MESO-PRIME Study Protocol

Study Title:	**MESO-PRIME:** Pembrolizumab and Hypofractionated Stereotactic Radiotherapy in patients with Malignant Pleural Mesothelioma
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LIST OF ABBREVIATIONS

#	Fractions
AE	Adverse events
ALK	Anaplastic lymphoma kinase gene
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APC	Antigen presenting cell
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATP	Adenosine triphosphate
C	Cycle
CD	Cluster differentiation
CI	Chief Investigator
CNS	Central nervous system
CR	Complete response
CRFs	Case Report Forms
CT	Computerised tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte antigen-4
D	Day
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
DSUR	Development Safety Update Report
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor gene
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Gy	Gray
HIV	Human immunodeficiency virus
HMGB1	High-mobility group protein B1
HR	Hazard ratio
i.v.	Intravenous
IB	Investigator's Brochure
ID	Identification
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IR	Ionising radiation
irAE	Immune-related adverse events
IRD	Institutional Review Board
irECI	Immune-related events of clinical interest

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

Protocol Signatures

Chief Investigator Signatures:

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

Name: Dr Fiona McDonald

Signature:

Date:

Statistician Signature:

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

Sponsor representative: Ms Ranga Gunapala

Name:
Signature:

Date:

1 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and stereotactic radiotherapy
Trial Phase	Phase I
Clinical Indication	Advanced malignant pleural mesothelioma
Trial Type	Interventional
Type of control	Single arm study: No treatment control
Route of administration	Intravenous Pembrolizumab and External Beam Stereotactic Body Radiotherapy (SBRT)
Trial Blinding	Unblinded, open label, phase I study, with a subsequent cohort expansion phase.
Treatment Groups	**Part A – Initial safety cohort** • Patients will receive an initial dose of pembrolizumab in week 1 dosed at 200 mg. They will then receive SBRT dosed at 30 Gy in 3 fractions (#) alternate days in week 3. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks. • If dose limiting toxicities are seen the study will be terminated. **Part B – Expansion cohort.** An additional 12 patients will be recruited for this cohort. Patients will receive an initial dose of pembrolizumab at 200 mg in week 1. This will be followed in by SBRT dosed at 30 Gy in 3 fractions (#) alternate days in week 3. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks.
Number of trial patients	Up to 18 patients may be recruited to the study– 6 patients will be recruited in part A. The expansion phase will recruit a further 12 patients in part B.
Duration of trial	24 months
Participation	Until progression, intolerance or withdrawal from the trial.
Study Objectives	*Primary* 1. To assess the safety and tolerability of 30 Gy in 3 fractions over a week delivered via SBRT in MPM in combination with pembrolizumab. *Secondary* 1. To describe the safety profile of SBRT in MPM in combination with pembrolizumab. 2. To assess clinical benefit by calculating the overall responses rates (ORR) and disease control rate (DCR). 3. To assess responses rates in epithelioid versus sarcomatoid histological subtypes of MPM. 4. To assess response rates in relation to tumour PD-1/PD-L1 expression. 5. To assess progression free survival (PFS) and overall survival (OS). *Exploratory* 1. To identify biomarkers that correlate with immunological response to therapy. 2. To analyse peripheral blood samples for ctDNA.
Study Endpoints	*Primary* 1. To confirm that 30 Gy in 3 fractions over 1 week is a safe dose for phase 2 trials (RP2D) of SBRT in MPM combined with pembrolizumab.

	Secondary 1. To assess the rates of acute toxicity (defined as up to 12 weeks after the last fraction of SBRT) using CTC AE v5.0. 2. To assess the rates of late toxicity (defined as from 12 weeks after last fraction of SBRT in MPM until 28 days after the last dose of pembrolizumab) using CTC AE v5.0. 3. To calculate the ORR and DCR using mRECIST and RESIST 1.1. 4. To calculate the ORR and DCR in epithelioid versus sarcomatoid histological subtype using mRECIST and RESIST 1.1. 5. To assess the frequency of PD-1/PD-L1 expression distribution in responders and non-responders. 6. To measure the PFS and OS at 6 and 12 months. *Exploratory* 1. To characterize tumour infiltrating lymphocytes and tumour antigens in the tumour biopsies. These immunohistochemistry analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2. 2. To assess for levels of ctDNA pre- and post- SBRT.
Summary of **Main** Inclusion Criteria **¶Female of childbearing potential is defined as women following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.**	1. Patients should be ≥18 years old on the day of signing the informed consent. 2. Patients must have a histological or cytological diagnosis of MPM. 3. Patients should have non-radically treatable MPM (i.e. not being considered for extrapleural pneumonectomy or pleurectomy and decortication). 4. Patients must have measurable disease as assessed by mRECIST. 5. Patients must have had disease progression or be intolerant of standard first-line palliative chemotherapy for MPM. Patients who have declined first-line palliative chemotherapy must have been suitable for platinum-doublet combination chemotherapy. 6. Patient should have an ECOG performance status 0-1 7. Patients should be able to tolerate a course of SBRT as assessed by the investigator. 8. Patients should have pleural-based disease, away from critical structures, suitable for treatment to part of lesion with SBRT. 9. Patients must have adequate organ function including MRC dyspnoea score <3 and adequate baseline lung function tests, with an FEV_1 >0.8L or >30% of predicted and a TLCO >30% 10. Demonstrate adequate organ function as detailed in Table 2 (based on bloods within 10 days of C1D1). 11. Have provided tissue from an archival tissue sample or newly obtained tissue sample. 12. Female patient of childbearing potential¶ should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication (C1D1). 13. Female patients of childbearing potential should be willing to use highly effective methods of contraception for the course of the study through 120 days after the last dose of study medication. 14. Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. 15. Be willing to provide informed consent for the trial.

Summary of **Main** Exclusion Criteria	1. Patients who have taken any investigational medicinal product or have used an investigational device within 4 weeks of the first dose of pembrolizumab. Patients are allowed to participate in additional observational studies. 2. Patients who have received prior chemotherapy, targeted small molecule therapy or radiotherapy within 4 weeks prior to the first dose of pembrolizumab. 3. Patients with a diagnosis of immunodeficiency or be receiving systemic steroid therapy (>7.5 mg of prednisone / >1 mg of dexamethasone or their equivalent dose) or any other form of immunosuppressive therapy within 7 days prior to the first dose. 4. Patients with evidence of active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents or an autoimmune disease that is currently quiescent off any treatment, but deemed at risk of a significant flare if treated on this protocol. 5. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). 6. Patients with evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided the brain metastases are stable and there is no evidence of new or enlarging brain metastases. 7. Patients who have had previous radiotherapy to the thorax or other neighbouring region that would preclude the safe administration of SBRT for MPM. 8. Patients with evidence of interstitial lung disease, or history of pneumonitis (including non-infectious pneumonitis) that required steroids, or current pneumonitis (including non-infectious pneumonitis). 9. Patients with evidence of additional malignancy that is progressing or requires active treatment. 10. Patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound trial results, interfere with the patient's participation or is not in the best interest of the patient. 11. Patients with psychiatric or substance abuse disorders that would interfere with patients participation. 12. Patients who are pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 120 days after the last dose. 13. Patients with a history of HIV, HIV 1/2 antibodies, Hepatitis B or Hepatitis C. 14. Patients with any active infection requiring systemic treatment 15. Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment. 16. Patients with known hypersensitivity to the active substance pembrolizumab or to any of the excipients listed in the IB.
Treatment / Main Study Procedures	During the initial phase, patients will receive a dose of pembrolizumab during week 1 dosed at 200 mg, followed by SBRT in week 3 of 30 Gy in 3 fractions. Treatment with pembrolizumab will be continued dosed at 200 mg

	every 3 weeks. Subsequently, there will be an expansion cohort phase where patients will receive a dose of pembrolizumab at 200 mg in week 1, followed by SBRT delivered as in the initial cohort. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks. Patients will undergo clinical assessment on the day of each administration of pembrolizumab and during the week of SBRT. Patients will continue on maintenance until disease progression, unacceptable adverse events, discontinuation of study medication for any other reason or withdrawal from the trial. Treatment beyond disease progression may be considered if there is deemed to be clinical benefit. 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.

2 BACKGROUND & RATIONALE

2.1 Background

Malignant pleural mesothelioma (MPM) is a rare insidious disease that occurs many decades after occupational exposure to asbestos, however some patients without known asbestos exposure will develop MPM (1). In the United Kingdom, in 2012, the age-standardised incidence of 2688 per 100 000 population and the age-standardised mortality rate of 2429 per 100 000 population for MPM (2). Most commonly mesothelioma is derived from the mesothelial tissue lining the pleura, but can also arise from the pericardium, peritoneum, and tunica vaginalis (3). There are three primary histological subtypes of MPM, epithelioid, sarcomatoid, and biphasic (or mixed), with epithelioid histology being the most common (4).

2.2 Chemotherapy for patients with resectable MPM

For patients with operable disease without significant co-morbidities, surgical options include extrapleural pneumonectomy or pleurectomy and decortication. Single-institution and phase 2 trials have demonstrated the feasibility of multimodality therapy. The benefit of post/pre-operative chemotherapy is undefined (5).

Patients with unresectable disease or metastatic disease, without significant comorbidities, and good performance status, should be considered for systemic treatment. The systemic treatment of MPM in routine practice has remained unchanged since 2003, with more than a decade passing since any new treatment being approved for this disease. There is good evidence for first line palliative chemotherapy, however, less firm evidence supporting the role of palliative chemotherapy in the second-line setting.

2.2.1 First-line chemotherapy for unresectable MPM

Cytotoxic chemotherapy remains one of the few therapeutic options that improve survival in patients with unresectable MPM demonstrated in randomised controlled trials. The pivotal "Emphacis trial" demonstrated that the combination of cisplatin and pemetrexed gave a three month survival benefit over cisplatin alone, improving median survival from 9.3 to 12.1 months (P=0.02) in patients with unresectable MPM (6). A similar survival benefit was seen with the addition of raltitrexed to cisplatin, with survival increasing from 8.8 to 11.4 months, although objective radiological response rates were lower compared with cisplatin and pemetrexed (7). Whilst neither of these trials included a comparator arm of best supportive care, the British MS01 study did randomise patients to active symptom control (ASC) with or without either vinorelbine or MVP (mitomycin C, vinblastine, and cisplatin) (8). This trial accrued poorly, and after closing early, both chemotherapy arms were combined for analysis for the primary endpoint; no survival benefit was seen overall for the combined chemotherapy arms compared with ASC (HR 0.89; P=0.29). Nevertheless, when the two arms were analysed independently, there was a substantial difference between them with a non-significant trend in two month survival benefit for vinorelbine over ASC (HR 0.80, P=0.08), whilst MVP did not give a signal for benefit (HR0.99, P=0.95). Although no trial has demonstrated a benefit of platinum and an anti-

folate over supportive care, the weight of evidence suggests that an active platinum-based combination is likely to give a benefit of at least three months over best supportive care.

On the basis of these data, the combination of cisplatin and pemetrexed has become standard first-line therapy worldwide for patients who are not suitable for aggressive surgery or in whom chemotherapy is recommended as part of a multimodality regimen. Carboplatin is often substituted for cisplatin, due to shorter administration and a perception of less toxicity. Although the use of carboplatin is not supported by randomised evidence, and there has been no comparison between the two platinum agents, phase I and II studies have demonstrated similar activity of either carboplatin or cisplatin with pemetrexed, with objective radiological response rates between 20% and 30% (9, 10). Most importantly, although an expanded access program showed a slightly lower response rate for carboplatin-based therapy, one year survival and time to progression were very similar (11). Most oncologists will substitute carboplatin for cisplatin on the basis of clinical judgement, for example where patients have contraindications to cisplatin.

2.2.2 Second-line chemotherapy for unresectable MPM

After initial chemotherapy, or aggressive multimodality therapy, patients almost invariably experience disease recurrence or progression. Many patients will be fit for, and may want, second-line chemotherapy at this point. The only randomised clinical trial in this setting showing an improvement in progression free survival (PFS) was undertaken before the widespread use of pemetrexed as first-line treatment. This study compared second-line pemetrexed versus best supportive care, with a significantly higher rate of partial response, disease control, and longer PFS in the group receiving pemetrexed (12). However, there is no randomised trial testing the use of pemetrexed as re-treatment following first-line use. Nevertheless, a recent retrospective review of second-line chemotherapy found that disease control with second-line therapy was better in those patients who received pemetrexed, and those with a prolonged time to progression (≥12 months) after first-line therapy (13). Furthermore, patients re-treated with a platinum-pemetrexed combination had a lower risk of death than those treated with pemetrexed alone (HR=0.11, P<0.001), although this observation may be confounded by selection bias in this non-randomised comparison, with fitter patients potentially more likely to receive combination therapy. Together, this suggests that re-treatment with pemetrexed and platinum is a reasonable option for second-line therapy in fit patients with previous disease control after pemetrexed-based treatment.

A variety of cytotoxic agents have some activity in second-line treatment, but none have had the appropriate randomised controlled design to satisfy regulators or clinicians that any particular agent is the best choice. The lack of randomised designs also means that we do not know if survival benefits accrue from agents with modest objective radiological responses in the second-line setting. This also leads to the conundrum in the design of randomised second-line trials of novel agents: whilst patients commonly receive off-label second-line therapy, this is neither approved by regulatory authorities, nor standardised, making the choice of chemotherapy drug or placebo as a comparator arm open to debate. Single agent vinorelbine has a response rate (RR) of 16% and overall survival of 9.6 months at second-line (14). Combinations of gemcitabine and

vinorelbine (RR 10%, OS 10.9 moths, PFS 2.8 months) (15), gemcitabine and epirubicin (RR13%, OS 9.3 months, PFS 6.3 months in a high dose group) (16), irinotecan, cisplatin, and mitomycin C (RR 20%, OS 7.3 months, PFS 7.3 months) (17) and others have been reported. On balance, the tolerability and response rate to single agent vinorelbine has been favoured in practice and as a proposed control arm for a new generation of second-line trials. The second-line setting is still waiting for a new agent, which can demonstrate both responses and survival benefits in a randomised trial.

2.2.3 Immune Evasion in Cancer

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (18). Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies (19-23). 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 (24, 25). The immune system may then develop an adaptive immune response requiring competent cytotoxic T cells. This is mediated through the MHC system. Antigen presenting cells (APC) capture tumour antigens priming them to T cells in regional lymph nodes. 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 (26).

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

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

2.2.4 Targeting the PD-1/PD-L1 axis

PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 and has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) (24, 25). The structure of murine PD-1 has been resolved (27). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding

and a cytoplasmic tail which is responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade (24, 28-30). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signalling proteins (31, 32). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells (33, 34). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (34).

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours (31, 35-37). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signalling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (31).

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 of PD-L1 was identified in 20.7% of patients with MPM in one study. This study looked at 119 patients, where 77 had tissue available for analysis. Formalin-fixed paraffin embedded tissue, stained with anti-PD-L1 (clone E1L3N). Staining was considered positive if >1% of tumour cells expressed PD-L1. Of the samples scored as being positive, 14 had membranous staining, 16 had cytoplasmic staining, and 4 had staining in the TILs. PD-L1 positivity is more common in non-epithelioid histology (37.5%) compared epithelioid histology (13.2%). PD-L1 expression is also a poor prognostic factor for MPM, with PD-L1 positive patients having median OS of 4.79 months, compared with 16.3 months in PD-L1 negative patients (38). Similarly, the Mayo Clinic looked at 106 patient samples and analysed them for PD-L1 expression using immunohistochemistry on FFPE using an anti-PD-L1 antibody (clone 5H1-A3). Positivity was defined as >5% membranous and/or cytoplasmic staining. Using this method, PD-L1 expression was seen in 40% of cases. All samples with sarcomatoid histology expressed PD-L1 and one desmoplastic subtype. Again, PD-L1 expression was a poor prognostic factor for MPM, withPD-L1 positive patients having a median OS of 5 months, compared with 14.5 months in PD-L1 negative patients. PD-L1 expression was an independent risk factor for survival, independent of histological diagnosis (RR 1.71) (39).

~~H~~igh PD-L1 positive frequencies have also been seen in non-small cell lung cancer (19-100%), 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 (45). 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.

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

It is now well recognised that the host's immune system senses the effects of ionising radiation in irradiated tissues. Evidence that the integrity of the immune system determines the dose required to control experimental tumours is more than 30 years old when reduced therapeutic efficacy was noted in mice that lacked an adequate T cell response (46).

However it is only recently that the radiation oncology community has started to exploit the clinical potential of the immunogenic effect of ionising radiation (IR) (47). IR induced cell death can generate tumour cell antigens for dendritic cell presentation. IR can generate immunogenic cell death perhaps more effectively than chemotherapy. The 3 steps required in this process include: cell surface translocation of calreticulin, the extracellular release of high-mobility group protein B1 (HMGB1) a non-histone nuclear protein, and release of adenosine triphosphate (ATP). Tumour cells that receive radiation undergo phenotypic changes that enhance their susceptibility to immune effectors (48-50). Enhanced expression of death receptors (51, 52), MHC class 1 molecules (48, 53, 54), co-stimulatory molecules (55), adhesion molecules (56-58), and stress-induced ligands (59-61) on tumour cells exposed to radiation increased their recognition and killing by T cells in vitro and/or in vivo in several cancer models.

Theoretically if combined with the ideal immunotherapeutic agent, radiotherapy can engage both the innate and adaptive arms of the immune system, with the potential to convert the irradiated lesion into an in situ vaccine that elicits tumour-specific T cells. Preclinical studies have demonstrated this in several tumour types with a variety of immunotherapeutic agents including Flt3 ligand, CpG, antiCTLA4, antiCD137 with anti-PD-1 and viral therapies. The majority of studies demonstrate release of tumour antigen leading to the induction of anti-tumour T cell effect, while other studies demonstrate up regulation of MHC class I on tumour cells. One study examined mice bearing established orthotopic AT-3 mammary tumours and strikingly all mice treated with anti -CD137 and anti-PD-1 combined with single- or low-dose fractionated radiotherapy were cured. $CD8^+$ T cells were essential for curative responses to this combinatorial regime. CD137 expression on tumour-associated $CD8^+$ T cells was largely restricted to a subset that highly expressed PD-1. PD-1 signalling within the AT-3 tumours was a critical limiting factor to the therapeutic efficacy of anti-CD137 therapy, alone and in combination with radiotherapy (62).

Stereotactic Body Radiotherapy (SBRT) has rapidly evolved over the past 5-10 years due to advances in radiation technology and is a focused radiation therapy that precisely and accurately delivers high biological doses of radiation to tumour lesions while sparing the nearby normal organs. The use of SBRT results in high rates of local tumour destruction with minimal side effects. In the UK, SBRT is actively being developed with support from the NCRI CTRad radiotherapy quality assurance group to ensure a high-quality SBRT National framework with unified protocols for clinical trials. It is therefore timely to appropriately evaluate the safety of this new technology in novel drug radiation combinations. Retrospective and prospective cohort studies reporting outcomes for SBRT for the treatment of oligo-metastatic disease sites have been succinctly reviewed (63). In general these studies demonstrate high rates of local disease control with acceptable rates of toxicity, using a risk adapted approach to dose and fractionation based on the surrounding normal tissue structures. There is a wealth of data supporting the safety of a dose of 55 Gy in 5 fractions over a week for peripheral thoracic lesions in contact with the chest wall (64, 65) despite there being no routine use of SBRT in the management of MPM.

The concept of combining SBRT with immune checkpoint inhibitors has been explored with pre-clinical work from some groups suggesting that combined modality treatment with SBRT may be more efficacious than low dose radiotherapy. In a mouse orthotropic cell line glioma model, stereotactic radiosurgery (SRS) with 10 Gy was tested in combination with anti-PD-1 antibodies. Anti-PD-1 antibodies led to long term cures in a subset of mice, which was not seen with either treatment modality alone (66). 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 melanoma were irradiated up to 15 Gy, given in various fraction sizes (67). For single fractions, tumour control and number of tumour-specific T-cells were radiation dose dependent. However, at the highest dose, there was also an increase in regulatory T-cells, which tend to down regulate the immune response. Fractionated irradiation at 7.5 Gy/fraction seemed to produce the best tumour control and tumour specific T-cell response while still maintaining low regulatory T-cell numbers. A further study supports fractionating radiation treatment in conjunction with immunotherapy, by testing anti-CTLA-4 antibodies with radiation in a mouse breast cancer model. Mice were treated with 20 Gy × 1, 8 Gy × 3, or 6 Gy × 5 fractions in combination with monoclonal antibody against CTLA-4. Authors found that fractionated but not single-dose radiotherapy induces an abscopal effect when used with anti-CTLA-4 antibody (68). However, another preclinical study comparing ablative radiation doses against fractionated radiation noted that ablative radiation, such as a single dose of 20–25 Gy, dramatically increased T cell activity and tumour control. When 5 Gy × 4 fractions given over 2 weeks were compared against a single 20 Gy dose, radiation-initiated immune responses and tumour reduction appeared to be abrogated by the fractionated radiation [48]. These pre-clinical data are not specifically in MPM models however extrapolations can be made for other disease sites as the mechanism of SBRT inducing ICD is the same regardless of disease site. As is evident the relationship between radiotherapy dose, fraction size and immune interplay is a complex one and

clinical studies are urgently needed to assess how to optimally harness the effect on radiation on the immune system.

2.2.6 Pembrolizumab Clinical Trial Data

2.2.6.1 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized 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.

2.2.6.2 Clinical Trial Data

KEYNOTE-028 is a phase 1b clinical trial, evaluating pembrolizumab as a potential treatment in a variety of advanced solid tumours. The study was enriched for PD-L1 positivity, defined as membranous expression in ≥1% of tumour nests, or PD-L1 positive bands in stroma, using the anti-PD-L1 antibody 22C3 clone (Merck) on immunohistochemistry. Of the 80 patients with MPM screened for PD-L1 expression, 38 patients (45.2%) were PD-L1 positive. 25 patients were enrolled onto the study, with a median age of 65 years, predominantly male (68%), with at least one prior line of treatment (88%). The most common histology was epithelioid (64%), followed by sarcomatoid (8%) and biphasic (8%) (69).

Pembrolizumab was dosed at 10 mg/kg intravenously every 2 weeks. Of the 25 patients with MPM, the disease control rate was 76% (95%CI: 55 – 91) - 7 patients with partial response and 12 patients with stable disease, as assessed by RECIST 1.1 The median duration treatment was 22.0 weeks (range: 0.1 – 34.1+ weeks) and the median number doses of treatment was 10 (range: 1 – 22+) (69). This compares with a response rate of <10% seen with second-line treatment (70). The treatment was well tolerated in this cohort, with any grade common adverse events being fatigue (24%), nausea (24%), arthralgia (16%), pruritus (12%), and dry mouth (12%). Grade ≥3 adverse events included raised ALT in 1 patient (4%) and thrombocytopenia in another patient (4%). There were no treatment-related deaths or discontinuations due to treatment-related adverse events (69). Given these results, pembrolizumab is being studied further in MPM, unselected for PD-L1 expression, in the second-line setting in the context of a phase 2 clinical trial (NCT02399371) (71).

2.3 Rationale for the Trial

The abscopal effect refers to a rare phenomenon of tumour regression at a site distant from the primary site of radiotherapy (76). Localised radiotherapy has been shown to induce abscopal effects in several types of cancer, including melanoma, lymphoma, renal-cell carcinoma and NSCLC (77-80). 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 (81). This effect may be more pronounced in response to ablative rather than conventional dosage or fractionation schedules (82). More recently, the abscopal effect has been described in the context of patients receiving immunotherapy concurrently with radiotherapy. For example, Formenti et al described a case of abscopal response in a patient with advanced NSCLC who received palliative hepatic radiotherapy while on ipilimumab. The response was seen 2.5 months following radiotherapy (83). Experimental data from multiple cancer models have provided sufficient evidence to propose a paradigm shift, whereby some of the effects of IR are recognized as contributing to systemic antitumor immunity. Therefore, the traditional palliative role of radiotherapy in metastatic disease is evolving into that of a powerful adjuvant for immunotherapy. This combination strategy adds to the current anticancer arsenal and offers opportunities to harness the immune system to extend survival, even among metastatic and heavily pretreated cancer patients (47). Combination trials of immunotherapy and SBRT are required to explore the potential for radiation enhancing the effects of immunotherapy, both locally and abscopally, with the aim of improving outcomes for patients with MPM. The initial step is to assess the tolerability and safety of immunotherapy with SBRT in MPM. This clinical trial protocol will look at the safety and tolerability of pembrolizumab, an anti-PD-1 monoclonal antibody, given in combination with SBRT in MPM in patients with unresectable MPM. It is expected that SBRT of a 3# regime at a dose level of 30Gy will be enough to stimulate the immune system.

3 STUDY OBJECTIVES & ENDPOINTS

3.1 Study Objectives & Hypothesis

3.1.1 Primary Objective & Hypothesis

- Objective: To assess the safety and tolerability of SBRT in MPM with pembrolizumab.
- Hypothesis: SBRT in MPM can be safely administered in combination with pembrolizumab without significant dose limiting acute toxicity.

3.1.2 Secondary Objectives

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

3.1.3 Exploratory Objectives

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

3.2 Study Endpoints

3.2.1 Primary Endpoint

- To assess the dose limiting toxicity (DLT) of SBRT in MPM at a dose level of 30 Gy given in 3 fractions when combined with pembrolizumab.

3.2.2 Secondary Endpoints

- To assess acute toxicity rates (defined as up to 12 weeks after last SBRT fraction) using CTC AE v5.0.
- To assess late toxicity rates (defined as from 12 weeks after last SBRT fraction in MPM until 28 days after the last dose of pembrolizumab) using CTCAE version 5.0.
- To calculate the ORR, DCR and DOR using mRECIST and RESIST 1.1.
- To calculate the ORR and DCR in epithelioid versus sarcomatoid histological subtype using mRECIST and RESIST 1.1.
- To assess the frequency of PD-1/PD-L1 expression distribution in responders and non-responders.
- To measure the PFS and OS at 6 and 12 months.

3.2.3 Exploratory Endpoints

- To characterise tumour infiltrating lymphocytes and tumour antigens in the tumour biopsies. These immunohistochemistry analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.

- To assess for levels of ctDNA pre- and post- SBRT.

4 STUDY DESIGN

4.1 Summary of Study Design

This is a non-randomised open-label phase 1 trial of pembrolizumab given in combination with SBRT to part of a pleural-based lesion in patients with unresectable MPM. This study will recruit up to 18 patients whose MPM has progressed beyond first-line of palliative chemotherapy, with a platinum-based doublet, and now requires further palliative systemic treatment, or have declined first-line palliative chemotherapy, however must have been considered suitable for a platinum doublet chemotherapy.

4.2 Treatment Regimen

The study will be conducted in two parts; an initial safety phase (Part A), followed by an expansion cohort (Part B). The initial safety phase (Part A) is based on a 3+3 design such that patients will be treated in a cohort of 3-6 patients. A maximum of 6 patients will be allocated to Part A exploring SBRT 30 Gy in 3 fractions in combination with pembrolizumab. If there is more than one DLT in the first 3 patients or two or more DLTs in the first 6 patients, this treatment combination will be deemed as being unacceptable and it would lead to termination of the study. During the expansion cohort (Part B), 12 patients will have SBRT 30 Gy in 3 fractions with pembrolizumab to obtain additional safety and response data. Maintenance pembrolizumab will continue until disease progression, unacceptable toxicities, the patient withdraws consent to the trial, or the patient has completed 35 cycles of treatment. A maximum of 18 patients will be treated in the study.

All patients will receive pembrolizumab on cycle (C) 1 day (D) 1, in Part A and B of the study. All patients will receive SBRT on C1D15, C1D17 and C1D19, as per SBRT protocol (See Appendix 3). Patients in part A will receive SBRT 30 Gy in 3#. Patients in Part B will receive 30 Gy in 3 fractions if considered safe after part A. All patients in Part A and Part B will receive pembrolizumab dosed at 200 mg every 3 weeks, until disease progression, unacceptable toxicities, the patient withdraws consent from the trial or the patient has completed 35 cycles of treatment.

In the initial safety cohort, a minimum of 3 patients will be treated at the SBRT dose of 30Gy in 3 fractions combined with pembrolizumab. The gap left between the treatments of each subsequent patient will start after the second cycle of Pembrolizumab in the previous dosed patient to mitigate against multiple patients suffering from acute toxicity. The DLT period for this study is 12 weeks from the last dose of SBRT (i.e. at C6D1). Patients included in Part A will be considered by the Safety Review Committee (SRC) once the 3rd and 6th patient in the Part A cohort has completed the DLT period. If 0 out of 3 patients experience a DLT, or if 1 out of 3 patients experience a DLT in Part A, then the cohort will be expanded to 6 patients. If 1 in 6 patients experience a DLT, then it will be acceptable to move forward to the expansion cohort (Part B). However, if ≥ 2 in 6 patients (or more than 1 in the first 3 patients) experience a DLT then the maximum administered dose

(MAD) will have been reached. If the MAD is seen at a dose level of 30 Gy in 3# then the study will be terminated.

While waiting for 3 or 6 patients to complete the DLT period, no additional patients will be recruited. Further patients can only be recruited after the SRC has reviewed the toxicity data for the cohort to proceed to Part B. Patients obtaining complete response or having completed 35 cycles of pembrolizumab must discontinue and may recommence for additional 17 cycles upon subsequent disease, the CI/PI will need to discuss with the sponsor and MSD, on a case by case basis for the continuation of pembrolizumab.

Table 1: SBRT dose level and pembrolizumab dosing during the initial safety cohort and expansion phase.

Dose Level	Pembrolizumab Dose	SBRT to part of a MPM lesion
Initial safety cohort	200 mg i.v. over 30 minutes, every 3 weeks	30 Gy in 3# (Monday, Wednesday, Friday)
Expansion cohort	200 mg i.v. over 30 minutes, every 3 weeks	30 Gy in 3# (Monday, Wednesday, Friday)

SBRT: Stereotactic Ablative Body Radiotherapy; Gy: Gray; i.v.: intravenous; mg: milligrams; #: fraction.

4.2.1 Dose Limiting Toxicities

Acute toxicity will be assessed up to and including 3 months following the final fraction of radiotherapy (i.e. at C6D1). The MRC dyspnoea score (Appendix 2) will be used to assess dyspnoea at baseline/on treatment and the Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0 will be used to grade all drug and SBRT observed toxicities (Appendix 4). The SRC will consider expansion after the 6th patient in the initial safety cohort has completed the DLT period and reviewed the toxicities before recruitment to the expansion cohort Part B.

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

Haematologic:

- Neutropenia with fever grade 3 or neutropenia grade 4
- Thrombocytopaenia with bleeding grade 3 or thrombocytopenia grade 4

Non-Haematologic:

Any ≥ 3 non-haematological toxicity which is definitely, probably or possibly related to the combination of pembrolizumab and SBRT for pleural mesothelioma including the following:

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

Progression of the study will not proceed until the following criteria are satisfied by the SRC:

- If 0 out of 3 patients experience a DLT, or if 1 out 3 patients experience a DLT, a further 3 patients will be recruited at the dose level in the initial safety cohort.
    - If 0 out of 6 patients experience a DLT, or if 1 out of 6 patients experience a DLT, then progression to Part B of the study can proceed.
    - If ≥ 2 out of 6 patients (or more than 1 in the first 3 patients) experience a DLT, then there will be no Part B expansion phase and the study will be terminated.

4.3 Study Schema

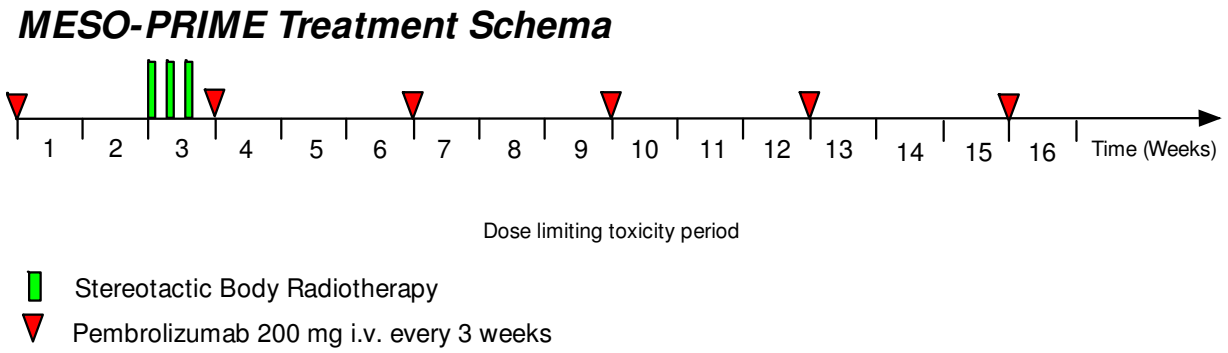


Figure 1: Schematic diagram of study events. Patients will receive pembrolizumab dosed at 200 mg i.v. every 3 weeks (as indicated by ▼). SBRT for pleural mesothelioma will be administered on cycle 1 days 15, 17 and 19 (as indicated by ■).

4.4 Follow-Up after stopping Pembrolizumab

4.4.1 30 Day Safety Follow-Up Visit

All patients will be required to attend a safety follow-up visit 30 days after the last dose of pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. Patients who restart treatment on disease progression, once completed the treatment period will also attend to a safety follow-up visit as detailed above. All adverse events (AEs) and serious adverse events (SAEs) that occur prior to the safety follow-up visit should be reported as described in section 8. 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.

4.4.2 Follow-Up for Discontinued Pembrolizumab without Disease Progression

Patients who discontinue pembrolizumab for any reason other than disease progression will move into the follow-up phase and should be assessed every 9 weeks (63 ± 7 days) and by radiologic imaging as per standard of care to monitor disease status. Every effort should be made to collect information regarding disease status

until the start of new anti-cancer therapy, disease progression, death, withdrawal or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

4.4.3 Survival Status Follow-Up Phase

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

4.5 Study Termination

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

4.5.1 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 DLT is seen in Part A in 2 out of 3 or 2 out of 6 patients.

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

4.6 Treatment after End of Study

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

5 SELECTION OF PATIENTS

5.1 Screening and Enrolment

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

5.2 Registration

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

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

Telephone: 020 8642 6503

Fax: 020 8915 6762

Email: MesoPrime.Trial@rmh.nhs.uk

Between Monday to Friday, 9 am to 4 pm.

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

5.3 Patient Replacement Strategy

Additional patients may be enrolled in a given cohort to ensure that the required number of evaluable patients in each cohort is achieved. A patient that discontinues the trial for progressive disease within 3 months of the last dose of radiotherapy will not be evaluable for DLTs and therefore will need to be replaced. A patient that discontinues the trial for a drug-related AE will not be replaced and will be counted in the evaluable population of patients for the respective cohort. However, patients found to have active pneumonitis on C1D1 of pembrolizumab or day 1 of radiotherapy will be removed from the trial and can be replaced. Also patients who

do not reach follow-up 3 months post completion of SBRT for MPM 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.

5.4 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.

5.4.1 Inclusion criteria

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

1. Patients should be ≥18 years old on the day of signing the informed consent.
2. Patients must have a histological or cytological diagnosis of MPM.
3. Patients should have non-radically treatable MPM (i.e. not being considered for extrapleural pneumonectomy or pleurectomy and decortication).
4. Patients must have measurable disease as assessed by mRECIST (i.e. at least a 1 cm rind of MPM at 2 sites on 3 different levels).
5. Patients must have had disease progression or be intolerant of standard first-line palliative chemotherapy for MPM. Patients who have declined first-line palliative chemotherapy must have been suitable for platinum-doublet combination chemotherapy.
6. Patient should have an ECOG performance status 0-1.
7. Patients should be able to tolerate a course of stereotactic radiotherapy as assessed by the investigator.
8. Patients should have pleural based disease, away from critical structures, and suitable for treatment to part of lesion with SBRT for pleural mesothelioma.
9. Patients must have adequate organ function including MRC dyspnoea score <3 and adequate baseline lung function tests, with an FEV_1 > 0.8L or >30% of predicted and a TLCO > 30%.
10. Demonstrate adequate organ function as detailed in Table 2 (based on bloods within 10 days of C1D1).
11. Have provided tissue from an archival tissue sample or newly obtained tissue sample.
12.
13. Female patient of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication (C1D1). Female patients of childbearing potential should be willing to use highly effective methods of contraception for the course of the study through 120 days after the last dose of study medication. Female of childbearing potential is defined as women following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation

methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

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

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
Haematological	
• Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
• Platelets	100 x 10^9/L
• Haemoglobin	≥90 g/L or ≥5.6 mmol/L
Renal	
• Serum creatinine **OR** • Measured or calculated[a] creatinine clearance	≤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

5.4.2 Exclusion Criteria

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

1. Patients who have taken any investigational medicinal product or have used an investigational device within 4 weeks of the first dose of pembrolizumab. Patients are allowed to participate in additional observational studies.
2. Patients who have received prior chemotherapy, targeted small molecule therapy or radiotherapy within 4 weeks prior to the first dose of pembrolizumab.

3. Patients with a diagnosis of immunodeficiency or be receiving systemic steroid therapy (>7.5 mg of prednisone / >1 mg of dexamethasone or their equivalent dose) or any other form of immunosuppressive therapy within 7 days prior to the first dose.
4. Patients with evidence of active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents or an autoimmune disease that is currently quiescent off any treatment, but deemed at risk of a significant flare if treated on this protocol.
5. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
6. Patients with evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided the brain metastases are stable and there is no evidence of new or enlarging brain metastases.
7. Patients who have had previous radiotherapy to the thorax or other neighbouring region that would preclude the safe administration of SBRT for MPM.
8. Patients with evidence of interstitial lung disease or active, non-infectious pneumonitis.
9. Patients with evidence of additional malignancy that is progressing or requires active treatment.
10. Patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound trial results, interfere with the patient's participation or is not in the best interest of the patient.
11. Patients with psychiatric or substance abuse disorders that would interfere with patients participation.
12. Patients who are pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 120 days after the last dose.
13. Patients with a history of HIV, HIV 1/2 antibodies, Hepatitis B or Hepatitis C.
14. Patients with any active infection requiring systemic treatment
15. Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment.
16. Patients with known hypersensitivity to the active substance pembrolizumab or to any of the excipients listed in the IB.

6 STUDY PLAN AND PROCEDURES

6.1 Study Schedule

From study entry, patients will be assessed every 21 days, prior to the administration of each dose of pembrolizumab. During week 3 of SBRT for MPM, patients will have an additional clinical review. Patients will continue to be assessed and stay on pembrolizumab until they have disease progression, suffer unacceptable toxicities, withdraw, the study ends or have completed 35 cycles of pembrolizumab. Treatment beyond progression or 35 cycles needs to be discussed with the study sponsor and MSD. Patients will be required to attend a safety visit 30 days after their last dose of pembrolizumab.

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

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

Table 3: Study Schedule of Assessments

Trial Phase:	**Screening period**	**Initial phase**					**Maintenance phase** DLT period (Pembrolizumab 200 mg q3wkly)			**Maintenance phase** [10] Beyond DLT period (Pembrolizumab 200 mg q3wkly)				**End of Treatment** *(If applicable)*	**Post-Treatment**		
		C1, D1	**Radiotherapy phase** (30 Gy 3#)			C2, D1									**Safety Follow-up (SFU)**	**Follow Up**	**Survival Follow Up**
Treatment Cycle/Title:			C1, D15	C1, D17	C1, D19		C3, D1	C4, D1	C5, D1	C6, D1	C7, D1	C8, D1	C X[10], D1	*Discontinuation of Pembrolizumab*	*30 days after last dose*	*Every 9 weeks from SFU*	*Every 12 weeks from SFU*
Scheduling (Day):	*-28 to -1*					*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±7*	*±7*	*±7*	*±7*
Informed Consent	X																
Inclusion/Exclusion	X																
Clinical history	X																
Full Physical Exam	X	X												X	X		
Directed Phys. Exam			X	X	X	X	X	X	X	X	X	X	X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MRC dyspnoea score	X		X	X	X	X	X	X	X					X			
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs[9] & Weight	X	X		X		X	X	X	X	X	X	X	X	X	X		
Height	X																
Haem & Biochem	X[6]	X[7]				X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X	X		
fT3, fT4 and TSH	X[6]	X					X		X		X		X	X	X		
PT and aPTT	X[6]																
Pregnancy Test	X[8]					X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]		
Urinalysis	X[6]																
Pembrolizumab		X				X	X	X	X	X	X	X	X				
Radiotherapy			X[5]	X[5]	X[5]												
Pulmonary function[3]	X																
Imaging	CT[1] & CXR[2]				CXR	HRCT	CXR	CT	CXR		CT		X[1]	CT		CT	
PD-L1 assessment[4]	X																
OPTIONAL Research Blood[7]		X				X			X					X			
Survival Status																	X

1. Imaging with a CT scan should occur during the screening period as a baseline and then every 9 weeks (3 cycles) for the first 6 months, then every 12 weeks after 6 months (regardless of treatment delays). Imaging with CT scanning can occur 7 days before the visit to ensure that the results are available at the visit.
2. Chest x-ray will be performed during the dose limiting toxicity period in order to monitor for pneumonitis. A High-Resolution CT chest should be performed prior to commencing C2D1.
3. Full pulmonary function tests should be performed at baseline.
4. PD-L1 testing will be batched and performed once all patients are on study.
5. SBRT for MPM will be administered on C1D15, C1D17 and C1D19.
6. Screening laboratory investigations will be performed within 10 days prior to C1D1.
7. Safety laboratory investigations will be performed no more than 72 hours prior to D1 dosing with Pembrolizumab.
8. Serum pregnancy test should be performed at baseline for females of childbearing potential within 72 hours of D1C1 Pembrolizumab. Additional urine pregnancy test would be performed at each cycle of Pembrolizumab during the treatment period and at the Safety Follow-up visit.
9. Vital signs include temperature, pulse, respiratory rate, oxygen saturation and blood pressure.
10. Maintenance pembrolizumab will continue until disease progression, withdrawal of consent, or unacceptable toxicity. The assessments at CXD1 will be repeated on D1 of each additional cycle until the end of patient maintenance phase participation and also if the patient restarts treatment on disease progression. Patients obtaining complete response or having completed 35 cycles of pembrolizumab must discontinue and may

recommence for additional 17 cycles upon subsequent disease progression. In patients who restart treatment on disease progression, once the treatment period is completed, they will also attend the Safety Follow-up Visit as detailed in the protocol.

6.2 Administrative Procedures/Assessments

6.2.1 Informed Consent

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

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

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

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

6.2.2 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.

6.2.3 Demographic Data, Medical History and Treatment History

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

6.2.4 Subsequent Anti-Cancer Therapy Status

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

6.2.5 Survival Status

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

6.2.6 Prior and Concomitant Medications Review

6.2.6.1 Prior Medications

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

6.2.6.2 Concomitant Medications

In addition the investigator or qualified designee will record all medication, if any, taken by the patient during the trial. All medications related to reportable SAEs and overdose and liver toxicity events of clinical interest (ECIs) should be recorded as defined in Section 8.

6.3 Clinical Procedures/Assessments

6.3.1 PD-L1 Assessment

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

6.3.2 Adverse Event (AE) Monitoring

The Investigator or qualified designee will assess each patient for potential new or worsening AEs as specified in the schedule of study assessments (Table 3) and more frequently if clinically indicated. AEs will be graded and recorded from confirmation of entry into the trial until the patients 30 day safety follow up visit according to CTCAE v5.0 (see Appendix 4). Toxicities will be characterised in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown aetiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) or a potentially an immune related adverse event (irAE). See Appendix 5 regarding the identification, evaluation and management of AEs of a potential immunological aetiology. Please refer to section 8 for detailed information regarding the assessment and recording of AEs.

6.3.3 MRC dyspnoea Score

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

6.3.4 Full Physical Exam

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

6.3.5 Directed Physical Exam

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

6.3.6 Vital Signs

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

6.3.7 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

6.3.8 Pulmonary Function Tests

Full lung function tests assessments will be performed at screening, prior to the dosing of pembrolizumab as specified in the study schedule of assessments (Table 3).

6.3.9 Pregnancy Tests

Female patients of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication as specified in the study schedule of assessments (Table 3).Additional urinary pregnancy test would be performed in these patients at the start of each cycle of Pembrolizumab during the treatment period and at the Safety Follow-up visit.

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

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

Table 4: Required Laboratory Assessments

Haematology	Chemistry	Urinalysis	Other
Haematocrit	Albumin	Blood	PT
Haemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	Free triiodothyronine (fT3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (fT4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If results are abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Uric Acid	Urine pregnancy test †	
Absolute Lymphocyte Count	Calcium Corrected		
	Chloride		
	Glucose		
	Phosphate		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	Creatinine Clearance		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

6.3.11 Tumour Imaging and Assessment of Disease

6.3.11.1 Baseline tumour imaging

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

6.3.11.2 Timing of Disease Assessment

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

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

6.3.11.3 Confirmation of Disease Response

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

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

Therefore, modified RECIST will be used with the following adaptations:

- If radiologic imaging shows initial progressive disease (PD), tumour assessment should be repeated 4-6 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression.
    - Patients may continue treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:
        - Absence of signs and symptoms indicating disease progression
        - No decline in ECOG performance status
        - Absence of rapid progression of disease
        - Absence of progressive tumour at critical anatomical sites requiring urgent alternative medical intervention. When feasible, patients should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumour flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

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

6.3.11.4 Confirmation of Disease Progression

Disease progression should be confirmed no sooner than 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

6.3.12 Tumour Tissue Collection and Correlative Studies Blood Sampling

6.3.12.1 Archival Tumour tissue samples

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

6.3.13 Tumour Biopsies and Research Blood Samples

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

- **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: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.
- **ctDNA & CTCs**
  Research blood samples will be analysed for ctDNA and CTCs. Analysis of CTCs will include, but not necessarily limited to the following, the diagnostic performance of PD-L1 testing will be assessed in CTC compared with IHC, correlation with response and disease progression.

6.3.14 Chain of Custody of Biological Samples

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

6.4 Total Blood Volume

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

Table 5: Volume of blood

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

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

7 TREATMENTS

7.1 SBRT for pleural mesothelioma

7.1.1 Planning and Delivery

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

7.1.2 Toxicity Assessments

Dyspnoea score and toxicity grading with CTCAE v5.0 will be recorded and will include pneumonitis, lung fibrosis, oesophagitis, skin toxicity, myelitis and fatigue. All other AEs will be documented in addition.

7.2 Pembrolizumab

7.2.1 Investigational Product

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

Table 6: Product Description

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

7.2.2 Product Preparation

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

7.2.3 Storage and Handling

7.2.3.1 Storage

Please refer to the RM Pharmacy Manual for stability information on drug stability and storage.

7.2.3.2 Handling

Please refer to the RM Pharmacy Manual for IMP handling instructions. Specific details on the preparation of the drug product can be found in the RM pharmacy manual. At each site the Principle Investigator/designee e.g. pharmacist at each participating site is responsible for ensuring that all trial Medication must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorised person at the trial site. Trial medication may not be used for any purpose other than that stated in the protocol.

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.

7.2.4 Packaging and Labelling Information

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

7.2.5 Returns and Reconciliation

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

7.2.6 Doses and Treatment Regimens

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

Table 7: Pembrolizumab and SBRT for MPM schedules

Dose level	Lung SBRT	Drug	Dose	Dose Frequency	Route of Administration
Part A	30 Gy in 3#	Pembrolizumab	200 mg	3 weekly	IV infusion
Part B	30 Gy in 3#	Pembrolizumab	200 mg	3 weekly	IV infusion

7.2.7 Timing of Dose Administration

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

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

All trial treatments will be administered on an outpatient basis. Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals or infusion length may be increased due to toxicity as described in Section 6.2.9.2). 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). The RM Pharmacy Manual contains specific instructions for pembrolizumab, reconstitution, preparation of the infusion fluid, and administration. In addition, infusion length may be increased due to toxicity as described in Section 6and Table 9.

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

7.2.8 Blinding/Masking

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

7.2.9 Dose Selection/Modification

7.2.9.1 Dose Selection

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

7.2.9.2 Dose Modification

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With Investigator and Sponsor agreement, patients with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of AEs, see Section 6 and Table 8.
Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

Events of Clinical interest (ECI) can be potential irAEs and dose modifications for these toxicities should they occur can be found in Appendix 5.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

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

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhoea/Colitis	2-3	Toxicity resolves to Grade 0-1/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
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 - 4	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.
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.

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
	4	Permanently discontinue	Permanently discontinue
Confirmed Stevens-Johnson Syndrome or Toxic-epidermal Necrolysis	-	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.

7.3 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.

7.3.1 Prohibited Concomitant Medications

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

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

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment, while participating in the trial and within the first 3 months after the last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines

and are allowed; however intra-nasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Chief Investigator or delegate.
- Radiotherapy not specified in this protocol:
    - Note: Subsequent radiotherapy whilst on maintenance treatment to the thorax will not be permitted. Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the chief investigator, as long as it does not involve re-irradiation to any part of the lung.

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

7.3.2 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescriptions, over-the-counter (OTC), herbal supplements, and i.v. 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 8.

7.4 Rescue Medications & Supportive Care

7.4.1 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:

7.4.1.1 Diarrhoea

Patients should be carefully monitored for signs and symptoms of:

- Enterocolitis (diarrhoea, abdominal pain, blood or mucus in stool, with or without fever)

- Bowel perforation (peritoneal signs and ileus).

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

- In patients with severe enterocolitis (Grade 4):
    - 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. If symptoms are not improving within 48 hours, consider infliximab. 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 2-3):
    - Pembrolizumab should be ***withheld*** and anti-diarrhoeal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). If symptoms are not improving within 48 hours of starting steroids for grade 3 enterocolitis, consider infliximab. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Guidelines for continuing treatment with pembrolizumab can be found in Appendix 5.

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

7.4.1.2 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.

7.4.1.3 Infection

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

7.4.1.4 Immune-related adverse events

Please see Section 6.5 and Table 10 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic aetiology.

7.4.1.5 Management of infusion reactions

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

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

Immune-related Adverse Events (irAEs) may be defined as an AE of unknown 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 cancer, infectious, metabolic, toxin or other etiologic causes prior to labelling an AE as an irAE. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the Chief Investigator or delegate.

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

Table 9: Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Paracetamol Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be pre-medicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Paracetamol 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Paracetamol Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) at http://ctep.cancer.gov		

Table 10: General Approach to Handling irAEs

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

Details for managing specific irAEs are summarised below:

Immune-mediated pneumonitis

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

Immune-mediated colitis

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

Immune-mediated hepatitis

Monitor subjects for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and exclude other causes of hepatitis. Administer corticosteroids (initial dose of 0.5 – 1.0 mg/kg/day for grade 2 events, and 1 – 2 mg/kg/day for grade 3 or greater events, of prednisone or equivalent, followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.

Immune-mediated nephritis

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

Immune-mediated endocrinopathies

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

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

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

Other immune-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 12 in section 8.5.2. Patients with symptomatic irECIs should immediately stop receiving pembrolizumab and be evaluated to rule out non-treatment related causes of the event. Overdose and liver toxicity irECIs irrespective of relationship to the study drug should be reported within 24 hours of the investigator being aware to the Sponsor (via RM-CTU) who will in turn notify MSD. If the irECI is determined to be associated please refer to Appendix 5 for the recommendations on the management of these irECIs. If the event is not considered to be associated with the study drug the physician should exercise individual clinical judgment on the event management based on the patient. Any additional questions of the collection or information on management of irECIs should be directed to the Sponsor (via RM-CTU).

7.6 Supportive Care Guidelines for Pneumonitis

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

Table 11: Recommended Approach to Handling Pneumonitis

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

		for opportunistic infections. The use of infliximab may be indicated as appropriate.

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

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

7.7 Diet/Activity/Other Considerations

7.7.1 Diet

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

7.7.2 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 highly effective methods of contraception or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilised, or 2) postmenopausal (a woman who has not had menses for 12 months without an alternative medical cause will be considered postmenopausal), or 3) not heterosexually active for the duration of the study and 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. Patients should start using birth control from screening throughout the study period up to 120 days after the last dose of study therapy. Male patients with partners of child bearing potential will also be required to agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
The following contraception methods are considered adequate:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable and implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner- highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.

- Sexual abstinence- is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

Patients should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

7.7.3 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 (via RM-CTU). 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 8.

7.7.4 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.

7.7.5 Treatment of Overdose of IMP

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. Please see section 8 for definitions and reporting procedures.

7.8 Permanent Discontinuation of Trial Medication and Withdrawal from the Study

7.8.1 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 5.3.11.4.

Note: For unconfirmed radiographic disease progression. A patient may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- The patient has a confirmed positive serum pregnancy test
- Non-compliance with trial treatment or procedure requirements
- Administrative reasons
- Completion of 35 cycles of pembrolizumab

Trial patients will not be enrolled more than once. The primary reason for discontinuation should be recorded on the CRF. Once the trial medication has been discontinued the patient should complete the end of treatment (if applicable) and safety follow-up visit procedures as listed in the schedule of study assessment (Table 3). After the end of treatment, patients will continue to be assessed for AE and SAE monitoring until completion of the safety follow up visit.

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

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

7.9 Withdrawal from the Study

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

- Patient decision
- Lost to follow-up
- Death
- Principle Investigator decision

Patients may withdraw consent at any time for any reason or have trial treatment stopped at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the Investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. When a patient discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation, these are listed in the schedule of study assessments (Table 3). Any AEs which are present at that time should be followed in accordance with the safety requirements outlined in Section 8.

Patients who a) attain a complete response or b) complete 35 cycles of treatment with pembrolizumab must discontinue and may recommence for additional 17 cycles upon subsequent disease progression. Retreatment should be discussed with the Chief Investigator, the Sponsor and MSD. Pembrolizumab retreatment will be allowed only if it is in the best interest of the patients and if any other proven effective therapeutic options are no available as per standard of care and based on the investigator criteria. Study related assessment and procedures should be as for the beyond Pembrolizumab Maintenance phase (see Table 3). Patients do not need to re-sign the consent form for restarting treatment, provided their consent is on the most up-to-date version of the Patient Information Sheet Consent Form. After discontinuing treatment following assessment of complete response, these patients should return to the site for a 30 days safety follow-up visit and then proceed to the follow-up period of the study.

8 PHARMACOVIGILANCE

8.1 Adverse events

8.1.1 Adverse Event Definition

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

8.1.2 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.

8.1.3 Disease Progression

Disease progression of the cancer under study is not considered an AE unless the investigator considers it to be IMP-related or it results in hospitalisation or prolongs existing in-patient hospitalisation or death.

8.1.4 New Cancers

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

8.1.5 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.

8.1.6 Pregnancy and Lactation

Pregnancy and lactation are not considered AEs, however these events should be reported to the RM-CTU following guidance in section 8.7

8.2 Assessing and Recording Adverse Events

All AEs will be recorded from the time of the first dose until the safety follow-up in the CRF. They will be followed up according to local practice until the event has stabilised or resolved, or the follow-up visit has taken place, whichever is the sooner. SAEs will also be recorded throughout the study. The reporting timeframe for AEs meeting any serious criteria is described in section 8.4.

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

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

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

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

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

8.3 Evaluating Adverse Events

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

8.3.1 Determining AE Severity and Grade

AE severity and grade will be evaluated according to the Common Terminology for Adverse Events (CTCAE), version 5.0. Any AE which changes CTCAE grade over the course of a given episode should be closed at the date the severity changed and a new AE recorded on the AE case report forms from that date at the new severity.

8.3.2 Determining AE Causality

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

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

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

8.4 Serious adverse events (SAEs)

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

- Results in death;
- Is life-threatening or places the patient, in the view of the investigator, at immediate risk of death from the event as it occurred[1];
- Requires in-patient hospitalisation or prolongs existing in-patient hospitalisation[2]

- Results in persistent or significant incapacity or disability;
- Is a new cancer
- Is a congenital anomaly or birth defect;
- Is associated with an overdose (whether accidental or intentional). Any AE associated with an overdose is considered a SAE.
- Is any other medically important event.[3]

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

8.4.1 Reporting SAEs

All SAEs regardless of causality, pregnancy or overdose that occur from the time of consent through 90 days following cessation of study treatment or 30 day following cessation of study treatment if the participant initiates a new anticancer therapy, whichever is earlier, must be reported on the SAE report form within 24 hours of the investigator / designee becoming aware of the event.

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

The SAE form must be completed, assessed for causality and expectedness against the current version of the Investigator Brochure, then signed and dated by the Principal Investigator or an appropriately qualified designated individual identified on the delegation log. The report will then be reviewed by the Chief Investigator (or a nominated representative) to confirm relatedness and expectedness. The CTCAE version 5.0 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Sponsor (via RM-CTU) on a new SAE report form. The Sponsor (via RM-CTU) will in turn submit the updated report to MSD. Please refer to the SAE completion guidelines for further information.

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

8.4.2 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 is not considered a SAE unless the patient requires in-patient hospitalisation or prolonged existing in-patient hospitalisation or death but will be reported in the CRFs

8.4.3 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 Investigator's Brochure (IB) (Reference Safety Information contained within the IB). 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. 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 expected side effects from thoracic SBRT include: Shortness of breath, cough, chest pain (including rib fracture), skin reactions where the beams entry the body, tiredness, pain on swallowing, scarring and local inflammatory changes around treatment site and longer term reduction in breathing capacity.

8.5 Events of Clinical Interest

8.5.1 Definitions of Evidence of Clinical Interest (ECI)

Selected non-serious and SAEs can also be classified as Events of Clinical Interest (ECI) and overdose and liver toxicity ECIs and must be reported as described in section 8.5.2.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 0 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 less 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 12 can be classified as immune-related events of clinical interest. A detailed narrative of overdose and liver toxicity ECIs should be reported as described in section 8.5.2

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.

8.5.2 Reporting of ECIs

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

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

When reporting an ECI or an overdose using the SAE report form, it should be clarified whether or not the ECI or overdose is also considered an SAE.

Table 12: Immune related AEs considered ECIs

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

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

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

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

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

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

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

When reporting an ECI or an overdose using the SAE report form, it should be clarified whether or not the ECI or overdose is also considered an SAE.

8.7 Reporting of Pregnancy and Lactation

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

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

8.8 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.

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

A SUSAR is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. reference safety information appendices of investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

8.10 Reporting of SUSARs

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

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

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

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

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

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

8.11 Annual Reporting of Serious Adverse Events

The Development Safety Update Report (DSUR) will be submitted annually within 60 days of 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. The DSUR will be prepared by the sponsor in collaboration with RM-CTU. It will be submitted by the Sponsor and copies will be forwarded to RM-CTU, MSD and Investigators.

8.12 Urgent Safety Measures

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

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

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

The notification must include:

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

RM-CTU will notify the MHRA, REC and the Sponsor immediately by telephone and within 3 days in writing of USM initiation. RM-CTU will distribute the response and any subsequent amendments to the trial site.

Chief Investigators Contact Details:		
Name:	Dr Fiona McDonald	Dr Stephen Harrow
Address:	The Royal Marsden NHS Foundation Trust Downs Rd Sutton SM2 5PT	Beatson West of Scotland Cancer Centre 1053 Great Western Road Glasgow G12 0YN
Email:	fiona.mcdonald@rmh.nhs.uk	stephen.harrow@ggc.scot.nhs.uk

9 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Statistical Analyses

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

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

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

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

9.1.1 Primary Endpoint

For the primary endpoint of establishing that SBRT 30 Gy in 3# in MPM can be safely combined with pembrolizumab, the toxicity rate will be stated as the proportion of patients who have had a DLT calculated along with an exact binomial confidence interval. All toxicities will be tabulated by type, grade and dose level. This will be assessed for Part A.

9.1.2 Secondary Endpoints

Acute and late toxicity data will be tabulated by type, grade and dose level with the number, proportions and frequencies of grades 1-4 and grade 3-4 grades reported. The duration of clinical benefit assessed by overall response rate (ORR) defined as complete response (CR) or partial response (PR) and disease control rate (DCR) defined as CR, PR or stable disease (SD) using modified RECIST (Appendix 6) and RECIST 1.1 will be calculated as a proportion of total treated with a 95% confidence interval. Response rates (ORR and DCR), will be calculated as proportions for all patients and in the epithelioid and sarcomatoid histological sub-type giving associated 95% confidence intervals. Any difference in response rates (for ORR and for DCR) between the two sub-types will be compared using a chi squared or Fisher's exact test as appropriate. These will be evaluated for Part A and Part B and for overall. PD-L1 staining is referred to as tumour proportion score, reported as a percentage from 0–100%. It is classed as weakly positive (1 – 49%); strongly positive if >50%; and negative if <1%. The effect of PD-L1 expression on response rates will be measured using the proportion

of patients recorded to be weakly positive, strongly positive or negative and tested using a Chi Squared or Fisher's exact test for proportions on expression level between responders and non-responders. PFS will be measured from the start of radiotherapy until radiological or clinical evidence of progression or death and will be censored at date of last follow-up for surviving patients. OS will be measured from the start of radiotherapy until death and will be censored at date of last follow-up for surviving patients. Duration of response (DOR) will be measured from the date of first response until radiological or clinical evidence of progression or death and will be censored at date of last follow-up for surviving patients. Median PFS, OS and DOR will be calculated using Kaplan-Meier methods giving associated 95% confidence intervals, respectively. PFS, OS and DOR rates at 6 and 12 months will be presented with associated 95% confidence intervals. PFS, OS and DOR will be assessed for overall i.e. Part A and Part B combined. Unless otherwise stated, all secondary endpoints will be analysed for Part A, Part B and overall.

9.1.3 Exploratory Endpoints

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

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

Exploratory endpoints will be analysed for Part A, Part B and overall.

9.1.4 Timing of analyses

Toxicity data will be reviewed by the Safety Review Committee after every three patients in the initial cohort (i.e. the 3rd and then 6th patient) has completed the DLT period prior to any decision regarding expansion phase.

Part A can be analysed once the last patient in initial safety cohort has completed the DLT period which is 12 weeks from the last dose of lung SBRT (i.e. at C6D1). For parts A and B, end of treatment is until disease progression, or unacceptable toxicities, or the patient withdraws consent to the trial or when patient has completed 35 cycles of treatment. End of study is when the last patient has completed the off-study or the final follow-up visit, whichever happens last.

9.2 Sample Size

During the Part A, a standard 3+3 design will be used to recruit patients into one SBRT dose cohort of 30 Gy in 3# with pembrolizumab at a fixed dose level. This means that there will be a minimum of 3 and maximum of 6 patients required for Part A. There will then be an additional 12 patients in Part B, for the expansion phase.

10 REGULATORY, ETHICAL AND LEGAL ISSUES

10.1 Good Clinical Practice

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

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

Before starting the trial, the protocol, patient information sheet, consent form, any other written information that will be provided to the patients and any advertisements that will be used and details of any patient compensation must be approved by the RM 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.

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.

10.3 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 within 60 days of the anniversary of the studies MHRA/REC approval. This will facilitate the authorities continuing review of the study. These authorities will also be informed of the end of the study by the Sponsor (via RM-CTU) within 90 days of the trial completion. Copies of these reports will also be held within the main trial master file.

10.4 Regulatory Authority Approval

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

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

The Sponsor (via GCP Compliance Team) will notify the MHRA and REC in writing of any serious breaches of:

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

b. The protocol.

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

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

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

b. The scientific integrity of the trial.

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

10.6 Insurance and Liability

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

10.7 Contact with General Practitioner (GP)

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

10.8 Confidentiality

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

In compliance with GCP guidelines, it is required that the investigator and institution permit authorised representatives of the Sponsor (Sponsor's Monitor) and of the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named

representatives to have access to his/her study-related records without violating the confidentiality of the patient.

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

10.9 Data Collection and Documentation

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

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor (Sponsor's Monitor) appointed to audit the trial, or by REC. Details will remain confidential and patients' names will not be recorded outside the hospital.
The Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure:

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

No study document will be destroyed without prior written agreement between the Sponsor 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.

10.10 End of Trial

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

11 DATA AND STUDY MANAGEMENT

11.1 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.

11.2 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.

11.3 Data Collection

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

11.4 Recording of Data

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

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

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

number 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.

11.5 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.

11.6 Study Management Structure

11.6.1 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:

11.6.1.1 RM-CTU

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

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

11.6.1.2 MSD

- Provision of pembrolizumab and study support costs

11.6.1.3 Participating Sites

- Putting and keeping in place arrangements to adhere to the principles of GCP

- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving of documentation once the trial has ended
- Taking appropriate urgent safety measures
- Centres wishing to recruit to this study will be asked to provide evidence that they can deliver protocol treatment.
- Responsibilities are defined in an agreement between an individual participating centre and RM-CTU, which must be signed and in place before recruitment can commence.

11.7 Protocol Compliance and Amendments

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

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

11.8 Trial Management

The RM-CTU will be responsible for the day-to-day coordination and management of the trial. This includes all duties relating to safety reporting. If applicable a trial agreement will be signed between the site and the Sponsor. 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).

11.9 Safety Review Committee (SRC)

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

The role of the SRC is to:

- Review relevant safety data and make cohort expansion 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.

11.10 Monitoring

During the trial, the Sponsor's Monitor 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. Again, these will raise queries via the trial coordinators.

If an on-site monitoring visit is required, the Sponsor's Monitor will contact the site to agree convenient date. The site must ensure that relevant site file and patient notes are available for review. The Sponsor's Monitor conducting onsite monitoring will review the investigator site file and carry out source data verification to confirm compliance with the protocol, trial agreement.

11.11 Quality Control and Quality Assurance

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

11.12 Clinical Study Report

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

11.13 Record Retention

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

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

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

11.14 Reporting and Publication

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that authorship credit should be based 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

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

12 APPENDICES

12.1 Appendix 1 – ECOG Performance status

0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
As published: Oken et al Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655. (84)	

12.2 Appendix 2 – MRC Dyspnoea scale

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

As published: *Bleehen et al. A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in SCLC: Survival and prognostic factors. Medical Research Council Lung Cancer Working Party Br J Cancer 1993; 68(6): 11506. (85)*

12.3 Appendix 3 – Radiotherapy Planning and Delivery Guidelines

Positioning and Immobilisation

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

Localisation Imaging

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

Target Delineation

- GTV = Radiologically visible peripheral pleural lesion or part of a lesion up to 3 cm and no greater than 5 cm in diameter, not in a 'central' location (See Figure A below). Ideally this should be in as thick an area of MPM as possible. GTV will be a minimum of 2 cm in one direction (SUP/INF, ANT/POST, LAT) and no less than 1 cm in any direction.
- CTV = GTV. No additional margin is added for microscopic disease.
- ITV = Encompasses either the CTV at maximum inhale and maximum exhale generated by fusing the individual GTV from 4DCT dataset.
- PTV = ITV + 5 mm.

Organ at Risk Delineation

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

Dose Fractionation Schedules

- 30 Gy in 3 fractions over 5 days

Physics Planning

- Type B or Monte Carlo algorithm is mandatory.
- Dose grid resolution on the final dose calculation must be ≤2 mm.
- The aim is to ensure the at least a portion of the dose fall off region from the prescription isodose occurs within disease with the aim of taking advantage of concentric isodose regions of differing dose per fraction to optimise the likelihood of immune priming with the RT. The choice of the area to irradiate will be at the discretion of the treating radiation oncologist taking into consideration the UK SABR Consortium Organs at Risk (OAR) constraints.

Table A: Contouring of normal tissue structures.

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

Target Coverage, Maximum Dose, Conformity Parameters and OAR Dose Constraints

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

Image Guidance for Treatment Verification and Delivery

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

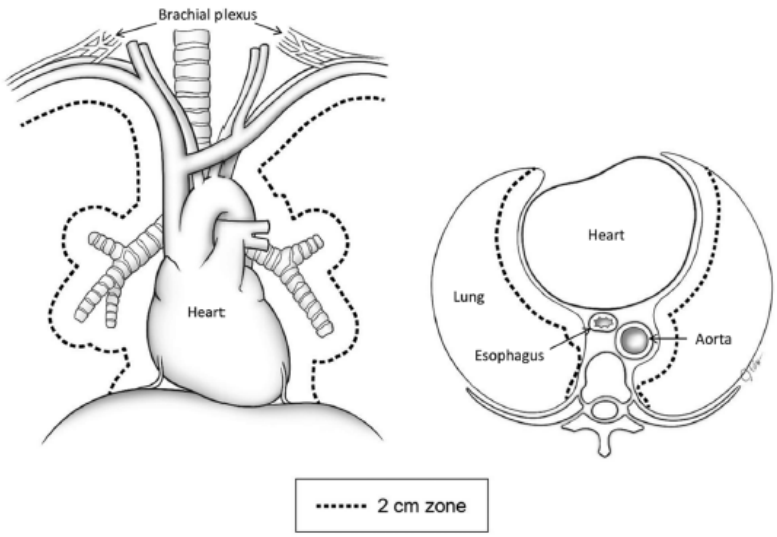


Figure A: Recommended definition of a **central thoracic lesion**: a lesion within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve.

Table B: Prescription dose spillage (PDS) requirements for both lung and non-lung lesions

PTV (cc)	Body $V_{100\%}$/PTV $V_{100\%}$		
	Target	Tolerance	Minor Deviation
<20	1.20	<1.25	1.25-1.40
20-40	1.10	<1.20	1.20-1.30
>40	1.10	<1.15	1.15-1.20

Table C: Modified Gradient Index (MGI) requirements for lung sites

PTV (cc)	Body $V_{50\%}$/PTV $V_{100\%}$			Body-PTVExp20 D_{max} (Gy)
	Target	Tolerance	Minor Deviation	3# Tolerance[$]
<20	7	9	9 – 11	<35.1
20-40	5.5	6.5	6.5 – 7.5	<37.8
40-60	5	6	6 – 7	<37.8
60-90	4	5	5 – 7	<37.8
>90	4	4.5	4.5 – 6.5	<37.8

Body-PTVExp20 D_{max} = Maximum point dose at least 2 cm from the PTV in any direction

[$]During CtE no lung plan exceeded the "Tolerance" level for Body-PTVExp20 D_{max} so the "Minor Deviation" level has been removed

Table D: OAR Dose Constraints

OAR parameter		Constraints for *3#*	
		Optimal	***Mandatory***
BrachialPlex	**$D_{0.5cc}$**	*24Gy*	*26Gy*
Bronchus_Prox	**$D_{0.5cc}$**	*30Gy*	*32Gy*
Chestwall	**$D_{0.5cc}$**	*37Gy*	-
	D_{30cc}	*30Gy*	-
GreatVes	**$D_{0.5cc}$**	-	*45Gy*
Heart+A_Pulm	**$D_{0.5cc}$**	*26Gy*	*30Gy*
Lungs-GTV (or ITV)	**V_{20Gy}**	-	*10%*
Oesophagus	**$D_{0.5cc}$**	-	*25.2Gy*
Skin	**$D_{0.5cc}$**	*33Gy*	-
	D_{10cc}	*30Gy*	-
SpinalCanal	**$D_{0.1cc}$**	*18Gy*	*21.9Gy*
	D_{1cc}	*12.3Gy*	-
Trachea	**$D_{0.5cc}$**	*30Gy*	*32Gy*

12.4 Appendix 4 - Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AR reporting. (http://ctep.cancer.gov/reporting/ctc.html)

1. Quick Reference

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

2. Components and Organization SOC

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

3. CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA LLT (Lowest Level Term).

4. Definitions

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

5. Grades

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

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

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

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

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

6. Activities of Daily Living (ADL)

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

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

ECI	Grade	Action to be taken	Supportive Care
Pneumonitis –	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• 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 7 and 8.
• 1st episode - May increase dosing interval by one week in subsequent cycles • 2nd episode of - Pneumonitis, permanently discontinue pembrolizumab if upon re-challenge patient develops Pneumonitis ≥ Grade 2			
Colitis	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
–			
	Grade 2 (For grade 2 diarrhoea that persists > 3 days)	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Symptomatic treatment ○ Consider GI consult & endoscopy to rule out colitis	• Prednisone 1-2mg/kg/day or equivalent • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg or less of prednisone or equivalent per days within 12 weeks. • If symptoms worsen or persist >1 week treat as grade 3.

	Grade 3	• 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 than 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 7 and 8.
	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	• 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.

		insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. • Consider endocrinologist consult.	
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 8.5.2. • 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 7 and 8. • 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 8.5.2. • Discontinue pembrolizumab	• Manage as per grade 3
Myocarditis¶ *¶"Ensure that other causes of myocarditis are adequately evaluated to exclude other aetiologies*	Grade 1 and 2	• Withhold Pembrolizumab • Consider Cardiology consult	• 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 1-2mg/kg daily of prednisone or equivalent.
	Grade 3 and 4	• Discontinue Pembrolizumab permanently • Obtain Cardiology consult	• Prednisone 1 – 2 mg/kg or equivalent • Permanently discontinue pembrolizumab
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[§].	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	• 1mg/kg/day prednisone or equivalent or dexamethasone 4mg 4xday.

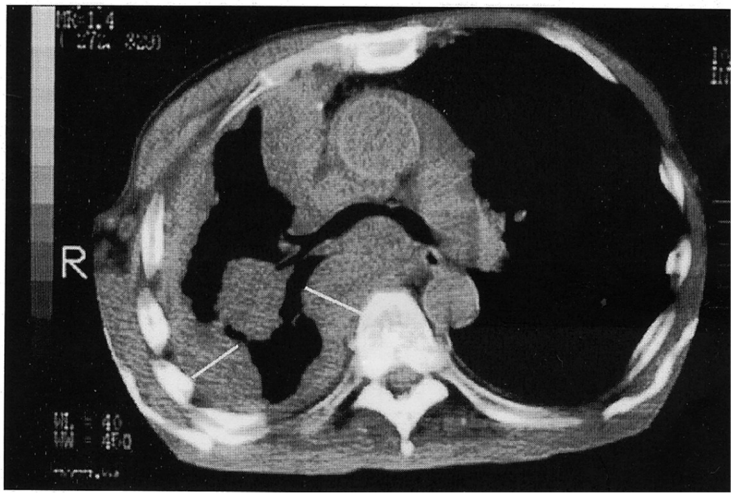
§ If it is suspected that the patient has SJS or TEN, pembrolizumab should be withheld. The patient should be referred to a dermatologist for management. If SJS and TEN is confirmed, then pembrolizumab should be permanently discontinued."		• Consider dermatology consultation and biopsy for diagnosis.	• Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Permanently 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: • **Pericarditis** • **Pancreatitis** • **Any additional Grade 3 or higher event which the physician considers to be immune related**	Grade 2 or Grade 1 that do not improve with symptomatic treatment.	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab • Consider biopsy for confirmation of diagnosis.	• Systemic corticosteroids may be indicated. • If so: • Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, Pembrolizumab treatment may be restarted and the dose modified as specified in the protocol
	Grade 3	• 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 – Modified Response Evaluation Criteria in Solid Tumours (mRECIST) Criteria for Evaluating Response in Malignant Pleural Mesothelioma

The modified RECIST criteria were developed by Bryne and Novak (2004). Tumour thickness perpendicular to the chest wall or mediastinum should be measured in two positions at three separate levels on transverse cuts of CT scan.

In this protocol, mRECIST for MPM criteria will be used to assess response to therapy as follows:

1. mRECIST for MPM criteria will be used for tumour response evaluation in sites of disease outside the radiotherapy field by 2 cm above and 2 cm below the margins of the irradiated volume.
2. mRECIST for MPM criteria will be used for tumour response evaluation in sites of disease inside the radiotherapy field by 2 cm above and 2 cm below the margins of the irradiated volume.
3. As this is evaluating tumour responses of an immunotherapy drug, responses will need to be confirmed 4 – 6 weeks after the initial response imaging.



The sum of the six measurements defined a pleural unidimensional measure. Transverse cuts should be at least 1 cm apart and related to anatomical landmarks in the thorax that allow reproducible assessment at later time points, as shown above. If measureable tumour is present, transverse cuts in the upper thorax, above the level of division of the main bronchi are preferred. At reassessment, pleural thickness should be measured at the same position at the same level and by the same observer. This should not necessarily be the greatest tumour thickness at that level. Nodal, subcutaneous and other bidimensionally measurable lesions should be measured unidimensionally as per the RECIST 1.1 criteria. Unidimensional measurements are added to obtain the total tumour measurement.

Complete response (CR) was defined as the disappearance of all target lesions with no evidence of tumour elsewhere, and **partial response (PR)** was defined as at least a 30% reduction in the total tumour

measurement. A confirmed response required a repeat observation on two occasions 4 weeks apart. **Progressive disease (PD)** was defined as an increase of at least 20% in the total tumour measurement over the nadir measurement, or the appearance of one or more new lesions. Patients with **stable disease (SD)** were those who fulfilled the criteria for neither PR nor PD.

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