B. Percutaneous Lung Biopsies have a mortality rate 0.15% and complications that can include pneumothorax (0-61%), pulmonary haemorrhage (5-16.9%) and haemothorax (1.5%) *(Thorax* 2001;**56**:i1-i21 doi:10.1136/thx.56.suppl_1.i1)
C. Bronchoscopic biopsies have a mortality rate of 0.04% and a major complication rate of 1.2 per 10 000 procedures based on a series of 40 000 UK patients. Major complications can include respiratory depression, pneumonia or pneumothorax *(Thorax* 2001;**56**:i1-i21 doi:10.1136/thx.56.suppl_1.i1).

5.3.17 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 at each site 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 sites.

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 6. Up to 60 mL of optional blood will be collected for translational research. Examples of tubes used to collect these samples include, but not limited to:

- 3 mL Tempus™ Blood RNA Tubes
- 4.5 mL Lithium Heparin Coated Tubes
- 5 mL or 9 mL K3 EDTA Coated Tubes

	Sample volume (mL)	No. of samples	Total volume (mL)
Routine Haematology	6[1]	14	84
Routine Clinical chemistry	8[1]	14	112
		Total:	196
Research Blood Samples – OPTIONAL	Up to 60	4	Up to 240
		Study Total:	436

Table 6: Volume of blood to be drawn from each trial patient for the duration of the trial; calculations based on 11 administrations of pembrolizumab (Duration of RT and 8 cycles of the maintenance phase), a screening visit and 30 days post end of treatment safety visit.

Blood volumes for haematology and clinical chemistry may vary according to local practice

6.0 TREATMENTS

Patients will be given pembrolizumab in addition to palliative RT.

6.1 Standard Treatment

6.1.1 External Beam radiotherapy – Planning and Treatment

Patients will be treated with external beam RT. Planning will be done by CT virtual simulation. Isodose intervention is required for the high dose group but not mandated for the low dose group. For the high dose group conformal planning with CT is permitted. The use of IV contrast is permitted if felt necessary. The gross target volume (GTV) will be defined as visible tumour on a planning CT scan (virtual simulation). 3D dose-volume information for the tumour and the normal tissues will be obtained for subsequent analysis. The normal structures to be outlined for post treatment analysis are lungs, heart and spinal cord. The CTV/PTV margin will be defined using standard Royal Marsden Hospital criteria. Dose will be prescribed at the midpoint or at 100% as per ICRU guidelines. Treatment verification with on-board imaging will be carried out as per departmental protocol.

6.1.2 Radiotherapy Dose

Lesion(s) will be irradiated to either a dose of 20Gy in 5 fractions or 36Gy in 12 fractions.

6.1.3 Radiotherapy Assessments and Procedures

6.1.3.1 Radiotherapy Toxicity Assessment

A baseline pneumonitis score should be documented on the basis of clinical symptoms and screening CT scan. If there is evidence of active pneumonitis at that visit, the patient will not be permitted to continue in the study.

RT toxicity will be documented at day 1, day 8 and 15 for low dose RT and day 1, 8, 15 and 22 for high dose RT. RT toxicity will be documented at cycle 1 (2 weeks from RT) ,2 (5 weeks from RT), 3 (8 weeks from RT) and maintenance. Specific toxicity with CTCAE v4.0 grading to be recorded for RT toxicity includes pneumonitis, lung fibrosis, oesophagitis, skin toxicity, myelitis and fatigue. All other AE are to be documented in addition.

6.2 Trial Treatment - Pembrolizumab

6.2.1 Investigational Product

The Investigational Medicinal Product (IMP) for this study is Pembrolizumab. A potent and highly-selective humanised 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 the table below. Additional information about the investigational product can be found in the Investigator's Brochure (IB) .

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

Table 7: Product Description

6.2.2 Product Preparation

The pembrolizumab solution for infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is preservative-free solution which is essentially free of extraneous particulates.

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 6 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 24 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.

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 IMP handling guidelines.

At each site the Investigator / designee e.g. pharmacist is responsible for ensuring that all trial medication is 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 authorised 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 Merck, Sharp and Dohme (MSD) as solution for injection. Pembrolizumab will be packaged, labelled and delivered to the participating sites 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 investigator / designee is responsible for keeping accurate accountability 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, partially used trial medication will be destroyed at the site per institutional policy. It is the Investigator's/designees responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Upon completion or termination of the study, all unused trial medication will be returned to MSD or destroyed at the site per institutional policy. It is the 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. Two dose levels of pembrolizumab will be studied to ensure tolerability of combining therapy with RT with the option after the first dose level to de-escalate. The treatment regimen to be used at each dosing level is outlined in Table 8 below.

Drug	Dose Level	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	-1	50mg	Q2W	IV infusion	During RT phase
Pembrolizumab	1	100mg	Q2W	IV infusion	During RT phase
Pembrolizumab	2	200mg	Q2W	IV infusion	During RT phase
Pembrolizumab	maintenance	200mg	Q3W	IV infusion	Maintenance phase
The pembrolizumab dosing interval may be increased due to toxicity as described in Section 6.2.9.2.					

Table 8: Pembrolizumab treatment regimens for each dosing level.

Trial treatment should begin within 3 days of confirmation of eligibility or as close as possible to the date on which treatment is allocated/assigned.

Details on the preparation and administration of pembrolizumab are provided in the IMP handling guidelines. These guidelines contain specific instructions for Pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

6.2.7 Timing of Dose Administration

Trial treatment should be administered on an outpatient basis on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the Study Flow Chart (Section 3.3) and on the schedule of study assessment (Table 3). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Trial treatment will be administered on day 1 of RT for low dose arm and day 1 and day 15 of the high dose arm. Both arms receive a preloading dose 2 weeks before RT. After RT patients will continue onto the maintenance phase. This will begin at week 5 for low dose patients and week 6 for high dose patients. Trial treatment during the maintenance phase of the trial is administered on a 3 weekly cycle. Maintenance

Pembrolizumab will continue until disease progression, withdrawal of consent, or unacceptable toxicity. Patients obtaining CR or having completed 35 cycles 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 and the study sponsor. Study related assessment and procedures should be as for the Pembrolizumab Maintenance phase, during the non-DLT period (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 6.2.9.2). 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). In addition, infusion length may be increased due to toxicity as described in Section 6.4.1.4.

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

6.2.8 Trial Blinding/Masking

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

6.2.9 Dose Selection/Modification

6.2.9.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 1.3 – Background and Rationale.

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 below.

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhoea/Colitis	2-3	Toxicity resolves to Grade 0-1/baseline.	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

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
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 2 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
Hepatitis	1	Continue treatment	
	2	Withhold treatment	Treat with steroids (prednisone 1 – 2 mg/kg or equivalent). Restart treatment when all liver function tests are down to grade 1 and steroid dose is down to 10 mg or less of prednisone or equivalent. Based on severity and symptoms you may wish to discontinue treatment.
	3 - 4	Permanently discontinue	Permanently discontinue
Encephalitis	3 - 4	Permanently discontinue	Permanently discontinue
Myocarditis	1 - 2	Withhold treatment	Treat with steroids (prednisone 1 – 2 mg/kg or equivalent). Restart treatment when symptoms are down to grade 1 and steroid dose is down to 10 mg or less of prednisone or equivalent.
	3-4	Permanently discontinue	Permanently discontinue
Skin reactions	1 – 2	Continue treatment	Manage with topical corticosteroids and oral anti-puritics
	3	Withhold treatment	Treat with steroids (prednisone 1 – 2 mg/kg or equivalent). Restart treatment when rash is down to grade 1 and steroid dose is down to 10 mg or less of prednisone or equivalent.
	4	Permanently discontinue	Permanently discontinue
Confirmed Stevens-Johnson Syndrome or	-	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Toxic-epidermal Necrolysis			
Guillain-Barré syndrome	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.

Table 9: Dose modification guidelines for drug-related AEs

If the toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued at the discretion of the investigator. Patients with a laboratory adverse event 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.

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. RT-related AEs will be managed as per institution clinical guidelines.

Events of Clinical interest (ECI) can be potential immune related AEs and dose modifications for these toxicities should they occur can be found in appendix 5

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.

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 trial. If there is a clinical indication for one of these or other prohibited medications or vaccinations then the patient may be discontinue from trial therapy. The investigator should discuss any questions regarding this with the Chief Investigator ([CI] 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 schedule requires the mutual agreement of the Investigator, CI/ delegate, 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
- Radiation therapy not specified in this protocol
    - Note: subsequent RT whilst on maintenance treatment will not be permitted. Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor providing it does not involve re-irradiation of any part of the lung
- 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 intranasal 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 CI/delegate.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for 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 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 etiologies 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). 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 IV 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 Anti-infectives:

Patients with a documented infectious complication should receive oral or IV 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 6.5 below 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; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumour pain (onset or exacerbation of tumour pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

The table below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

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 Acetaminophen 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). Acetaminophen 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; hospitalisation indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen 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. Hospitalisation 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 v4.0 (CTCAE) at http://ctep.cancer.gov		

Table 10: Infusion Reaction Treatment Guidelines

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 adverse event of unknown aetiology, 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 neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labelling an adverse event as an irAE. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the CI/designee.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in the table below.

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 utilise 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.		

Table 11: General Approach to Handling irAEs

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

Immune-mediated nephritis

Monitor subjects for changes in renal function 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), 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. 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 life-threatening (Grade 4) hypophysitis.

Monitor subjects for hyperglycemia or other signs and symptoms 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. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue Pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism. 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-mediated 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 Table 13 in section 7.5. 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 who will in turn notify MSD. If the irECI is determined to be associated please refer to 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.

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 12.

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	Consider pulmonary consultation with bronchoscopy and biopsy/BAL. Conduct an in person evaluation approximately twice per week

	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 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 symptomsimprove to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day ordexamethasone 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 retapering 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.

Table 12: Recommended Approach to Handling Pneumonitis

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 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 1 highly effective method of birth control that can be combined to a second method of contraception (not considered highly effective) or they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilised, 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. Thehighly effective birth control method can be combined to the adequate barrier methods of contraception. Patients should start using birth control from screening throughout the study period up to 6 months 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 6 months after the last dose of study therapy.

The following are considered as highly effective birth control methods: Combined oral/intravaginal/transdermal contraceptive agent associated with inhibition of ovulation (which contains estrogen and progestogen both), Progestogen only oral/injectable/implantable hormonal contraception associated with inhibition of ovulation, Copper intrauterine device (IUD), Intrauterine hormone-releasing system (IUS), Bilateral tubal occlusion, Vasectomised partner provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success and Sexual abstinence, the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

The following are considered adequate barrier methods of contraception and can be combined to a highly effective birth control method: diaphragm, condom (by the partner), sponge, or spermicide.

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 safety 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 RM-CTU without delay and within 24 hours to the sponsor. 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 over 20% . Please see section 7.6 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 5.3.13

  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 as described in Section 6.2
- 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
- Completed 35 cycles of treatment with 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 trial medication and future study visits / 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 havetrial treatment stopped at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator 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. Any AEs that are present at that time should be followed in accordance with the safety requirements outlined in Section 7.

Patients who a) attain a CR or b) complete 35 cycles of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment on disease progression. Retreatment should be discussed with the Chief Investigator and the study sponsor. Study related assessment and procedures should be as for the Pembrolizumab Maintenance phase, during the non-DLT period (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 CR, 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.

7.0 PHARMACOVIGILANCE

7.1 Adverse events

7.1.1 Adverse Event Definition:

An adverse event 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 adverse event.

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 adverse event 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 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.

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)
- 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 CTCAE v4.0 and LENT SOMA radiation toxicity grading system. Any adverse event 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 e-case report forms from that date at the new severity.

Grade 1	Mild; asymptomatic or mid 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; hospitalisation or prolongation or hospitalisation indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

7.3.2 Determining AE Causality

The Principal 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)

A 'serious adverse event' is defined in Article 2(o) of Directive 2001/20/EC as follows:

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 adverse event associated with an overdose is considered a serious adverse event.
- 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 serious adverse event 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 days 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 to the sponsor of the investigator / designee becoming aware of the event.

The SAE form should be sent to **Email: Pear.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 Reference Safety Information. then signed and dated by the Principal Investigator or an appropriately qualified designated individual identified on the delegation log. The IB as last amended and approved by the national competent authority serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial. 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 on a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. The sponsor 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 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 SAE's but 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 Reference Safety Information. The IB as last amended and approved by the national competent

authority serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial. . If updated versions of the IB are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.

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 ECI and **overdose and liver toxicity ECIs 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 than 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 13 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:

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	Enterocolitis hemorrhagic	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)	
Endocrine - ***(classified as ECI)***		
Type 1 diabetes mellitus (if new onset)		
Haematologic - ***(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 (ALTand/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 syndromw		
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 - (classify 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.		

Table 13: Immune related AEs considered ECIs

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 by fax 020 8915 6762 or email Pear.Trial@rmh.nhs.uk who will in turn notify MSD.

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 adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) should be recorded on the AE CRF and reported as a serious adverse event, 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 Event of Clinical Interest (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 by Fax 020 8915 6762 or Email Pear.Trial@rmh.nhs.uk who will inform MSD.

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 SAEs (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 by Fax 020 8915 6762 or Email Pear.Trial@rmh.nhs.uk who will inform MSD

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. The IB as last amended and approved by the national competent authority serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.

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 by fax 020 8915 6762 or email Pear.Trial@rmh.nhs.uk. The sponsor will in turn notify 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 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 to the Sponsor, 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/DI must notify the Medicines and Healthcare Products Regulations (MHRA) the Research Ethics Committee (REC) and the Sponsor 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 RM-CTU immediately either by:

Email:	Pear.Trial@rmh.nhs.uk
Tel:	020 8915 6667
Fax:	020 8915 6762

The notification must include:

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

RM-CTU will then inform the Sponsor who 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 sites.

CI Contact Details:	
Name:	Dr Merina Ahmed
Address:	Royal Marsden NHS Foundation Trust
	Downs Rd
	Sutton
	SM2 5PT
Tel:	020 8661 3374
Email:	merina.ahmed@rmh.nhs.uk

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The primary endpoint is the safety and tolerability of pembrolizumab in combination with RT to the lung. A standard 3+3 dose escalation design will be used in Part A to establish the MTD of study drug when given in combination with RT. This will be run in two different dose RT cohorts in parallel with each other. The final review of toxicity of each dose level will be completed at 2 months following the final fraction of RT of the last patient in each cohort. If a DLT is seen in more than or equal to 2/3 patients at dose level 1, 3 patients will be recruited at dose level -1. If ≥ DLT is seen in no more than 1/3 patients, a further 3 patients will be recruited at dose level 1. If a DLT is seen in no more than 1/6

patients, proceed to the next dose level otherwise 3 patients will be recruited at dose level -1. The same rules apply to the next dose level until the MTD is achieved.

8.2 Endpoints

8.2.1 Primary endpoints

1. To establish the MTD that can be safely combined with RT to the lung in the absence of DLTs (Part A)
2. To measure the toxicity rate of DLTs assessed at 2 months following final fraction of RT (Part A)

The toxicity rate will be stated as the proportion of patients who have had a DLT calculated with a 95% confidence interval. Other toxicities will be tabulated with the proportions and frequencies of all grades described.

Tolerability will be assessed by recording toxicity. Acute and late toxicity data will be tabulated by grade. Number and proportion of toxicity grades 1-4 and grade 3-4 will be reported. Toxicity data should include AEs, laboratory values, spirometry data, vital signs and irAEs.

Toxicity rates will be reported for both RT arms, respectively.

8.2.2 Secondary endpoints

1. To measure the PFS and OS at 6 months and 1 year. (Part A and B)
2. To measure PFS and OS in PD-L1 strong population at 6 months and 1 year. (Part A and B)
3. To measure the duration of clinical benefit using RECIST v1.1 including the different RR between squamous and non-squamous sub-types at 6 months and 1 year. (Part A and B)

Progression-free survival (PFS) will be measured from the start of RT until radiological or clinical evidence of progression or death and will be censored at date of last follow-up for surviving patients.
Overall survival (OS) will be measured from the start of RT 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.

The duration of clinical benefit (CR/PR/SD) assessed by the investigator using RECIST v1.1 will be calculated using Kaplan-Meier methods.

Differential response rates will be calculated as proportions and compared in the high and low RT arms, in the squamous and non-squamous cell histological sub-types, and the PD-L1 strong and non-strong, respectively, giving associated 95% confidence intervals.

The first response assessment occurs at cycle 2, which is approximately 5 weeks following RT and will be used to document initial RT response. A subsequent scan at cycle 5 will document the RT response. Thereafter scans are performed every 3 cycles (every 9 weeks) for the first 6 months (± 7 days) then every 12 weeks after 6 months. Efficacy will be evaluated separately in each RT cohort. Proportions will be compared using the Chi Squared test for proportions or for small expected frequencies Fisher's exact test as appropriate.

8.2.3 Exploratory analyses

1. To evaluate the abscopal effect of pembrolizumab and RT. (Part A and B)
2. Characterisation of TILs and tumour antigens in the tumour biopsies. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2. (Part A and B)
3. Analysis of research bloods for ctDNA.

The abscopal response rate will be calculated as the proportion with the appropriate 95% confidence interval.

Abscopal responses will only be evaluated on the scans acquired at cycle 2 and cycle 5.

The effect of PD-L1 expression on response rate will be measured using the proportion of patients recorded to be strong expression and tested using a Chi Squared test for proportions on expression level between responders and non-responders.

8.2.4 Sample Size

The is a 3+3 design in two RT dose cohorts each with 2 pembrolizumab dose levels (1 & 2) and the first 3 patients are recruited at dose level 1 in each cohort. This means that there will be a minimum of 6 and maximum of 12 patients in each cohort. This will give a total minimum of 12 and a maximum of 24 patients in the dose escalation phase. The expansion phase will then include an additional 12 patients receiving high dose RT only. The expansion cohort will NOT be enriched for PD-L1 strong patients.

8.2.5 Data analysis

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 with 95% confidence intervals. Baseline characteristics will be summarised for all enrolled patients. Treatment administrations will be described for all cycles. Dose administration, dose modifications or delays and duration of therapy will be described.

9.0 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)

9.2.1 Initial Approval

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 RM/ICR joint 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 R&D 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.

9.2.2 Approval of Amendments

Any protocol amendment should be agreed with the trial management group (TMG) and be approved by the sponsor prior to submission and review by the relevant Ethics Committee. Once favourable opinion from IEC has been obtained the amendment can be distributed to sites and implemented. It is the responsibility of the Principal Investigator to submit amendment to their 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.

9.2.3 Annual Safety Reports and End of Trial Notification

It is the responsibility of the sponsor to submit the Development Safety Update Report 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 within 90 days of the trial completion. Copies of these reports will also be held within the main trial master file.

9.3 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.

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

The Sponsor 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 a breach 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.

9.5 Insurance and Liability

The Sponsors have 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.

9.6 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 to all participating sites.

9.7 Patient Confidentiality

9.7.1 Patient Confidentiality and Data Sharing

The Principal 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.

9.7.2 Pharmacogenetics Confidentiality

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.

9.8 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, patient's eligibility for participation in the trial, study treatment administration (pembrolizumab and RT), 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 or personal information will not be recorded outside the hospital.

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

- sufficient data is recorded for all participating 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 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.

9.9 End of Trial

The end of the trial is defined as the last patient's last visit.

10.0 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 to allow for 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 recorded on a trial specific CRF designed by RM-CTU. Upon signing the informed consent form, the patient is assigned to the next sequential patient trial identification number available. To ensure recruitment is not delayed in any way a paper CRF will be available for use in the event that the electronic CRF is not ready for use.

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). If a patient withdraws from the study, the reason must be noted on the CRF.

Authorised site personnel must not enter study-specific data directly into CRFs and must ensure all results are appropriately documented in the patients' medical records. 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 only.

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 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:

RM-CTU

RM-CTU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting all analyses.

The responsibilities of RM-CTU for the day-to-day management of the trial will include the following.

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

MSD

- Provision of pembrolizumab

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 that includes requirement to sign and adhere to the trial protocol.

Any protocol amendment should be agreed with the trial management group (TMG) and be approved by the sponsor prior to submission and review by the relevant Ethics Committee and the MHRA where required. Once favourable opinion from REC and if applicable the MHRA has been obtained the amendment can be distributed to sites and 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. 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).

10.8.1 Trial Management Group (1 per study)

A Trial Management Group (TMG) will be set up and membership will include Chief Investigator, Co-Investigators, Trial Statistician and Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG has operational responsibility for the conduct of the trial. The TMG is bound to act on the advice of the PPSRC but is also responsible for monitoring recruitment, safety and governance of the trial as well as collaborating with subsequent translational sub-studies. The TMG will also review any safety concerns and can convene a meeting of the PPSRC if significant concerns exist. The TMG will meet weekly to review results and side effects of all patients in the PEAR study. The statistician may not be required at every meeting but should be called upon if necessary. The format of this meeting will be concordant with that used for Phase I studies at RMH.

10.8.2 Pembrolizumab Project Safety Review Committee (PPSRC)

PPSRC has been established to coordinate the management and governance of 4 phase 1 trials evaluating Pembrolizumab in combination with standard of care RT in different tumour types (bladder, cervix, head and neck, or lung). The PPSRC will include the chief investigators of all 4 Pembrolizumab trials (Dr Tree, Professor Harrington, Dr

Lalondrelle and Dr Ahmed), Dr James Larkin, Representative from RM-Clinical Trials Unit, Senior Statistician and be chaired by a clinician independent of study investigators. The PPSRC will meet monthly and at every dose escalation point, the meeting frequency maybe decreased during the expansion phases of all the studies if considered safe to do so. The role of the PPSRC is:

- 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.

The PPSRC terms of reference, roles and responsibilities will be defined in a charter. Further internal or external experts may be consulted as necessary.

10.9 Monitoring

During the trial RM-CTU is responsible for monitoring data quality in accordance with relevant standard operating procedures (SOPs). 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 (for example clinic visits on Sundays). 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.

10.10 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.

10.11 Clinical study report

Clinical data will be presented at the end of the trial based on final data listings. The CI/designee 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.

10.12 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 RM G-SOPs 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.

10.13 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 submitted to the RM-CTU for 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.

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12.0 APPENDICES

12.1 Appendix 1:

Patients will be treated with external beam RT using a linear accelerator with photon energy of 4-15 MV. A standard non-contrast planning CT thorax will be obtained with 2-3mm slice thickness from cricoid cartilage to below diaphragm. If supraclavicular disease is being treated the CT scan will extend up to mastoid. The gross tumour volume is determined from CT and/or PET scans. PTV incorporates the GTV with a 1.5 to 2cm margin. Field margin will be defined using standard RMH criteria.

If the field size is > 12cm X 12cm equivalent square, consider using low dose fractionation or excluding disease from the field . Any thoracic disease out of field should be documented and can be used to assess abscopal response. Alternatively if lung constraints are maintained then high dose fractionation can be used with a larger field size, Planning will be in accordance with RMH protocols for palliative planning of lung tumours, ensuring that there are no hotspots over cord > 105% for the 36Gy dose fractionation.

In general, parallel-opposed (AP-PA) fields can be used. Isodose intervention should be considered for 36Gy in 12 fractions. If it is anticipated that parallel-opposed fields will lead to severe toxicity, a conformal plan using planning CT-scan is indicated to keep the V20 (EQD2) below 35%. Mean lung dose should be maintained at an EQD2 of ≤ 18Gy. In all treatment planning, lung correction is required. Dose will be prescribed at the midpoint or at 100% as per ICRU guidelines.

3D dose-volume information for the tumour and the normal tissues will be obtained for subsequent analysis. The following normal tissues should be contoured: lung, heart, spinal cord and oesophagus.

Lung V20, Mean Lung Dose in EQD2 should be obtained for all patients. Dose volume histogram data will be obtained for heart, lungs oesophagus and spinal cord. The length of oesophagus in high dose radiotherapy field will be documented.

Verification will proceed in accordance with RMH RT department's standard policies.

12.2 Appendix 2: 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 utilised for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

12.3 Appendix 3: LENT SOMA Scales for all Anatomical Sites

This study will utilise the LENT SOMA radiation toxicity grading system (Int. J. Radiation Oncology Biol. Phys., Vol. 31, No. 5, 1049-1091, 1995). All appropriate treatment areas should have access to a copy of the LENT SOMA scoring system.

12.4 Appendix 4: Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumours

RECIST version 1.1 (50) will be used in this study for assessment of tumour response. While either MRI or PET-CT may be utilised, as per RECIST v1.1, MRI is the preferred imaging technique in this study.

12.5 Appendix 5: Identification, Evaluation and Management of irECIs.

NOTE: ECIs that are thought to be related to an overdose should be reported to the sponsor within 24 hours, as described in Section 7.5.2.

ECI	Grade	Action to be taken	Supportive Care
Pneumonitis –	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• 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	• 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)	• 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	• 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	• 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	• 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	• 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	• Discontinue pembrolizumab	• Manage as per grade 3
Endocrine – Hypophysitis or other symptomatic endocrinopathy	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 – 4	• Withhold pembrolizumab • 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.	• 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. • 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	• 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	• 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	• 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	• 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 liver toxicity ECIs** within 24 hours, as detailed in Section 7.5.2. • 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 liver toxicity ECIs** within 24 hours, as detailed in Section 7.5.2. • 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 liver toxicity ECIs** within 24 hours, as detailed in Section 7.5.2. • Discontinue pembrolizumab	• Manage as per grade 3
Neurologic	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated

	Grade 2	• 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	• Discontinue pembrolizumab • Obtain Neurology consultation • Consider biopsy for diagnosis.	• 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.
Ocular	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Evaluation by ophthalmologist recommended	• Topical steroids – 1%prednisolone acetate suspension and iridocyclitics • Permanently discontinue **IF** symptoms persist despite treatment.
	Grade 3	• 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	• Evaluation by ophthalmologist recommended • Permanently discontinue pembrolizumab	Manage as per grade 3
Renal	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• 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	• 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	• 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	• 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.
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	• Symptomatic treatment	• Topical glucocorticosteroids or urea-containing cream in combination with oral anti-pruritics. Treatment with oral steroids at PIs discretion
	Grade 3	• • 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	• 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.	• 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	• 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	• Discontinue Pembrolizumab	• Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.

12.6 Appendix 6: MRC Dyspnea Scale

Grade	Description
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. (59)*	