Randomised Phase II Trial of Pembrolizumab and Radiotherapy in Melanoma (PERM)

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Table of revisions made to protocol v2.0 (dated 10Jul2015)

Page/Section	Previous Wording	New Wording (tracked)	Comments/explanation/rationale for substantial amendment
Page 6- Exclusion criteria	-	-	Exact text from the main part of the protocol was copied here to ensure consistency throughout
Exclusion Criteria- Page 16	-	8. Has history of Sjogren's Syndrome	These patients have been excluded because these patients are a group of patients where radiation toxicity may be greater and more unpredictable. Therefore they have been excluded in the event that radiation exacerbates their condition
Pages 19, 20 and 21	-	-	The CI, Statistician and PI Signature Pages were moved to the front of the protocol from the back to ensure these are not overlooked.
Section 4.2, page 23	Registration Following the patient's signature of the consent form, this information must be entered into the electronic database which will allocate a unique trial identification number to be used to identify the patient throughout the study. Once all the screening assessments have been completed and the data entered into the eCRFs; the patient will be assessed for eligibility. If eligible, the patient will be randomised into a treatment group. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient.	Registration Following the patient's signature of the consent form, this information must be entered into the electronic database which will allocate a unique trial identification number to be used to identify the patient throughout the study. A copy of the consent form must also be faxed to the Trials office to enable source data verification and confirm patient's participation in the study. NOTE: Sites must alert the trials office to confirm receipt once the consent form has been faxed. Once all the screening assessments have been completed and the data entered into the eCRFs; the patient will be assessed for eligibility. If eligible, the patient will be randomised into a treatment group. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient	As per sponsor requirements, signed copies of consent forms will be sent into the trials office to safely confirm participation.
-	-	-	The word "patient" has been replaced by the text "participant" throughout the protocol as recommended by REC to be consistent.

Page/Section	Previous Wording	New Wording (tracked)	Comments/explanation/rationale for substantial amendment
Table 2- Schedule of Assessments- page 29	-	-	Optional Research Blood sample taken at Screening has been removed from the table as this is a duplicate of the sample taken at Cycle 1, Wk0 sample and is unnecessary. Also the radiotherapy administration timepoint has been re-formatted to appear much clearer to the user
Table 4, Section 5.3.7, page 33	-	-	Removal of Chloride from listing as this is not clinically required for this study
Figure 2-Blood and tumour sample schedule-page 36	-	-	Updated as per Table 2 changes including stating how much volume of Optional Research Blood that will be taken
Table 5-Total Blood Volume, page 37	-	-	This table has been updated with the correct total volume of blood that will be taken throughout the study talking into account the 50ml which will now be taken instead of 24ml
Section 7.4, page 57, page70	-	Removal of the requirement to report ECIs to MSD	An extensive study performed by (Merck, Sharpe & Dohme) MSD has managed to characterise the safety profile of Pembrolizumab and therefore no longer require the reporting of ECIs to MSD in an expedited manner. These events apart from those described in current protocol under "Definitions of Evidence of Clinical Interest" section and should be reported as per AE guidelines.
Section 8.3, page 63	**Randomisation** Patients will be randomised in a 1:1 ratio to receive pembrolizumab alone or pembrolizumab in combination with radiotherapy using random permuted blocks within strata to take account of their LDH level at baseline and previous anti-CTLA4 treatment. Randomisation of enrolled patients will be stratified based on LDH (below or within normal range / above upper limit of the normal range) and previous anti-CTLA4 treatment (yes/no). The randomisation number is a unique number; once assigned, it becomes the permanent study identifier for that patient when they receive their treatment	**Randomisation** Patients will be randomised in a 1:1 ratio to receive pembrolizumab alone or pembrolizumab in combination with radiotherapy using random permuted blocks within strata to take account of their LDH level at baseline and previous anti-CTLA4 treatment. Randomisation of enrolled patients will be stratified based on the following parameters; 1. LDH (below or within normal range / above upper limit of the normal range) And 2. Previous anti-CTLA4 treatment (yes/no) The randomisation number is a unique number. Patients will be identified using the number generated by the database which will become their unique identifier throughout the study and in all future correspondence.	This is to clarify that the study database will auto-generate a trial reference number which will be used as the unique patient identifier throughout the study.

Page/Section	Previous Wording	New Wording (tracked)	Comments/explanation/rationale for substantial amendment
Section 8.4.1, page 63	Analysis populations The efficacy results of the trial will be analysed on an intention to treat (ITT) basis. The ITT population is defined as all patients randomised in the study and are analysed as randomised for response rate, PFS and OS. The safety data will be analysed by treatment received, irrespective of randomisation, in patients who received at least one treatment dose. Patients withdrawn prior to the first treatment dose will be excluded	Analysis populations The efficacy results of the trial will be analysed on an intention to treat (ITT) basis. The ITT population is defined as all patients randomised in the study and are analysed as randomised for response rate, PFS and OS. The safety data will be analysed by treatment received, irrespective of randomisation, in patients who received at least one treatment dose. Patients withdrawn prior to the first treatment dose will be excluded. In addition, after 50% of the patients have been randomised and are evaluable for the primary endpoint an interim analysis will be carried out to assess the difference between the two trial arms. In the event that both arms showed a RECIST response rate of 30% when approximately 120 patients are evaluable then it will be judged unlikely that the pembrolizumab and radiotherapy arm will show a RECIST response rate of 50% relative to the 30% RECIST response rate in the pembrolizumab only arm at the end of the trial and the trial will be stopped.	As per REC recommendations following Favourable Opinion, a formal interim analysis was designed into the study to enable safe and efficient review of any developing issues during the study
Section 8.7, page 66	**Early Discontinuation of the Study** No formal stopping rules are planned either for efficacy, futility or toxicity since this study is similar to routine standard of care with the addition of radiotherapy. The Trial Steering Committee will monitor trial progress including for significant safety / toxicity issues should they arise	**Early Discontinuation of the Study** An interim analysis will be carried out when approximately 120 patients (50%) are evaluable for the primary endpoint, this will allow for the early termination of the trial should there be no difference between the two arms, respectively. The Trial Steering Committee will monitor trial progress including for significant safety / toxicity issues should they arise.	As above
Section 9.7.1, page 68	The Principal investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Act of 1998. On the e-CRFs or other documents submitted to the RM-CTU, patients should be identified by their initials and a patient study number only.	The Principal Investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Act 1998. In all study correspondence submitted to the RM-CTU (apart from signed consent forms) all participants will be identified by their initials and unique Trial Reference study number only which will be used in all e-CRFs or other documents submitted to the RM-CTU.	Grammatical correction
Appendix 1- Radiotherapy Treatment	-	-	The text in this Appendix 1 which includes; *Summary of Immune Priming Radiotherapy and Organs at Risk* Information is subject to change at any point and has been removed from the protocol and placed in a separate document called the *"Radiotherapy Planning and QA Guidelines Manual"*. However, some text has been retained and moved to Section 6.2.5 to 6.2.8 of the protocol. All other Appendix documents have been rearranged in number order.

Revisions made to PIS/Consent Form v2.0 dated 23Jul15

Page/Section	Previous Wording	New Wording (tracked)	Comments/explanation/rationale for substantial amendment
-	-	-	For consistency, references to "patient" has been replaced with "participant" throughout the document.
Question 5, page 2	**Extra Tests** **Optional:** Collection of a research blood sample (approximately 6 teaspoons /24mL) before you start pembrolizumab	Text removed	The Optional Research Blood collection at screening is a duplication of the sample at Cycle 1, W0 time-point and has therefore been removed.
Question 5 – Step 1, bottom of page 2	If you are not confirmed to be suitable to take part in the study, you will not be able to take part in the study. However, your doctor will make alternative more suitable arrangements for the treatment of your condition	If you are confirmed not to be suitable to take part in the study, you will not be able to take part in the study. However, your doctor will make alternative more suitable arrangements for the treatment of your condition	Grammar correction
Question 5 - Step 2, page 3	**Extra tests:** Administer 200mg of pembrolizumab by IV infusion (the medication will be given directly into your vein) and will take 30 minutes every 3 weeks. Administer radiotherapy of 24Gy over 3 days. This will only be given to participants randomised to receive radiotherapy and will only happen between the first and second dose of pembrolizumab in the first Cycle; **Optional:** Collection of up to 2 tumour biopsies before your second dose of pembrolizumab and after radiotherapy if you are receiving it; AND Collection of research blood samples (approximately 6 teaspoons/24mL) will be done on the first 5 occasions at each visit where you will be given pembrolizumab. This is to carry out tests that will help us understand how the body deals with the drug and what effect it has on your body when it is given with radiotherapy. These samples will be taken at the same time as the routine samples. Every effort will be made to take all blood samples from a single needle stick.	**Extra tests:** Administer 200mg of pembrolizumab by IV infusion (the medication will be given directly into your vein) and will take 30 minutes every 3 weeks. Administer radiotherapy of 24Gy over 3 days. This will only be given to participants randomised to receive radiotherapy and will only happen between the first and second dose of pembrolizumab in the first Cycle; **Optional:** Collection of up to 1 tumour biopsy before your second dose of pembrolizumab and after radiotherapy if you are receiving it; AND Collections of Research Blood samples (approximately 12 teaspoons/50mL) before you start pembrolizumab; at Cycle 1(wk0), Cycle 2(wk3), Cycle 3(wk6), Cycle 4(wk9) and Cycle 5(wk12)). This is to carry out tests that will help us understand how the body deals with the drug and what effect it has on your body when it is given with radiotherapy. These samples will be taken at the same time as the routine samples. Every effort will be made to take all blood samples from a single needle stick.	The volume of Optional Research Blood has been changed to ensure enough cells are available to be analysed.

Page/Section	Previous Wording	New Wording (tracked)	Comments/explanation/rationale for substantial amendment
Question 5 – Step 1, top of page 5 part b	**b. Punch biopsy:** A small circle of tissue sample will be taken using a sharp, hollow device. You may have this test under local anaesthetic. If you do not wish to give us this sample it will not affect your ability to take part in the main study.	**Punch biopsy:** A small circle of tissue sample will be taken using a sharp, hollow device. You may have this test under local anaesthetic. If you do not wish to give us this sample it will not affect your ability to take part in the main study. There is a more complex test that is part of our biomarker research which needs to be carried out on your samples and this test can only be performed by a specialised laboratory which is based in the United States as they are specially equipped to do so. This means that we will need to send part of your samples outside of the EEA to the United States for further processing	
Question 9, page 7	**Common side effects:** • Tiredness • Lack of energy • Rash • Joint pain • Frequent or excessive bowel movements, • Itchy skin, • Feeling sick or being sick (nausea) **Rare side effects:** • Fever • Headache • Muscle cramps • Shortness of breath, loss of appetite • Cough • Weight loss, • Pain in the back, • Arms or legs, • Red rash, • Swelling of the legs, • Flu or flu like symptoms *(fever, chills, body aches, and feeling tired),* • Change in your vision, • Abnormal liver function *(leading to yellowing of the skin or whites of the eyes, fatigue, or leg swelling), feeling cold, loss of skin colour, vomiting, stomach pains, excessive sweating in the night, decrease in red blood cells (leading to tiredness or shortness of breath),* • Decreased thyroid activity *(leading to tiredness, weight gain, feeling cold easily, bowel movements occurring less often)* • Increased thyroid activity *(leading to anxiety, irritability, trouble sleeping, weakness, trembling, sweating, feeling uncomfortable in warm weather, fast*	**Common side effects:** Diarrhoea/Constipation **Other possible side effects:** • Pain in the back or abdomen, arms or legs • Change in your vision or Uevitis • Abnormal liver or pancreas • Other changes in the hormone system (endocrinopathies) • Reduction in how your kidneys are working • Blood-clot that may cause swelling in the arms or legs or shortness of breath • Liver inflammation (Hepatitis) • Type 1 diabetes and its complications • Reaction related to pembrolizumab infusion • Lung inflammation (Pneumonitis)	Updated as per amended Investigator Brochure (v10 dated 31Aug2015)

	or uneven heartbeats, feeling tired, weight loss, and frequent or excessive bowel movements).		
Question 18, page 9	When you sign the consent form, you agree to have your personal and medical information used as described in this section	When you sign the consent form, you agree to have your personal and medical information used as described in this section. This study will be monitored remotely from the Sponsor's trials office but in order to safely track and confirm your participation in this study, a copy of your signed consent form will be sent to the Sponsor for their records. This document will be kept confidential and store securely in a locked cupboard and will only be accessible to authorised personnel associated with this study. In addition to this, a copy of your anonymised images will be sent electronic via a secure network outside of your local hospital for Central Radiology Review by the Radiotherapy Quality Assurance team in the UK.	Sponsor requirements request that copies of consent forms sent to the trials office for verification and confirmation of study participation
Consent Form	-	13. I give permission for a copy of this signed consent form to be sent to the Sponsor for their records	Added as per information above
Consent Form	-	14. I give permission for a copy of my anonymised images to be sent via a secure electronic system to be reviewed by the Radiotherapy Quality Assurance team	The images taken for this study will be centrally reviewed by the Radiotherapy Quality Assurance team to assure consistency and uniform detection.
Consent Form	-	15. I agree that part of my tissue samples will be sent outside of the EEA to the United States for further analysis	Part of the tissue biopsy samples will be sent to a US based company who will perform specific tests (PD-L1 testing) on each sample.

Revisions made to protocol v3.0 (dated 21Dec2015)

Page/Section	Previous Wording	New Wording (tracked)	Comments/explanation/rationale for substantial amendment
Exploratory endpoints	***Peripheral blood analysis (in selected sites)*** • Absolute lymphocyte counts (ALC) to be measured by flow cytometry, lactate dehydrogenase (LDH) and c-reactive protein (CRP) to be assayed from plasma. • Peripheral blood mononuclear cell phenotype markers e.g. CD3, CD4, CD8, PD-1, ICOS and EOMES. • Evaluation of HMGB1 release by mass spectrometry (serum). • HLA-typing to permit analysis in HLA-defined patients (i.e. HLA-A201) of frequency of T cells specific for defined tumour associated antigens e.g NY-ESO-1. ***Tumour Biopsy samples (in selected sites)*** • Immunohistochemical (IHC) analysis of tumour infiltrating immune cell populations and microenvironment e.g. CD8, CD4, FOXP3, PD-1, Granzyme B, PD-L1. Analysis will also include evaluation of TIL infiltration pattern (in relation to tissue architecture). • Optional expansion to permit isolation of DNA and RNA from tumour biopsy (non-laser capture) for expression analysis.	***Peripheral blood analysis (in selected sites)*** • ~~Absolute lymphocyte counts (ALC) to be measured by flow cytometry, lactate dehydrogenase (LDH) and c-reactive protein (CRP) to be assayed from plasma.~~ • ~~Peripheral blood mononuclear cell phenotype markers e.g. CD3, CD4, CD8, PD-1, ICOS and EOMES.~~ • ~~Evaluation of HMGB1 release by mass spectrometry (serum).~~ • ~~HLA-typing to permit analysis in HLA-defined patients (i.e. HLA-A201) of frequency of T cells specific for defined tumour associated antigens e.g NY-ESO-1.~~ Peripheral blood collected from patients at baseline, during and follow-up of treatment will be analysed to assess immune function in response to pembrolizumab ± radiotherapy. Assays to examine innate and/or adaptive immune functional response may include, for example, immunophenotyping, cytokine/chemokine arrays. For details, refer to the associated Trial Manual. ***Tumour Biopsy samples (in selected sites)*** • ~~Immunohistochemical (IHC) analysis of tumour infiltrating immune cell populations and microenvironment e.g. CD8, CD4, FOXP3, PD-1, Granzyme B, PD-L1. Analysis will also include evaluation of TIL infiltration pattern (in relation to tissue architecture).~~ • ~~Optional expansion to permit isolation of DNA and RNA from tumour biopsy (non-laser capture) for expression analysis.~~ Tumour biopsy tissue collected from patients at baseline & during treatment will be examined to assess the tumour microenvironment in response to therapy. Tumour may be used in, for example, multi-colour immunohistochemistry and RNA sequence analysis to investigate TIL infiltration & expression of known tumour-associated antigens. For details, refer to the associated Trial Manual.	The section is revised across the protocol for minor clarification.
Table 1: Schedule of Study		***g***8. A follow-up OPTIONAL Research Blood Sample can be taken at either time of response or progression (to be determined by treating	Clarification for additional blood sample can be taken at either time of response or progression.

Assessments		clinician)	
5.4.3.1 Peripheral Blood Analysis	Consenting participants will be asked to provide an additional 50ml of blood at each visits prior to the administration of pembrolizumab for the first 12 weeks of treatment. Detailed processing procedures will be provided in a separate laboratory manual. These additional research bloods are considered to be research samples and will be retained under the University of Leeds Tissue Bank. All samples will undergo the following analysis: • Peripheral blood mononuclear cell phenotype markers e.g. CD3, CD4, CD8 with PD-1, ICOS, and EOMES. • Evaluation of HMGB1 release by mass spectrometry (serum). • HLA-typing to permit analysis (in HLA-defined participants i.e. HLA-A201) of frequency of T cells specific for defined tumour associated antigens e.g. NY-ESO-1.	~~Consenting participants will be asked to provide an additional 50ml of blood at each visits prior to the administration of pembrolizumab for the first 12 weeks of treatment. Detailed processing procedures will be provided in a separate laboratory manual. These additional research bloods are considered to be research samples and will be retained under the University of Leeds Tissue Bank. All samples will undergo the following analysis:~~ • ~~Peripheral blood mononuclear cell phenotype markers e.g. CD3, CD4, CD8 with PD-1, ICOS, and EOMES.~~ • ~~Evaluation of HMGB1 release by mass spectrometry (serum).~~ • ~~HLA-typing to permit analysis (in HLA-defined participants i.e. HLA-A201) of frequency of T cells specific for defined tumour associated antigens e.g. NY-ESO-1.~~ Consenting participants will be asked to provide an additional 50ml of blood at each visit prior to the administration of pembrolizumab for the first 12 weeks of treatment and a further blood sample at either time of response or progression (to be determined by the relevant clinician). Detailed processing procedures will be provided in a separate laboratory Trial Manual. These additional research bloods are considered to be research samples and will be retained under the PERM Trial ethics until used for analysis or destroyed following completion of the trial.. All samples will be analysed to assess immune function in response to pembrolizumab ± radiotherapy. Assays to examine innate and/or adaptive immune functional response may include, for example, immunophenotyping, cytokine/chemokine arrays. For details, refer to the associated Trial Manual.	
5.4.3.2 Tumour Biopsy Samples	For consenting participants post treatment biopsies will be taken at their second cycle of pembrolizumab ideally from the same lesion that was used to confirm metastatic disease at screening. If this biopsy was from a lesion that had been irradiated then if possible an additional biopsy outside the radiotherapy field should also be collected. Biopsies will be core or punch biopsies. Detailed processing, handling and shipping procedures for these biopsies will be provided in a separate laboratory manual. These additional tissue biopsies are considered to be research samples and will be retained under the Manchester Cancer research Centre Tissue Bank.	For consenting participants post treatment biopsies will be taken at their second cycle of pembrolizumab ideally from the same lesion that was used to confirm metastatic disease at screening. If this biopsy was from a lesion that had been irradiated then if possible an additional biopsy outside the radiotherapy field should also be collected. Biopsies will be core or punch biopsies. Detailed processing, handling and shipping procedures for these biopsies will be provided in a separate laboratory Trial manual. These additional tissue biopsies are considered to be research samples and will be retained under the Manchester Cancer research Centre ~~Tissue Bank~~. Tumour biopsy tissue collected from patients at baseline & during treatment will be examined to assess the tumour microenvironment in response to therapy. Tumour may be used in, for example, multi-colour immunohistochemistry and RNA sequence analysis to	

	The following analyses are planned to be performed on the above samples: • Immunohistochemical (IHC) analysis of tumour infiltrating immune cell populations and microenvironment e.g. CD8, CD4, FOXP3, PD-1, Granzyme B, PD-L1. Analysis will also include evaluation of TIL infiltration pattern (in relation to tissue architecture). • Optional expansion to permit isolation of DNA and RNA from tumour biopsy for expression analysis	investigate TIL infiltration & expression of known tumour-associated antigens. For details, refer to the associated Trial Manual. ~~The following analyses are planned to be performed on the above samples:~~ • ~~Immunohistochemical (IHC) analysis of tumour infiltrating immune cell populations and microenvironment e.g. CD8, CD4, FOXP3, PD-1, Granzyme B, PD-L1. Analysis will also include evaluation of TIL infiltration pattern (in relation to tissue architecture).~~ • ~~Optional expansion to permit isolation of DNA and RNA from tumour biopsy for expression analysis~~	
6.2.3. Radiotherapy Techniques		As the radiotherapy fractionation schedule employed for this trial, 24Gy/3# is not a recognised palliative dose for melanoma at present, and giving it concurrently with Pembrolizumab is not the standard of care, maintaining the safety of patients recruited into the study should be our absolute priority. Therefore only CtE SABR centres with established clinical experience in irradiating sites close to critical organs at risk (such as mediastinal lymph nodes, thoracic oligometastases, hepatic metastases and paravertebral soft tissue metastases) in their routine clinical practice should irradiate these targets in this trial. Patient recruited at sites which are non-SARB CtE centres, patients will still receive pembrolizumab locally at the site but may be irradiated at other CtE centre. It is anticipated that for centres with limited experience in delivering SABR, cutaneous metastases or superficial lymph nodes would be the most common targets for radiotherapy in this study.	Clarification that for the PERM patient recruited at sites which are non-SARB CtE centres, patients will still receive pembrolizumab locally at the site but may be irradiated at other CtE centre.
Figure 1: Blood and tumour sampling schedule.	NA	NA	Figure 2 is updated for additional blood sample that can be taken at either time of response or progression.

Table of revisions made to PIS v3.0 (dated 29Dec2015)

What will happen to me if I take part?		Collections of Research Blood samples (approximately 12 teaspoons/50mL) before you start pembrolizumab; at Cycle 1(wk0), Cycle 2(wk3), Cycle 3(wk6), Cycle 4(wk9) and Cycle 5(wk12) plus an additional sample taken at time of response or progression (to be determined by treating clinician).	Clarification for additional blood sample can be taken at either time of response or progression.
		Take photographs of any skin lesions you may have	Take photographs of any skin lesions you may have (only if done routinely at your hospital)

TRIAL SUMMARY

Title	Randomized Phase II Trial of **Pe**mbrolizumab and **R**adiotherapy in **M**elanoma (PERM)
Trial Phase	II
Clinical Indication	Advanced Melanoma
Trial Type	Randomised
Type of control	Pembrolizumab alone
Route of administration	Intravenous and external radiotherapy
Trial Blinding	None
Treatment Groups	2
Number of trial patients / Sites	234 patients / 15-24 UK investigational sites
Estimated duration of trial	4 Years
Duration of Participation	Until progression or intolerance
Study Objectives	*Primary Objective* • To evaluate if radiotherapy will enhance the efficacy of pembrolizumab in the treatment of patients with metastatic melanoma by induction of an abscopal effect. *Secondary Objective* • To evaluate response rates by RECIST v1.1 post treatment • To evaluate response in non-irradiated lesions • To assess the efficacy of pembrolizumab based on Progression Free Survival (PFS). • To assess the efficacy of pembrolizumab based on Overall Survival (OS). • To assess the safety and tolerability of pembrolizumab alone and in combination with high dose radiotherapy. *Exploratory Objective* • Identification of biomarkers that correlate with immunological response to therapy
Study Endpoints	*Primary Endpoint* • Improvement in tumour response rate (RR) measured by RECIST 1.1 after 12 weeks of treatment of pembrolizumab alone or with radiotherapy. *Secondary Endpoints* • Determine response rates by RECIST v1.1 at 6 months post treatment • To measure individual lesion response assessment every 12 weeks taking

	account of within patient data. • To assess the toxicity of the combination of pembrolizumab and high dose radiotherapy after 12 weeks of treatment. • To assess PFS at 1, 2 and 3 years post treatment. • To assess OS in the arms of the study. *Exploratory Endpoints* ***A. Peripheral blood analysis (in selected sites)*** Peripheral blood collected from patients at baseline, during and follow-up of treatment will be analysed to assess immune function in response to pembrolizumab ± radiotherapy. Assays to examine innate and/or adaptive immune functional response may include, for example, immunophenotyping, cytokine/chemokine arrays. For details, refer to the associated Trial Manual. ***B. Tumour Biopsy samples (in selected sites)*** Tumour biopsy tissue collected from patients at baseline & during treatment will be examined to assess the tumour microenvironment in response to therapy. Tumour may be used in, for example, multi-colour immunohistochemistry and RNA sequence analysis to investigate TIL infiltration & expression of known tumour-associated antigens. For details, refer to the associated Trial Manual.
Summary of Main Inclusion Criteria	1. Be willing and able to provide written informed consent for the trial. 2. Have a diagnosis of stage III (unresectable) or stage IV cutaneous melanoma or melanoma of unknown primary, as per AJCC staging system. 3. Confirmed metastatic disease by diagnostic biopsy. 4. Be ≥ 18 years of age on day of signing informed consent. 5. Have at least one lesion and a maximum of 3 which are appropriate targets for high dose radiotherapy. This lesion must be 1cm-5cm in size and measurable by RECIST v1.1. The lesions should also be asymptomatic or, in the opinion of the investigator, threaten to become symptomatic. 6. Have in addition at least one other lesion which will not be irradiated but must be measurable by RECIST v1.1 to assess the abscopal effect of the treatment. 7. Have a performance status of 0 or 1 on the ECOG Performance Scale. 8. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 7 days of randomisation. 9. Female patient of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to randomisation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. 10. Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Patients of childbearing potential are those who have not been

	surgically sterilized or have not been free from menses for > 1 year. 11. 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.
Summary of Main Exclusion Criteria	1. Has lesions that if irradiated would result in unacceptable radiation induced toxicity to normal tissue, in particular to the CNS and bowel 2. Requires palliative radiotherapy for symptom control 3. Is currently participating in or has participated in a study of an investigational agent or device within 4 weeks of the first dose of trial treatment. 4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. 5. Has had a monoclonal antibody within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. 6. Has had chemotherapy, targeted small molecule therapy, or radiation therapy within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. **Note**: participants with an AE ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. **Note**: if participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. 7. Has history of severe colitis related to previous immunotherapy treatment 8. Has a past or current history of Sjögrens Syndrome. 9. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy. 10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. 11. Has an 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. Participants with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Participants that require

	intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Participants with hypothyroidism stable on hormone replacement will not be excluded from the study. 12. Has evidence of interstitial lung disease or active, non-infectious pneumonitis. 13. Has an active infection requiring systemic therapy. 14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator. 15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment. 17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137. 18. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies). 19. Has known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected). 20. Has received a live vaccine within 30 days prior to the first dose of trial treatment
Treatment / Main Study Procedures	Patients will be randomised to receive pembrolizumab 3 weekly either alone or in combination with a course of high dose radiotherapy. Clinical assessments will be undertaken every 3 weeks on the day on which the drug is administered. Patients will continue on this regimen until disease progression, unacceptable toxicities, discontinuation of study medication or withdrawal. Patients in the radiotherapy arm will receive 24Gy in 3 fractions over a course of 3 consecutive days between the first and second doses of pembrolizumab. Patients will also undergo tumour assessment by RECIST 1.1 every 12 weeks from the first dose of pembrolizumab (irrespective of delays in treatment) to establish disease response. Please note: • The 1st patient should be followed for 6 weeks or until the resolution of local acute toxicity to grade 1 before the second patient can begin treatment. • The first 3 patients randomised to receive both pembrolizumab and

	radiotherapy will be seen weekly for the first 6 weeks of treatment to assess for any grade 3 or grade 4 toxicity. If no toxicity is seen the remaining patients in this arm will be seen as described above. If toxicity is seen an additional 3 patients from this arm should been seen weekly for the first 6 weeks. **OPTIONAL**: Patients in selected sites will be asked to consent to the collection of tumour biopsies and research bloods for translational endpoints. If a patient consents they will be agreeing to give **both** post treatment tumour biopsies **and** research blood samples. Tumour biopsies will be taken at their second cycle of pembrolizumab ideally from the same lesion that was used to confirm metastatic disease at screening. If this biopsy was from a lesion that had been irradiated then if possible an additional biopsy outside the radiotherapy field should also be collected. Biopsies will be core or punch biopsies. 24mls of research blood will be taken at day 1 of the first 5 cycles of pembrolizumab plus an additional sample at either time of response or progression (to be determined by treating clinician).

CHIEF INVESTIGATOR AND SPONSOR SIGNATURE PAGE

Study Title: Randomised Phase II Trial of **Pe**mbrolizumab and **R**adiotherapy in **M**elanoma (PERM)

Sponsor Protocol Number: CCR4251

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

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

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

Name of Chief Investigator: James Larkin	
Title: Dr	
Signed: 	**Date:** 14Jan2016

STATISTICIAN SIGNATURE PAGE

Study Title: Randomised Phase II Trial of **Pe**mbrolizumab and **R**adiotherapy in **M**elanoma (PERM)

Sponsor Protocol Number: CCR4251

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to EMEA ICH Topic E9 'Statistical Principles for Clinical Trials' and the relevant standard operating procedures and policies used by RMH.

Name of Statistician: ANN PETRUCKEVITCH

Title: LEAD STATISTICIAN

Signed: A. Petruckevitch

Organisation/Company: RMH

Date: 14/1/2016

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Title: Randomised Phase II Trial of **Pe**mbrolizumab and **R**adiotherapy in **M**elanoma (PERM)

Sponsor protocol number: CCR4251

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[1], the guidelines of Good Clinical Practice (GCP) the Declaration of Helsinki and 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 who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Site Address: _____

_____

_____

Name of Investigator: _____

Title: _____

Signed: _____

Date: _____

1The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALC	Absolute Lymphocyte Counts
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APCs	Antigen Presenting Cells
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
CI	Chief Investigator
CNS	Central Nervous System
CR	Complete Response
CRP	C-Reactive Protein
CT	Computed Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTV	Clinical Target Volume
DAMPs	Damage Associated Molecular Patterns
DNA	Deoxyribonucleic acid
DVH	Dose Volume Histograms
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Forms
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FFPE	Formalin Fixed Paraffin Embeded
GCP	Good Clinical Practice
GP	General Practitioner
GTV	Gross Tumour Volume
Gy	Gray
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HMGB1	High Mobility Group Box 1
IB	Investigator Brochure
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICR	Institute of Cancer Research
ID	Identification
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board

LIST OF ABBREVIATIONS

Abbreviation	Definition
irAE	Immune Related Adverse Event
irECI	Immune Related Event of Clinical Interest
ISF	Investigator Site File
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
ITT	Intention to Treat
IV	Intravenous
LDH	Lactate Dehydrogenase
LENT-SOMA	Late Effects of Normal Tissue – Subjective, Objective, Management.
mAb	Monoclonal Antibody
mg	milligram
MHRA	Medicines and Healthcare Regulations Agency
MRI	Magnetic Resonance Imaging
MSD	Merck, Sharp & Dohme
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NHS	National Health Service
NSAIDS	Non-steroidal anti-inflammatory drugs
NSCLC	Non Small Cell Lung Cancer
OAR	Organ At Risk
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over the Counter
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTV	Planning Target Volume
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development
RDSU	Research and Development Statistical Unit
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RM-CTU	Royal Marsden Clinical Trials Unit
RNA	Ribonucleic acid
RR	Response Rate
RT	Radiotherapy

LIST OF ABBREVIATIONS

Abbreviation	Definition
RTTQA	NCRI Radiotherapy Trials QA Group
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT	Stereotactic Body Radiation Therapy
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Total Triiodothyronine
T4	Free Tyroxine
TILs	Tumour-Infiltrating Lymphocytes
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USM	Urgent Safety Measure
WBC	White Blood Cell
WFI	Water for Injection

1. BACKGROUND & RATIONALE

1.1. Background

1.1.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours. 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. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. 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 CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade [7; 10; 11; 12]. 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 [13; 14]. 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 [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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 [18; 19; 20; 13]. 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 [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumour-specific T-cell expansion in patients with melanoma [21]. 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.

Pembrolizumab (previously known as MK-3475 or SCH 900475) 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.

1.1.2. Preclinical and Clinical Trial Data

Refer to the current Investigator's Brochure for Preclinical and Clinical data.

1.2 Rationale

1.2.1 Background

Around 13,000 patients are diagnosed with melanoma in the UK each year; the incidence of this disease is increasing more rapidly than any other type of cancer [22]. About 20% of all patients will experience metastatic relapse following primary treatment, and prognosis is poor with a median survival ranging from 9-12 months [23].

In recent years, the development of new effective drugs has revolutionized the treatment of advanced melanoma [24]. However, the response rates are still low and novel therapeutic strategies are needed. The aim of this study is to confirm whether the combination of radiotherapy and the immunotherapeutic agent pembrolizumab can increase immune responses at distant sites in advanced melanoma.

1.2.2 Pembrolizumab in melanoma

Clinical data from 135 patients with advanced melanoma treated with pembrolizumab have recently become available [25]. Confirmed response rate evaluated by central radiologic review according to the RECIST version 1.1, was 38% (95% CI, 25 to 44). The response rate did not differ significantly between patients who had received prior treatment with the anti-CTLA-4 antibody ipilimumab and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively).

Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median PFS among the 135 patients was longer than 7 months. Common adverse events were fatigue, rash, pruritus, and diarrhoea. The majority of the adverse events were low grade.

Although no direct comparison has been made, efficacy results with anti-PD-1 compounds such as pembrolizumab in melanoma are superior to those achieved with the licensed anti CTLA-4 mAb ipilimumab. Thus, response rates with ipilimumab are in the order of 20% whereas with the anti-PD-1 drugs pembrolizumab or nivolumab the response rates are around 40% [26].

1.2.3 Rationale for Dose Selection

Available pharmacokinetic (PK) results in patients with melanoma, non-small cell lung cancer (NSCLC), and other solid tumour types support a lack of meaningful difference in PK exposures obtained at a given dose among tumour types. An open-label Phase 1 trial (PN001) [27] in melanoma patients has been conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in patients with advanced solid tumours. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumour size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed [28]. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma patients who had received prior ipilimumab therapy were randomised to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full

analysis set (FAS)). The proportion of patients with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in patients with melanoma, NSCLC, and other solid tumour types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumour types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumour indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 patients from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumour types and indication settings.

1.2.4 Radiotherapy in combination with PD1 axis blockade.

In addition to its well documented cytoreductive effect preclinical evidence demonstrates that treatment with RT can lead to the generation of a $CD8^+$ T lymphocyte response that has the capacity to mediate tumour cell kill [28; 29]. Treatment with radiotherapy can lead to expression of ecto-calreticulin on tumour cells as well as the release of several damage-associated molecular patterns (DAMPs) including High Mobility Group Box 1 (HMGB1) and ATP which can lead to recruitment and activation of antigen presenting cells (APCs) and priming of tumour antigen-specific T-cell responses [30; 31; 32] the potential for the generation of effective anti-cancer immune responses following radiotherapy tumour microenvironments are typically characterised as immunosuppressive, attenuating the therapeutic capacity of the immune response [33]. More recently several studies have demonstrated that the

efficacy of radiotherapy can be enhanced by combination with immunotherapy which modulates the immune response to radiation-induced tumour cell death [34; 35].

Recent preclinical data in mouse models of cancer including melanoma, demonstrate that radiotherapy leads to an increase in PD-L1 expression on the surface of cancer cells which may limit anti-tumour immune activity. These data demonstrate that blockade of the PD-1 / PD-L1 axis with either anti-PD-1 or anti-PD-L1 monoclonal antibodies leads to the generation of durable anti-tumour $CD8^+$ T cell responses which significantly improve local disease control and overall survival [36]. Recently published data support this finding that local radiotherapy may generate T cell responses that are limited by PD-1 signalling [37] strongly supporting the combination strategy for the present study. Moreover, preclinical data demonstrate that only concurrent but not sequential blockade of the PD-1 / PD-L1 axis with respect to radiotherapy was effective at improving tumour control [36]; providing proof of principle for the proposed clinical trial design.
The rationale for radiotherapy dose selection is specified in Appendix 1.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

Objective: To evaluate if radiotherapy will enhance the efficacy of pembrolizumab in the treatment of patients with metastatic melanoma by induction of an abscopal effect.
Hypothesis: Radiotherapy can potentiate the systemic immunotherapeutic activity of pembrolizumab by induction of an abscopal effect in patients with advanced melanoma.

2.1.2 Secondary Objectives

Objectives:

- To evaluate response rates by RECIST v1.1 post treatment
- To evaluate response in non-irradiated lesions
- To assess the efficacy of pembrolizumab based on Progression Free Survival (PFS).
- To assess the efficacy of pembrolizumab based on Overall Survival (OS).
- To assess the safety and tolerability of pembrolizumab alone and in combination with high dose radiotherapy.

Hypothesis: High dose radiotherapy results in immunogenic cell death resulting in release of antigens that stimulate a systemic immune response, converting the irradiated tissue into an *in situ* vaccine.

2.1.3 Exploratory Objective

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

Hypothesis: Pembrolizumab will favourably alter the anti-tumour immune response in patients which an effect that may be increased with the combination of radiotherapy**.**

2.2 Study Endpoints

2.2.1 Primary Endpoint

- To evaluate improvement in tumour response rate (RR) measured by RECIST 1.1 after 12 weeks of treatment (4 cycles) of pembrolizumab or pembrolizumab and high dose radiotherapy.

2.2.2 Secondary Endpoints

- To determine response rates by RECIST v1.1 at 6 months post treatment
- To measure individual lesion response assessment every 12 weeks taking account of within patient data
- To assess the toxicity of the combination of pembrolizumab and high dose radiotherapy after 12 weeks of treatment.
- To assess PFS at 1, 2 and 3 years post treatment.
- To assess OS in the arms of the study.

2.2.3 Exploratory Endpoints

Exploratory immunological endpoints will be determined from patients consenting to both peripheral blood and tumour biopsy sampling at selected sites.

A. Peripheral blood analysis

Peripheral blood collected from patients at baseline, during and follow-up of treatment will be analysed to assess immune function in response to pembrolizumab ± radiotherapy. Assays to examine innate and/or adaptive immune functional response may include, for example, immunophenotyping, cytokine/chemokine arrays. For details, refer to the associated Trial Manual.

B. Tumour Biopsy samples

Tumour biopsy tissue collected from patients at baseline & during treatment will be examined to assess the tumour microenvironment in response to therapy. Tumour may be used in, for example, multi-

colour immunohistochemistry and RNA sequence analysis to investigate TIL infiltration & expression of known tumour-associated antigens. For details, refer to the associated Trial Manual.

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicentre, open label, randomised phase II study. 234 patients with advanced melanoma will be randomised to either pembrolizumab alone or in combination with high dose radiotherapy. Randomisation will be in a 1:1 ratio and stratified to take account of their baseline LDH and previous treatment with an anti-CTLA4 agent. Patients will continue their allocated treatment regimen until they progress, discontinue study medication or withdraw. The study will be performed at a number of investigational sites in the UK.

3.2 Treatment Regimens

Patients will receive either 200mg of pembrolizumab 3 weekly alone or in combination with a high dose regimen of radiotherapy of 24Gy in 3 fractions given between the first and second doses of pembrolizumab. The patients will continue on 3 weekly doses of 200mg of pembrolizumab until disease progression, the development of unacceptable toxicities or withdrawal.

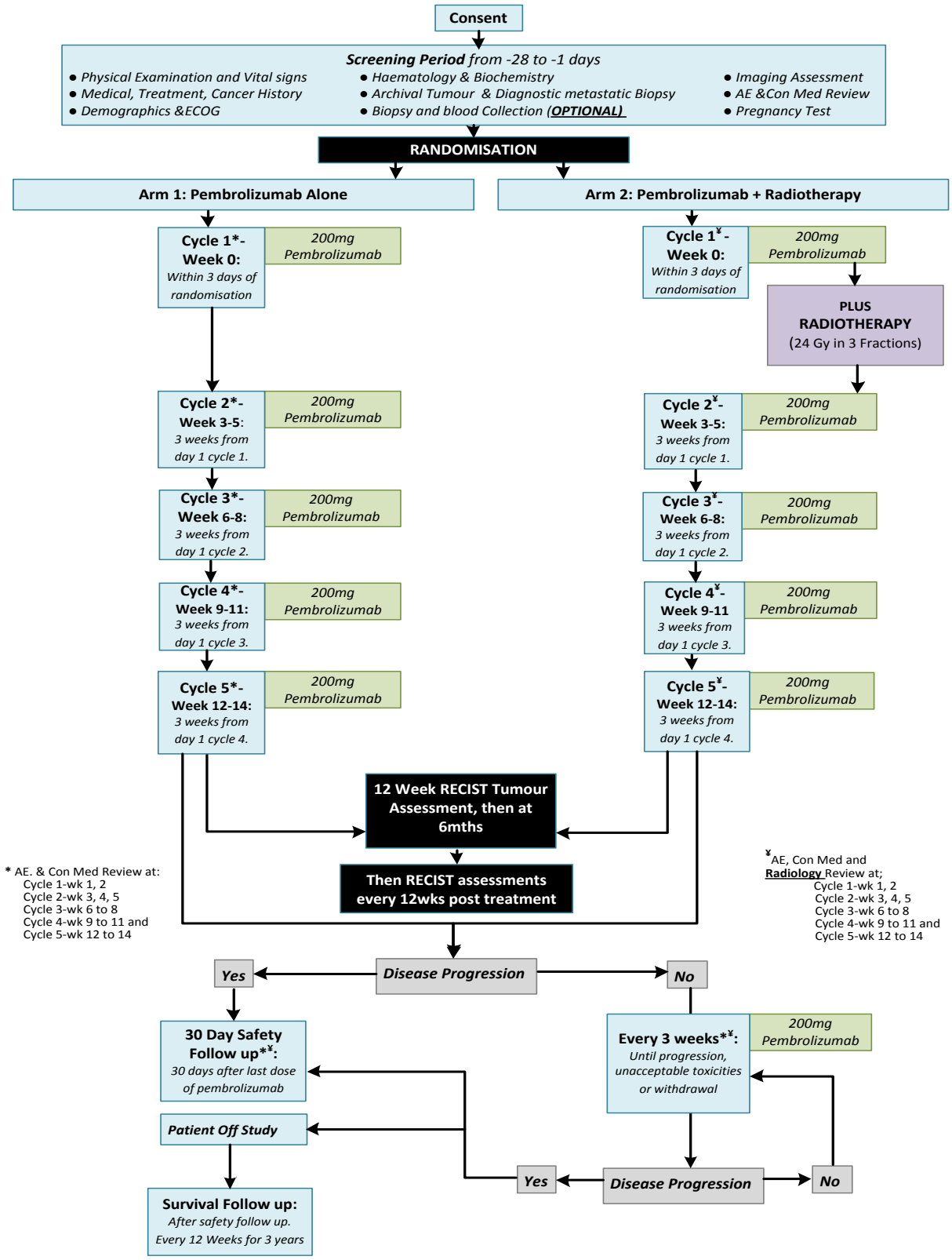
3.2.1 Additional Safety Evaluations

To ensure the safety of patients the 1st patient will be followed for 6 weeks or until the resolution of local acute toxicity to grade 1 before the second patient can begin treatment.

In addition the first 3 patients randomised to receive both pembrolizumab and radiotherapy will be seen weekly for the first 6 weeks of treatment to assess for any grade 3 or grade 4 toxicities. If no toxicity is seen the remaining patients in this arm will be seen as described above. If toxicity is seen an additional 3 patients from this arm should been seen weekly for the first 6 weeks.

3.3 Study Flow Chart

Figure 2: Study Flowchart



3.4 Follow Up

Patients will be required to attend a safety follow-up visit 30 days after the last dose of pembrolizumab and will be assessed for survival every 12 weeks for 3 years post treatment. Patients will not be expected to attend a visit for survival follow-up but information will be gathered by the research team from the patients' medical notes, the patients GP and telephoning the patients directly is applicable.

3.5 Study Termination

The end of the study is defined when the last patient has completed 3 years survival follow-up or has discontinued the study for other reasons.

3.6 Treatment after Study Termination

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

4.0. PATIENT SELECTION AND ENROLMENT

4.1. Screening and Enrolment

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

4.2. Registration

Following the patient's signature of the consent form, this information must be entered into the electronic database which will allocate a unique trial identification number to be used to identify the patient throughout the study. A copy of the consent form must also be faxed to the Trials office to enable source data verification and confirm patient's participation in the study.

NOTE: Sites must alert the trials office to confirm receipt once the consent form has been faxed.

Once all the screening assessments have been completed and the data entered into the eCRFs; the patient will be assessed for eligibility. If eligible, the patient will be randomised into a treatment group. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient.

4.3. Randomisation

Patients will be randomised to receive pembrolizumab alone or in combination with radiotherapy. Randomisation will be performed on a 1:1 ratio basis and will be stratified based on the results of;

1. **LDH (below or within normal range/above upper limit of the normal range) and**
2. **previous treatment with anti-CTLA4 agent (yes/no)**

Each site will be required to complete all screening eCRFs prior to randomisation to ensure that the eligibility of the patient may be confirmed. Further information regarding randomisation procedures will be provided to sites in the study specific registration and randomisation SOP.

The patients' trial ID will be a unique that once assigned will become the permanent study identifier for that patient. In the event a patient is randomised onto the study but does not begin treatment, then that patient's trial ID will not be reassigned. **Treatment will begin within 3 days from the date of randomisation**. To ensure participant confidentiality, participants will only be identified by their assigned trial ID on eCRFs as well as on other trial specific forms and all communication to RM-CTU. It is the PI's responsibility to maintain a confidential record of the identity i.e. full name, date of birth and hospital number for the participants 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.

PLEASE NOTE: To ensure participant safety, the first participant will be followed **for 6 weeks** or until the resolution of local acute toxicity to grade 1 **before** the second participant may commence treatment.

4.4. Entry Criteria

4.4.1. Participant Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.
2. Have a diagnosis of stage III (unresectable) or stage IV cutaneous melanoma or melanoma of unknown primary, as per AJCC staging system.
3. Confirmed metastatic disease by diagnostic biopsy.
4. Be $\geq$ 18 years of age on day of signing informed consent.
5. Have at least one lesion and a maximum of 3 which are appropriate targets for high dose radiotherapy. This lesion must be 1cm-5cm in size and measurable by RECIST v1.1. The lesions should also be asymptomatic or, in the opinion of the investigator, threaten to become symptomatic.

6. Have in addition at least one other lesion which will not be irradiated but must be measurable by RECIST v1.1 to assess the abscopal effect of the treatment.

7. Have a performance status of 0 or 1 on the ECOG performance scale.

8. Demonstrate adequate organ function as defined in table 1 below. All screening labs should be performed within 7 days of randomisation.

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥ 5.6 mmol/L
Renal	
Serum creatinine OR Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for participant 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 participants with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for participants with liver metastases
Coagulation	
Prothrombin Time (PT)	≤1.5 X ULN unless participant 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 participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Table 2: Adequate Organ Laboratory Values

9. Female participant of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to randomisation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
11. Male participants 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.

4.4.2. Participant Exclusion Criteria

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

1. Has lesions that if irradiated would result in unacceptable radiation induced toxicity to normal tissue, in particular to the CNS and bowel
2. Requires palliative radiotherapy for symptom control
3. Is currently participating in or has participated in a study of an investigational agent or device within 4 weeks of the first dose of trial treatment.
4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
5. Has had a monoclonal antibody within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had chemotherapy, targeted small molecule therapy, or radiation therapy within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: participants with an AE ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   Note: if participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. Has history of severe colitis related to previous immunotherapy treatment.
8. Has a past or present history of Sjogren's Syndrome
9. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
11. Has an 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. Participants with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Participants that require intermittent use of

bronchodilators or local steroid injections would not be excluded from the study. Participants with hypothyroidism stable on hormone replacement will not be excluded from the study.

12. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137.
18. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
19. Has known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).
20. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.0. STUDY PLAN AND PROCEDURES

5.1. Study Schedule

Whilst on treatment participants will be reviewed every 3 weeks until disease progression, discontinuation of the study medication or withdrawal from the trial. When participants permanently discontinue pembrolizumab they will be required to attend a safety visit 30 days after their last dose. If a participant 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. Upon completion of the safety visit the participants will then be followed up every 12 weeks for survival status.

The schedule of study assessments (Table 2) summarises the trial procedures to be performed at each visit. 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 participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.). Such evaluations/testing will be performed in accordance with local regulations.

Table 3: Schedule of Study Assessments

Trial Period:	Screening	Treatment Cycles – Every 3 Weeks [1] to be repeated until participants discontinues trial treatment										End of Treatment [7]	Safety Follow-Up	Survival Follow-Up
Treatment Cycle:		Cycle 1			Cycle 2			Cycle 3	Cycle 4	Cycle 5	Cycle [*1]	*At discontinuation of IMP*	*30 days after last dose.*	*Every 12 weeks from safety follow up, up to 3yrs*
		Wk 0	Wk 1[2]	Wk 2[2]	Wk 3	Wk 4[2]	Wk 5[2]	Wk 6-8	Wk 9-11	Wk 12-14				
Visit Window (Days):	-28 to -1	± 3			± 3			± 3	± 3	± 3	± 3	± 3	± 3	± 7
Administrative Procedures:														
Informed Consent	x													
Inclusion/Exclusion Criteria	x													
Demographic, Medical & Treatment History	x													
Survival Status														x
Clinical Procedures / Assessments:														
Full Physical Exam	x													
Urinalysis	x													
PT and aPTT	x													
Pregnancy Test	x													
Adverse Events Review		x	x	x	x	x	x	x	x	x	x	x	x	
Radiation Toxicity Review			x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	
Con Medication Review	x	x	x	x	x	x	x	x	x	x	x	x	x	
Haematology & Biochemistry	x	x			x			x	x	x	x	x	x	
Vital Signs and Weight	x	x			x			x	x	x	x	x	x	
ECOG Performance Status	x	x			x			x	x	x	x	x	x	
Tumour Imaging	x									x[3]		x[4]		
Targeted Physical Exam		x			x			x	x	x	x	x	x	
PEMBROLIZUMAB		x			x			x	x	x	x			
RADIOTHERAPY		Over 3 days x[6]												
Tumour Biopsies/Archival Tissue Collection/Correlative Studies Blood:														
Archival Tumour Collection **(MANDATORY)**	x													
Diagnostic Metast'c Biopsy **(MANDATORY)**	x													
Tissue Biopsy **(OPTIONAL)**					x									
Research Blood Samples **(OPTIONAL)**		x			x			x	x	x	x[8]			

1 Cycles to be extended past cycle 5 for as long as applicable.
2. First 3/6 randomised to Pembrolizumab and Radiotherapy arm only.
3. Tumour imaging to be done every 12 weeks from the date of the 1st dose irrespective of delays in treatment cycles. Can be up to 7 days before visit to ensure results at the visit.
4. Only if no RECIST assessment has been completed in the last 6 weeks.
5. If the participant has been randomised to receive radiotherapy.
6. For participants randomised to radiotherapy this should be administered **between** the 1st and 2nd dose of pembrolizumab i.e. 24Gy in 3 fractions over 3 consecutive days
7. End of treatment visit assessments are only applicable if the participant comes off treatment between cycles.
8. A follow-up OPTIONAL Research Blood Sample can be taken at either time of response or progression (to be determined by treating clinician)

5.2. Administrative Procedures/Assessments

5.2.1. Informed Consent

It is the responsibility of the Principal Investigator/designee to provide each participant, prior to inclusion in the trial with full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. At least 24 hours should be allowed for the participant to consider their participation into the trial. Participants must be informed about their right to withdraw from the trial at any time. Written participant information must be given to each participant before enrolment. The written participant information is an approved participant information sheet (PIS) according to national guidelines.

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial. Consent must be documented by the participant by signing and dating the consent form along with the dated signature of the person delivering the consent discussion. If a translator is required to fully explain the trial they are also required to sign and date the consent form under the witness signature line. Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, having signed the delegation of responsibilities log, are permitted to gain informed consent from participants and sign the consent form. **All signatures must be obtained prior to the occurrence of any medical intervention required by the protocol.**

A copy of the signed and dated consent form should be given to the participant before participation in the trial. The original consent form should be stored in the site file with a copy also being placed in the participants' medical notes.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the REC approval/favourable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's or the participant's legally acceptable representative's dated signature. The informed consent will adhere to REC requirements, applicable laws and regulations.

5.2.2. Inclusion/Exclusion Criteria

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

5.2.3. Demographic Data, Medical History & 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(s) that are considered to be clinically relevant by the Investigator. Details regarding the disease for which the participant 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 participant's treatment history including:

-Prior and current details regarding disease status

-Review all prior cancer treatments including systemic treatments, radiation and surgeries

5.2.4. Prior and Concomitant Medications Review

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement. In addition they will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.

5.2.5. Survival Status

The investigator or qualified designee will assess the participant for survival status at specified visits as defined in the schedule of study assessment (Table 2) The assessment will include the participant status, details of anti-cancer treatments administered and if applicable details of participant death or details if participant has been lost to follow-up.

5.3. Clinical Procedures/Assessments

5.3.1. Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant for potential new or worsening AEs at specified visits as defined in the schedule of study assessments (Table 2) or more frequently if clinically indicated. Adverse experiences will be graded and recorded from randomisation until the Safety follow-up. (Any clinical abnormalities found between informed consent and randomisation will be documented on the medical history form). AEs will be graded according to NCI CTCAE Version 4.0 and LENT SOMA radiation toxicity grading system (see Appendices Section). Toxicities will be characterised in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 7

regarding the identification, evaluation and management of AEs of a potential immunological etiology. Please refer to Section 7 for detailed information regarding the assessment and recording of AEs.

5.3.2. Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings during this period should be recorded as medical history with the start date and end date if applicable. If a condition is ongoing and not currently stable the CTCAE grade should also be recorded on the eCRF.

5.3.3. Targeted Physical Exam

Targeted physical exams will be performed at every visit as per the schedule of study assessments (Table 2), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration

5.3.4. Vital Signs, Weight & Height

The investigator or qualified designee will take vital signs and weight measurements at screening, prior to the administration of each dose of trial treatment and the safety follow up as specified in the schedule of study assessments (Table 2). Vital signs should include temperature, pulse, weight and blood pressure. Height will be measured at screening only.

5.3.5. Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

Table 4: ECOG Performance Status

5.3.6. Pregnancy Tests

Female participants of childbearing potential should have a negative urine or serum pregnancy during screening and within 72 hours prior to randomisation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.3.7. Haematology, Clinical Biochemistry, PT and aPTT, Urinalysis & T3, FT4 and TSH

Laboratory tests will be performed at screening and every visit as defined in the schedule of study assessments (Table 2). Sample will be analysed by the local study site laboratory using standard methods for routine tests. The following variables (Table 4) will be measured:

Haematology	Chemistry	Urinalysis	Other
Haematocrit	Albumin	Blood	PT
Haemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	Total triiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)
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	C reactive Protein (CRP)
	Calcium		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	Creatinine Clearance		

Table 5: Laboratory tests

Laboratory tests for screening should be performed during the screening period and within 7 days prior to the randomisation and any abnormal results at screening should be documented on the medical history form. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed and signed by the investigator or qualified designee and found to be acceptable before the next dose of trial treatment is administered.

Participant treatment and overall management decisions will be based on local laboratory data. The date the sample was taken and result for each test must be recorded in the appropriate e-CRF. After randomisation

laboratory values that are considered to be of clinical concern must be recorded as an adverse event (AE) as described in Section 7.1.3. Unless explained by a clinical condition, these tests must be followed up at appropriate intervals until they reach a level deemed acceptable by the local PI.

5.3.8. Tumour Imaging and Assessment of Disease

Tumour response assessments will be carried out by physical examination, and tumour imaging by CT scan and/or MRI. CT scans are the preferred modality for measureable disease unless a participant has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. Tumour response will be assessed based on RECIST v1.1. (See Appendix 4) Baseline lesions must be selected before the start of the treatment. Tumour assessments by CT scan or MRI must be done at 12 weeks, and then 12 weekly thereafter until the end of treatment, progression or withdrawal of the study for any cause. RECIST scans can be performed up to and including 7 days before the participant is due for their next visit to allow the assessment of the scan to be available at the visit.

If no imaging/measurement of the lesion is completed at the requested time point, then the participant cannot be evaluated for progression. If only a subset of the lesions are measured, then this is also considered not evaluable, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time-point response.

Progression of disease should be verified by RECIST 1.1. In cases where progression is equivocal the participant should be re-imaged in 6 weeks. If repeat CT scans or MRI confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the participant is considered not to have progressive disease per RECIST v1.1 and the participant will return to the original imaging schedule. Confirmation of response is not required in these scans. Participants are allowed to continue on treatment beyond progression if there is clinical benefit at investigator's criteria.

Best overall response is determined once the participant has discontinued the study medication. It is defined as the best response designation, as determined by the investigator, recorded between the date of randomisation and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the best overall response assessment. The participant's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. The duration of objective response is measured from the time

measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that PD is objectively documented.

5.4. Tumour Biopsies, Archival Tissue Collection & Correlative Blood Studies

5.4.1. Archival Tumour tissue samples - MANDATORY

Archival tissue samples will be collected all participants that have consented and have available samples. FFPE tumour blocks will be requested and where it is not possible to obtain the whole block, 10-15 slides freshly prepared unstained 5 micron sections may be provided instead. Archival tumour blocks will be returned to source at the end of the study or, upon request, earlier if required for the participant's clinical management. Cut sections will be retained by the study team. These are archived samples and as such participating participants will not need to attend extra visits or undergo extra procedures.

5.4.2. Diagnostic Metastatic Tumour Biopsy - MANDATORY

All participants will be required to consent to a diagnostic metastatic tumour biopsy during screening to confirm the presence of metastatic disease. If the participant has already had a biopsy of a metastatic lesion (stage 4) there is no requirement to repeat this. In addition, participants will be also asked to consent for this biopsy to be used in the exploratory endpoint analysis as described in section 5.4.3.2.

5.4.3. Tumour Tissue Collection and Correlative Studies Blood Sampling - OPTIONAL

Exploratory immunological endpoints will be determined from peripheral bloods and from tumour biopsy samples. Participants will be asked to consent to both tumour biopsy and blood collection to take part in this exploratory research.

5.4.3.1. Peripheral Blood Analysis

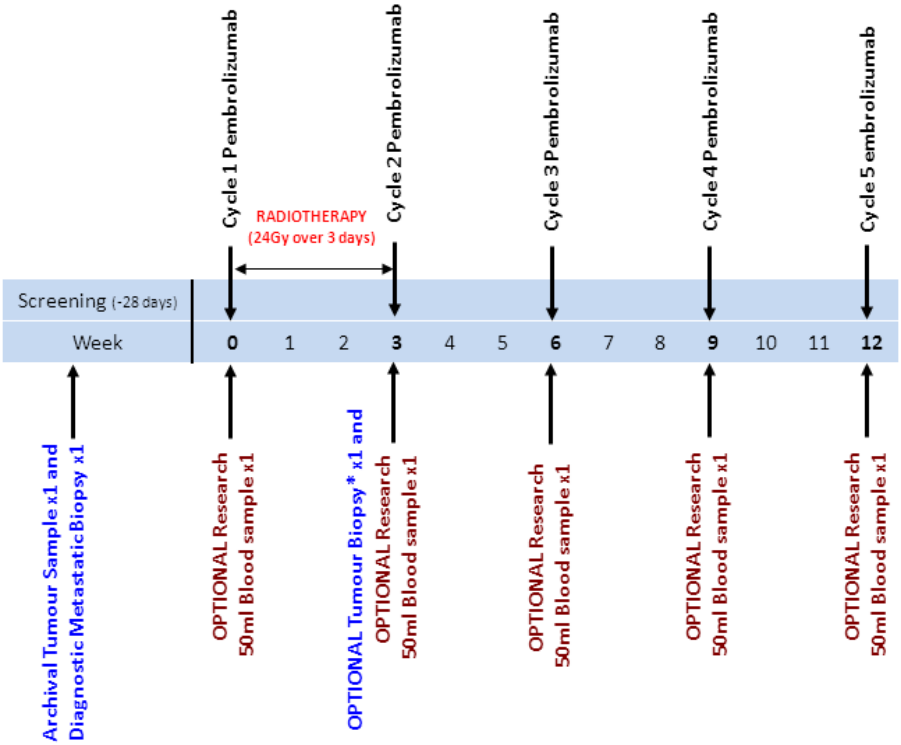
Consenting participants will be asked to provide an additional 50ml of blood at each visits prior to the administration of pembrolizumab for the first 12 weeks of treatment and a further blood sample at either time of response or progression (to be determined by the relevant clinician). Detailed processing procedures will be provided in a separate laboratory trial manual. These additional research bloods are considered to be research samples and will be retained under the PERM Trial ethics until used for analysis or destroyed following completion of the trial. All samples will be analysed to assess immune function in response to pembrolizumab ± radiotherapy. Assays to examine innate and/or adaptive immune functional response may include, for example, immunophenotyping, cytokine/chemokine arrays. For details, refer to the associated Trial Manual.

5.4.3.2. Tumour Biopsy Samples

For consenting participants post treatment biopsies will be taken at their second cycle of pembrolizumab ideally from the same lesion that was used to confirm metastatic disease at screening. If this biopsy was from a

lesion that had been irradiated then if possible an additional biopsy outside the radiotherapy field should also be collected. Biopsies will be core or punch biopsies. Detailed processing, handling and shipping procedures for these biopsies will be provided in a separate laboratory trial manual. These additional tissue biopsies are considered to be research samples and will be retained under the Manchester Cancer research Centre.

Tumour biopsy tissue collected from patients at baseline & during treatment will be examined to assess the tumour microenvironment in response to therapy. Tumour may be used in, for example, multi-colour immunohistochemistry and RNA sequence analysis to investigate TIL infiltration & expression of known tumour-associated antigens. For details, refer to the associated Trial Manual.



*Ideally from the same lesion that was used to confirm metastatic disease at screening. If this biopsy was from a lesion that had been irradiated then if possible an additional biopsy outside the radiotherapy field should also be collected.

Figure 3: Blood and tumour sampling schedule.

5.4.4. Chain of Custody of Biological Samples

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

RM-CTU will keep overall oversight of the entire lifecycle through internal procedures and monitoring of study sites. Tissue samples retained for further use will be registered with the Manchester Cancer Research Centre and research blood samples retained for further use under the PERM trial ethics.

5.5. Total Blood Volume

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

	Sample volume (mL)	No. of samples	Total volume (mL)
Routine Haematology	6	18[1]	108
Routine Clinical chemistry	8	18[1]	144
		Total Routine	**252**
Peripheral Blood Sampling (Optional)	50	5	250
		Total:	**502**[2]

Table 6: Total Volume of blood
To be drawn from each trial participant for the duration of the trial; calculations based on 1 year on treatment, plus end of treatment visit and 30 days post end of treatment safety visit (where applicable).

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

2 *The total volume of blood drawn from each trial participant for the duration of the trial depends on the time to progression for each participant.*

6.0. STUDY TREATMENT

6.1. Trial Treatment

Participants will be randomised to receive either pembrolizumab alone or pembrolizumab and high dose radiotherapy. **Images will be reviewed centrally by the Radiotherapy Quality Assurance team to ensure consistency in reviewing images[2].** The doses to be administered are:

1. **Pembrolizumab 200mg** every 3 weeks by intravenous infusion until progression, intolerance or withdrawal.
2. **High dose radiotherapy**, 24Gy in 3 fractions over 3 consecutive days to a deposit of melanoma after the first and before the second pembrolizumab infusion is given. Radiotherapy will be targeted at one or more suitable lesions (maximum of 3). At least one of the lesions will be left un-irradiated and will serve as the index lesion for subsequent evaluation.

6.2. Standard of Care Treatment – Radiotherapy[3]

6.2.1. Timing of radiotherapy

Radiotherapy (RT) should begin after the first and before the second dose of pembrolizumab. For participants due to receive RT to their internal metastases, radiotherapy planning should commence as soon as they have been recruited into the study to allow adequate time for prospective case reviews and feedback of radiotherapy plans.

6.2.2. Sites suitable for radiotherapy

Participants must have at least two sites of metastatic disease from their primary melanoma. One of the metastatic sites will serve as the index lesion for subsequent assessment of the abscopal effect and should not receive RT. A maximum of 3 Lesion(s) can be irradiated and must be at least 1 cm but no more than 5 cm in size, as measured by its widest dimension on CT scan (for internal lesions) or on clinical inspection (for superficial lesions). Metastatic lesions must not be an intra-cranial, intra-ocular lesion or intra-mesenteric lesion to receive RT. The choice of the lesion(s) to be irradiated will be left to the discretion of the attending oncologist, taking into account the Organs At Risk (OAR) normal tissue tolerance constraints associated with irradiating each lesion, and importantly the ease of obtaining pre and post radiotherapy biopsies from the index lesion(s) for the associated translational study. For example, if there is one internal and one superficial

[2] Patients will be consented to allowing their images to be sent outside of their institution. Please refer to the current Radiotherapy Imaging Manual for further guidance

[3] Further information on this section is available in the current Radiotherapy QA Guidelines Manual which will be provided by the trials office

lesion, it may be preferable to irradiate the internal lesion so that biopsy can be taken from the superficial lesion pre and post irradiation.

6.2.3. Radiotherapy techniques

Appropriate radiotherapy techniques should be used to ensure dose coverage of the irradiated lesions and to respect the organs at risk constraints as specified (see the current Radiotherapy QA Guidelines Manual for further information). It is envisaged that the majority of metastases to be irradiated will be those on the skin and in the superficial nodes, in which case either electron or 3D conformal radiotherapy can be used. The attending oncologist may choose to irradiate metastases in the liver, lung, para-vertebral region or deep seated nodes. In these cases complex IMRT or SBRT techniques may be appropriate and will be permitted.

As the radiotherapy fractionation schedule employed for this trial, 24Gy/3# is not a recognised palliative dose for melanoma at present, and giving it concurrently with Pembrolizumab is not the standard of care, maintaining the safety of patients recruited into the study should be our absolute priority. Therefore only CtE SABR centres with established clinical experience in irradiating sites close to critical organs at risk (such as mediastinal lymph nodes, thoracic oligometastases, hepatic metastases and paravertebral soft tissue metastases) in their routine clinical practice should irradiate these targets in this trial. Patient recruited at sites which are non-SARB CtE centres, patients will still receive pembrolizumab locally at the site but may be irradiated at other CtE centre.

It is anticipated that for centres with limited experience in delivering SABR, cutaneous metastases or superficial lymph nodes would be the most common targets for radiotherapy in this study.

6.2.4. Radiotherapy Dose

Lesion(s) will be irradiated to the dose of 24Gy in 3 fractions delivered over 3 consecutive days in cycle 1.

6.2.4.1. Radiotherapy Quality Assurance

The QA programme for the study will be designed and implemented by the NCRI Radiotherapy Trials QA (RTTQA) Group. The programme will compose pre-trial and on-trial QA components to ensure adherence to protocol requirements.

6.2.4.2. Pre-Accrual QA

1. Facility Questionnaire

Participating centres will be asked to complete a facility questionnaire on general and trial specific questions on recent independent audit history, equipment, software and techniques to be used for the trial.

2. Process Document

Participating centres will be asked to submit a process document, detailing the entire radiotherapy planning chain for all of the radiotherapy techniques to be used by the site in this trial.

3. Dummy run

Participating centres may be asked to export a centre participant planned and treated according to the trial protocol. The outlining and planning for this case will be independently reviewed in terms of protocol adherence.

6.2.4.3. IMRT and SABR use for the trial

All centres intending to use IMRT techniques must be IMRT credentialed through the RTTQA group or accepted equivalent. Further information on this process is available at www.rttrialsqa.org.uk. Those centres intending to use SABR techniques, to irradiate internal metastatic lesions, must have completed the UK SABR audit.

6.2.4.4. On Trial Quality Assurance

1.***Plan Assessment Form:*** An electronic copy of the plan assessment form containing key treatment details must be completed and submitted for all participants. These will be reviewed prospectively for all participants.
2.***Export of electronic data:*** structure sets, dose and plan data for all recruited participants to be exported to the RTTQA group.
3. ***Prospective (real time) review:*** For participants with internal metastases: all cases will be participant to prospective review of outlining and planning.
4. ***For all other cases:*** prospective review of the Plan Assessment Form only.

Non-compliance of outlining or planning for the trial will be highlighted to the Chief Investigator (CI) and local Principal Investigators (PIs) and appropriate action taken.

6.3. Trial Treatment - Pembrolizumab

6.3.1. 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 current Investigator's Brochure (IB).

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection

Table 7: Product Description

6.3.2. Product Preparation

The powder for infusion is a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use Type I glass vial containing 50mg of pembrolizumab. The product is preservative-free, white to off-white powder and free from visible foreign matter.

The powder will need to be reconstituted with 2.3 mL sterile water for injection (WFI) to yield a 2.4 mL solution containing 25 mg/mL of pembrolizumab at pH 5.2 – 5.8. Each vial contains an excess fill of 10 mg (equivalent to 0.4 mL of reconstituted solution) to ensure the recovery of label claim of 50 mg MK-3475 per vial (equivalent to 2.0 mL of reconstituted solution).

6.3.3. Storage and Handling

6.3.3.1. Storage

The original powder for infusion should be stored at refrigerated conditions (2 – 8°C). Prior to reconstitution, the vial can be out of refrigeration (temperatures at or below 25°C (77°F)) for up to 24 hours.

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

6.3.3.2. Handling

Infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent and the final concentration of pembrolizumab in the infusion solutions should be between 1.0 mg/mL and 10.0 mg/mL. If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent

(5% dextrose) is permissible, Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Pembrolizumab should **NOT** be mixed with other diluents unless instructed by the sponsor in writing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed. Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the reconstituted drug product between the pharmacy and the clinic.

DO NOT:

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

Further details on the preparation of the drug product can be found in the IMP handling guidelines.

At each site the Investigator / designee e.g. pharmacist is responsible for ensuring that all trial medication is stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Trial medication may not be used for any purpose other than that stated in the protocol.

6.3.4. Supply, Packaging and Labelling Information

Pembrolizumab will be supplied by Merck, Sharp and Dohme (MSD) as lyophilized powder for injection. Pembrolizumab will be packaged, labelled and delivered to the participating sites by MSD. The IMP will be supplied specifically for the trial and should not be used for any other purpose than that stated in this protocol. The drug will be labelled in accordance to Good Manufacturing Practice Annex 13. As a minimum the labels will include the following information;

a. name of the Sponsor

b. name of drug, dose, quantity of dose units and route of administration

c. batch number to identify the contents and packaging operation

d. blank space for recording the trial ID

e. directions for use

f. PI name

g. protocol number

h. storage conditions

i. expiry date

j. “for clinical trial use only”

k. “keep out of reach of children”

6.3.5. Returns and Reconciliation

The Investigator/designee is responsible for keeping accurate accountability records for pembrolizumab including the amount dispensed to and returned for each participant and the amount remaining on site at the conclusion of the trial.

Upon completion or termination of the study, it is the Investigators/designee responsibility to ensure all unused and partially used trial medication will be destroyed at the site per local guidelines and provide appropriate records of disposal to the sponsor with a copy being stored in the pharmacy site file.

6.3.6. Dose Selection

The rationale for selection the dose to be used in this trial is provided in Section 1.0 – Background and Rationale. All randomised participants will receive pembrolizumab given as 200mg every 3 weeks by intravenous infusion until progression, intolerance or withdrawal from the trial.

6.3.7. Administration of Pembrolizumab

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

6.3.8. Dose Modification

Pembrolizumab will be withheld for drug-related haematological and non-haematological of toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 7 below.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhoea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.

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

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

If the toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued at the discretion of the investigator. Participants with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see section 7.

Participants 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.

6.3.9. Timing of Dose Administration

Pembrolizumab will be administered on an outpatient basis on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the schedule of study assessments (Table 2).

Pembrolizumab will be administered via a 0.2-5µm in-line filter as a 30 minute IV infusion (treatment cycle intervals or infusion length may be increased due to toxicity as described in Section 6.3.3). Due to the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). In addition, infusion length may be increased due to toxicity as described in Section 6.3.3.

6.3.10. Trial Blinding/Masking

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

6.4. Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the trial. If there is a clinical indication for one of these or other prohibited medications or vaccinations then discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the CI/designee/RM-CTU. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on trial therapy schedule requires the mutual agreement of the Investigator, CI/ designee, and the participant.

6.4.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the standards of medical care. All concomitant medication will be recorded on the e-case report form (e-CRF) including all prescriptions, over-the-counter (OTC), herbal supplements, and IV medications and fluids. All concomitant medications received within 28 days before the first dose and until the safety follow up visit should be recorded.

6.4.2. Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the screening and treatment phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Radiotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Palliative radiotherapy for symptom control
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.

Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the CI/designee.

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

6.5. Rescue Medications & Supportive Care

6.5.1. Supportive Care Guidelines

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

6.5.1.1. Diarrhoea:

Participants 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 participants, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

- In participants with severe enterocolitis (Grade 3):
    - Pembrolizumab will be ***permanently discontinued*** and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
- In participants with moderate enterocolitis (Grade 2):
    - Pembrolizumab should be ***withheld*** and anti-diarrhoeal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or

less, corticosteroid taper should be started and continued over at least 1 month. Guidelines for continuing treatment with pembrolizumab can be found in Appendix 5.

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

6.5.1.2. 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. Participants should be strongly encouraged to maintain liberal oral fluid intake.

6.5.1.3. Anti-infectives:

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

6.5.1.4. Immune-related adverse events:

Please see Section 6.5.2 below regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

6.5.1.5. Management of Infusion Reactions:

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 **Mild reaction; infusion interruption not**	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of	None

indicated; intervention not indicated	the investigator.	
Grade 2 **Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs**	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant 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 participant should be pre-medicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Participant may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 **Grade 3:** **Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)** **Grade 4:** **Life-threatening; pressor or ventilatory support indicated**	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalisation may be indicated. Participant is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Table 8: below shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab.

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

Immune-related Adverse events (IrAEs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. IrAEs may be predicted based on the

nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Participants who develop a Grade 2 or higher irAE should be discussed immediately with the CI/designee.

Recommendations to managing irAEs not detailed elsewhere in the protocol;

irAE	Withhold/Discontinue pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	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.
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.
Please Note: If an irAE does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of pembrolizumab, study therapy discontinuation should be considered after discussion with a Merck Clinical Director via the RM-CTU trial manager..		

Table 9: General Approach to Handling irAEs

Details for managing specific irAEs are summarised below:

Immune-mediated pneumonitis

Monitor participants for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging. Exclude other causes of pneumonitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis.

Immune-mediated colitis

Monitor participants for signs and symptoms of colitis. Exclude other causes of colitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, 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 participants for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis. Exclude other causes of hepatitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.

Immune-mediated nephritis

Monitor participants for changes in renal function. Exclude other causes of nephritis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold pembrolizumab for moderate (Grade 2), and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) nephrits.

Immune-mediated endocrinopathies

Monitor participants for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency). Exclude other causes of hypophysitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold pembrolizumab for moderate (Grade 2), withhold or discontinue pembrolizumab for severe (Grade 3) and for life-threatening (Grade 4) hypophysitis.

Monitor participants 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 participants receiving pembrolizumab and can occur at any time during treatment; therefore, monitor participants 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. Administer corticosteroids, withhold pembrolizumab for severe (Grade 3) hyperthyroidism, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hyperthyroidism. Treat symptoms of hyperthyroidism as appropriate. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. For participants with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that resolved and is controlled with hormone replacement, continuation of pembrolizumab may be considered.

Other immune-mediated adverse events

Across clinical studies with pembrolizumab in approximately 5000 participants, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of participants: uveitis and severe skin reactions.

In addition a set of irAEs have also been classified as immune-related events of clinical interest (irECI) a full list of these can been found in events of clinical interest guidance in Section 7.4. Participants 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 of the event to the Sponsor who will in turn notify MSD. If the irECI is determined to be associated please refer to Appendix 4 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 participant. Any additional questions of the collection or information on management of irECIs should be directed to the Sponsor.

6.5.3. Supportive Care Guidelines for Pneumonitis

Participants 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 participant is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 10.

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 participant 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 participant

		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.

Table 10: Recommended Approach to Handling Pneumonitis

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

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

6.6. Diet/Activity/Other Considerations

6.6.1. Diet

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

6.6.2. Contraception

Pembrolizumab may have adverse effects on a foetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either, two barrier

methods or a barrier method plus a hormonal method to prevent pregnancy. Participants should start using birth control from screening throughout the study period up to 120 days after the last dose of study therapy. Male participants with partners of child bearing potential will also be required to agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an oestrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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

6.6.3. Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. If the outcome of the pregnancy is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) this will be reported to RM-CTU without delay and **within 24hours of becoming aware of the event to the Sponsor**. 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. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to RM-CTU and followed as described above and in Section 7.

6.6.4. 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, participants who are breast-feeding are not eligible for enrolment.

6.7. Treatment of Overdose of IMP

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by over 20%. Please see section 7.7 for definitions and reporting procedures.

6.8. Safety Follow-Up Visit

The mandatory safety follow-up visit should be conducted 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the safety follow-up visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

6.9. Survival Follow-up

Once a participant experiences confirmed disease progression or starts a new anti-cancer therapy, the participant moves into the survival follow-up phase. Participants will not be expected to attend clinic visits during the survival follow-up but information on the participant's status will be gathered by the research team from the participant's medical notes, the participant's GP and telephoning the patients directly is applicable. The survival period will continue every 12 weeks for 3 years until death, lost to follow up, withdrawal of consent or the end of the study.

6.10. Permanent Discontinuation of Trial Medication and Withdrawal from the Study

6.10.1. 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

  Note: For unconfirmed radiographic disease progression, please see Section 5.3.8

  Note: A patient may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences as described in Section 6.2
- Intercurrent illness that prevents further administration of treatment
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons

Trial patients will not be replaced or enrolled more than once. The primary reason for discontinuation should be recorded on the eCRF. 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 assessments (Table 2). After the end of treatment, patients will continue to be assessed for AE and SAE monitoring until completion of the safety follow up visit.

6.11. Withdrawal from the Study

Withdrawal from the study refers to discontinuation of both trial medication and future study visits / assessments; this can occur at any time according to the following reasons:

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

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. When a patient discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at that time should be followed in accordance with the safety requirements outlined in Section 7. Patients who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment dependant on the investigators clinical judgement. After discontinuing treatment following assessment of CR, these patients should return to the site for a safety follow-up visit and then proceed to the survival follow-up period of the study as described in the schedule of study assessments (Table 2).

7.0. PHARMACOVIGILANCE

7.1. Definition of an Adverse Event (AE)

An AE is defined as any untoward medical occurrence (including deterioration of a pre-existing medical condition) in a patient or clinical trial patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or disease temporally associated with the use of a medicinal product or protocol-

specified procedure, whether or not considered related to the medicinal product or protocol-specified 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 the pembrolizumab and/or radiotherapy, is also an adverse event. Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time. Adverse events may also occur in screened patients during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

7.1.1. Disease Progression

Disease progression of the cancer under study is not considered an adverse event unless it results in hospitalisation or death.

7.1.2. New Cancers

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

7.1.3. Abnormal Laboratory Test Results

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

7.1.4. Pregnancy and Lactation

Pregnancy and lactation are not considered adverse events, however these events should be reported to the RM-CTU following guidance in section 7.2.2.

7.2. Assessing and Recording Adverse Events

All adverse events will be recorded from randomisation until completion of the safety follow-up in the eCRF. AEs will be followed up until resolution, stability or it is clinically feasible to do so. The final outcome must not only be documented in the eCRF but also recorded in the participants medical records. Serious Adverse Events

(SAEs) will also be recorded throughout the study until the safety follow-up visit. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.5

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 eCRF. If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to pembrolizumab, the Investigator should notify the RM-CTU.

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

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

In addition, any adverse events occurring during the screening period that are a result of a protocol-specified intervention should also be recorded according to guidelines for standard AE reporting.

7.2.1. Evaluating Adverse Events

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

7.2.1.1. Determining AE Severity and Grade

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

Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation or hospitalisation indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

Table 11: AE severity

7.2.1.2. Determining AE Causality

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc.) and must provide his/her opinion of the causal relationship between each AE and IMP. 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.

Table 12: Determining causality relationship of AE to an IMP

7.2.2. Reporting of Pregnancy and Lactation

It is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), including the pregnancy of a male patient's female partner 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 and female partners of male 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 stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24hours of becoming aware of the event to the Sponsor by Fax 0208 915 6762 who will also inform MSD.

7.3. Definitions of Serious Adverse Events (SAE)

An SAE is an AE occurring during any part of the study that meets one or more of the following criteria:

- 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]
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalisation[2];
- Is a congenital anomaly/birth defect(in offspring of patient taking the product regardless of time to diagnosis);
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event.
- Is an important medical event that may not result in death, not be life threatening, or not require hospitalisation but may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardise the patient and require medical or surgical intervention to prevent such an outcome.

[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).*

7.4. Definitions of Evidence of Clinical Interest (ECI)

Selected non-serious and serious adverse events can also be classified as Events of Clinical Interest (ECI) and must be reported as described in section 7.6.

The following ECIs for this study must be reported to the Sponsor within 24hrs of learning of the event:

1. An overdose of pembrolizumab, as defined in Section 7.7 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.

NOTE: These events will also be reported to MSD by the sponsor.

3. Any AEs identified in the below table can be classified as immune-related events of clinical interest. A detailed narrative of the event should be recorded as an ECI as described in section 7.6:

Pneumonitis - ***(deemed as an ECI if ≥ Grade 2 to be reported through the AE reporting pathway)***		
Acute interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis
Colitis - ***(deemed as an ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE to be reported through the AE reporting pathway)***		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotising colitis	Diarrhoea	
Endocrine - ***(deemed as an ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE and will be reported through the AE reporting pathway)***		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine ***(deemed as an ECI and will be reported through the AE reporting pathway)***		
Type 1 diabetes mellitus (if new onset)		
Hematologic - ***(deemed as an ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE and will be reported through the AE reporting pathway)***		
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 - ***(deemed as an ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE and will be reported through the AE reporting pathway)***		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALTand/or AST)
Infusion reactions - ***(deemed as an ECI for any grade to will be reported through the AE reporting pathway)***		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic - ***(deemed as an ECI for any grade and will be reported through the AE reporting pathway)***		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndromw		
Ocular - ***(deemed as an ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE and will be reported through the AE reporting pathway)***		
Uveitis	Iritis	
Renal - ***(reported as ECI for ≥ Grade 2 and will be reported through the AE reporting pathway)***		
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 - ***(deemed as an ECI for any grade and will be reported through the AE reporting pathway)***		
Dermatitis exfoliate	Erythema multiforme	Stevens-Johnson Syndrome
Toxic epidermal necrolysis		
Skin - ***(deemed as an ECI for ≥ Grade 3 and will be reported through the AE reporting pathway)***		
Pruritus	Rash	Rash generalised
Rash maculo-papular	Any rash clinical significant in the physicians judgement.	
Other - ***(deemed as an ECI for any grade and will be reported through the AE reporting pathway)***		
Myocarditis	Pancreatitis	Percarditis
Any other grade 3 event which is considered immune-related by the physician.		

Table 9: Immune related AEs considered ECIs.

Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.5. Reporting of SAEs

Any SAE whether or not related to pembrolizumab, occurring from randomisation until 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, must be reported on an SAE report form within 24hours to the Sponsor of the PI or designee becoming aware of the event to the via Fax **0208 915 6762 or email to perm.trial@rmh.nhs.uk**. It will be the responsibility of the Sponsor to also inform MSD at the same time. All SAEs regardless of causality, pregnancy (as per section 7.2.2) or overdose (as per section 7.7) should be documented and each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4 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 using a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. 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 pembrolizumab that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor who will also inform MSD.

7.5.1. 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 electronic case report form (eCRF).

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 according to the trial protocol, is also exempt from being reported as an SAE.

7.5.2. 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 current version of the Investigator Brochure section on Reference Safety Information. If updated versions of the Investigator Brochure are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.

7.6. Reporting of ECIs

An ECI, irrespective of etiology or 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 eCRF. ECIs as described in Section 7.4 should be reported within 24 hours of the PI/designee becoming aware of the event to the sponsor. Please refer to the current Investigator Brochure for further information in the Reference Safety Information section. All other ECIs described in Table 10 will be reported as per adverse event reporting pathways.

7.7. 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% over the prescribed dose. In the event of overdose the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) should be recorded on the AE eCRF and documented in the patients' medical records. The AE should also be reported as a serious adverse event, even if no other seriousness criteria are met. If an overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is again recorded as an AE on the eCRF and reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose either SAE or ECI must be reported within 24 hours of the PI or designee becoming aware of the event to the Sponsor via Fax 0208 915 6762 who will also inform MSD.

7.8. Definition of a Serious Adverse Reaction (SAR)

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

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

A SUSAR is any SAR that is NOT consistent with the applicable product information as set out in the current Summary of Product Characteristics (SPC).

7.10. Reporting of SUSARs

The Investigator and local study team will rapidly report all SUSARs to the Sponsor within 24 hours of becoming aware of the event. The Sponsor will ensure that SUSARs are notified to the appropriate Regulatory Authority, the relevant Research Ethics Committee (REC)/Regulatory Authority (RA), MSD, the Sponsor and the participating Principal Investigators as appropriate in accordance with regulatory requirements and within the required timelines. Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

7.11. Annual Reporting of Serious Adverse Events

Annual reports will be submitted to the RA and REC by the Sponsor in accordance with all applicable global laws and regulations. Copies will be forwarded to the Sponsor and Investigators.

7.12. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health. USMs may be taken without prior authorisation from the competent authority. The Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) must be notified within three days of such measures being taken. Should the site initiate a USM, the Investigator must inform RM-CTU either by:

Email: Perm.trial@rmh.nhs.uk

Telephone: 0208 915 6666

Fax: 0208 915 6762

The notification must include:

- the date of the USM
- who took the decision; and
- why action was taken

RM-CTU will then inform the Sponsor who will notify the MHRA and the REC immediately and in writing within three days of USM initiation. RM-CTU will distribute the response and any subsequent amendments to the trial sites.

CI Contact Details:

Name: Dr James Larkin

Address: Renal and Melanoma Unit

The Royal Marsden NHS Foundation Trust

203 Fulham Road

London SW3 6JJ

Tel: 0208 915 6666 Fax: 0208 915 6762

Email: perm.trial@rmh.nhs.uk

8.0. STATISTICAL ANALYSIS

8.1. Statistical Analysis Plan Summary

This is a multicentre, open label, randomised phase II study to assess the efficacy of pembrolizumab alone and in combination with high dose radiotherapy. Patients will be randomised into either arm of the study in a 1:1 ratio and stratified to take account of their baseline LDH and previous anti-CTLA4 treatment.

8.2. Sample Size and Power Considerations

The sample size of this study was calculated using a 2-sided α of 5%; power of 80%; RECIST response rate in the pembrolizumab arm is 30%; RECIST response rate in the pembrolizumab and radiotherapy arm is 50%. The study will randomise 234 patients in total (210 minimally required for statistical power calculation purposes, 105 patients in each arm; 20 additional patients to account for potential drop outs – an expected drop out rate of 10%) over 18 months i.e. 11-12 patients per month in approximately 15 to 24 UK centres. In the event that enrolment is slower than expected the Trial Steering Committee will consider adding additional UK sites. Patients enrolled in the trial are expected to be recruited from the routine clinics of the participating centres.

8.3. Randomisation

Patients will be randomised in a 1:1 ratio to receive pembrolizumab alone or pembrolizumab in combination with radiotherapy using random permuted blocks within strata to take account of their LDH level at baseline and previous anti-CTLA4 treatment.

Randomisation of enrolled patients will be stratified based on the following parameters;

1. **LDH (below or within normal range / above upper limit of the normal range) and**
2. **Previous anti-CTLA4 treatment (yes/no)**

The randomisation number is a unique number. Patients will be identified using the number generated by the database which will become their unique identifier throughout the study and in all future correspondence..

8.4. Data Analysis

The clinical data will be entered and stored in the PERM electronic database. Statistical analysis will be conducted using STATA software version 13.

8.4.1. Analysis populations

The efficacy results of the trial will be analysed on an intention to treat (ITT) basis. The ITT population is defined as all patients randomised in the study and are analysed as randomised for response rate, PFS and OS.
The safety data will be analysed by treatment received, irrespective of randomisation, in patients who received at least one treatment dose. Patients withdrawn prior to the first treatment dose will be excluded.

In addition, after 50% of the patients have been randomised and are evaluable for the primary endpoint an interim analysis will be carried out to assess the difference between the two trial arms. In the event that both arms showed a RECIST response rate of 30% when approximately 120 patients are evaluable then it will be judged unlikely that the pembrolizumab and radiotherapy arm will show a RECIST response rate of 50% relative to the 30% RECIST response rate in the pembrolizumab only arm at the end of the trial and the trial will be stopped.

Furthermore when 50% of the patients have been recruited this will be reviewed by the independent members of the TSC only, within a closed session. They will also decide if the results of the analysis needs to be released to the TMG, and whether any changes to the study should be implemented in terms of its continuance

8.4.2. Study Endpoints

Primary Endpoint:

The difference in RR between the treatment arms will be calculated at 12 weeks post treatment start in the ITT population. This will be presented using the percentage of patients, including 95% confidence intervals, who achieve CR or PR according to the RECIST v1.1 criteria in each treatment group. Analysis of the primary endpoint will be carried out when all patients have completed treatment and 12 week follow-up assessments.

Secondary Endpoints:

- To determine RR at 6 months post treatment start. This is defined as the percentage of patients achieving confirmed PR or CR as per RECIST v1.1 in the ITT population.
- To measure individual lesion response assessment every 12 weeks taking account of within patient data. Individual lesion response for each patient will be measured over time by assessing PR, CR or SD as per RECIST v1.1 at each time point.
- Toxicity will be graded according to CTCAE version 4.0 and LENT SOMA radiation toxicity grading system after 12 weeks of treatment.
- PFS will be calculated at 1, 2 and 3 years from treatment start until PD or death from any cause.

Patients alive and progression free will be censored at 1, 2 and 3 years, and those patients who are lost to follow-up, withdrawn from follow-up will be censored at the date of last assessment whichever is sooner, respectively.

- OS will be calculated from treatment start until date of death from any cause. Patients, in whom no death is recorded, will be censored at the date they were last seen alive.

Exploratory Endpoints:

Peripheral blood analysis

Peripheral blood collected from patients at baseline, during and follow-up of treatment will be analysed to assess immune function in response to pembrolizumab ± radiotherapy. Assays to examine innate and/or adaptive immune functional response may include, for example, immunophenotyping, cytokine/chemokine arrays. For details, refer to the associated Trial Manual.

Tumour Biopsy samples

Tumour biopsy tissue collected from patients at baseline & during treatment will be examined to assess the tumour microenvironment in response to therapy. Tumour may be used in, for example, multi-colour immunohistochemistry and RNA sequence analysis to investigate TIL infiltration & expression of known tumour-associated antigens. For details, refer to the associated Trial Manual.

8.5. Planned method of analysis

Continuous data will be summarised using means, standard deviations, medians, minimum and maximum values and where appropriate 95% confidence intervals. Nominal and ordinal categorical data will be summarised using the number of observations and percentages. All significance tests will be two-sided using an overall alpha level of 5%. It is anticipated that adjustment will be made for repeated significance testing using a Bonferroni correction specifically for all secondary endpoints.

Primary Endpoint:

- The RR 12 weeks post treatment will be summarized as the percentage (including 95% confidence intervals) of responders and will be compared between treatment arms using the chi-squared test for proportions.

Secondary Endpoints:

- The RR at 6 months will be summarized as a percentage (including 95% confidence intervals) of responders and will be compared between treatment arms using the chi-squared test for proportions.

- To measure individual lesion response assessment every 12 weeks within each patient using McNemar's test of paired proportions between time points.
- The proportion of patients experiencing grade 3-5 toxicity will be compared on a regimen basis using the chi-squared test. Fishers exact test will be used when expected cell frequencies are <5.
- PFS and OS at 1, 2 and 3 years, respectively, will be calculated using Kaplan-Meier methods. Median PFS and OS with associated 95% confidence intervals will be presented by treatment and compared using the log rank test. Cox Proportional hazards regression model analysis will be used to calculate the hazard ratio between treatments along with its 95% confidence intervals and will be adjusted for other identified prognostic factors in a multivariate setting.

Exploratory Endpoints:

- Continuous exploratory data will be summarised using means, standard deviations, medians, minimum and maximum values attaching 95% confidence intervals where appropriate. Categorical data will be summarised using frequencies and proportions, attaching confidence intervals where necessary.

8.5.1. Safety Review Meeting

To ensure the safety of the patients an assessment of toxicity of the first 6 randomised to receive both pembrolizumab and radiotherapy will be performed when they have completed 12 weeks of treatment. A listing of AEs will be produced for these patients identifying toxicity grades after they have completed 12 weeks of treatment.

8.6. Deviations from the Statistical Plan

Statistical methods to handle deviations from protocol (e.g. changes in final sample size) will be described in the analysis plan. The analysis plan of the handling and analysis methods of secondary variables may be updated following review of data during the study. The statistical analysis plan will be finalised / approved prior to the analysis. Deviations in implementation of the finalised analysis plan will be documented for affected results in the clinical study report.

8.7. Early Discontinuation of the Study

An interim analysis will be carried out when approximately 120 patients (50%) are evaluable for the primary endpoint, this will allow for the early termination of the trial should there be no difference between the two arms, respectively. No formal stopping rules are planned either for efficacy, futility or toxicity since this study is similar to routine standard of care with the addition of radiotherapy. The

Trial Steering Committee will monitor trial progress including for significant safety / toxicity issues should they arise.

9.0. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1. Good Clinical Practice

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

9.2. Research Ethics Committee (REC)/Regulatory Authority (RA)

9.2.1. Initial Approval

Before starting the trial, the protocol, patient information sheet, consent form, any other written information that will be provided to the patients and any advertisements that will be used and details of any patient compensation must be approved by the Royal Marsden/Institute of Cancer Research joint Committee for Clinical Research. Once approved, the study will then be submitted to the relevant Ethics Committee for their review and approval.

Prior to the shipment of IMP and the enrolling any patients the Investigator at each site is responsible for any site specific assessments and obtaining local R&D approval for the study . All participating sites will be required to sign an agreement with RM-CTU which includes requirement to sign and adhere to the trial protocol.

9.2.2. Approval of Amendments

Any protocol amendment should be agreed with the trial management group (TMG) and be approved by the sponsor prior to submission and review by the relevant Ethics Committee. Once favourable opinion from IEC has been obtained the amendment can be distributed to sites and implemented. It is the responsibility of the Principal Investigator to submit amendment to their R&D department for R&D approval Amendments requiring REC approval may be implemented only after a copy of the REC/RA'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 REC/RA approval. However, in this case, approval must be obtained as soon as possible after implementation.

9.2.3. Annual Safety Reports and End of Trial Notification

It is the responsibility of the sponsor to submit the Development Safety Update Report annually to the MHRA/ REC on the anniversary of the studies MHRA/REC approval. This will facilitate the authorities continuing review

of the study. These authorities will also be informed of the end of the study by the sponsor within 90 days of the trial completion. Copies of these reports will also be held within the main trial master file.

9.3. Regulatory Authority Approval

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

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

The Sponsor will notify the MHRA and REC in writing of any serious breaches of:

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

b. The protocol

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

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

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

b. The scientific integrity of the trial.

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

9.5. Insurance and Liability

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

9.6. Contact with General Practitioner (GP)

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

9.7. Patient Confidentiality

9.7.1. Patient Confidentiality and Data Sharing

The Principal investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Act 1998. In all study correspondence submitted to the RM-CTU (apart from signed consent forms) all participants will be identified by their initials and unique Trial Reference study number only which will be used in all e-CRFs or other documents submitted to the RM-CTU.

In compliance with GCP guidelines, it is required that the investigator and institution permit authorised representatives of the sponsor and of the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient. In addition to this, anonymised images will be sent via a secure network to the approved Radiotherapy Quality Assurance team.

9.7.2. Pharmacogenetics Confidentiality

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

9.8. Data collection and documentation

It is the Investigator's responsibility to ensure that all relevant data is clearly recorded in the medical records. The Investigator must allow the RM-CTU direct access to relevant source documentation for verification of data entered into the e-CRF, taking into account data protection regulations. The clinical data should be recorded in the e-CRF and the must be verifiable by the source data.

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

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

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

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

9.9. End of Trial

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

10.0. DATA AND STUDY MANAGEMENT

10.1. Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as original documents, data, and records e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.2. Language

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

10.3. Data Collection

The medical records/medical notes should be clearly marked and to allow for easy identification of a patient's participation in the clinical trial. The Investigator (or delegated member of the site study team) must record all

data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy data into the e-CRF.

10.4. Electronic Recording of Data

Patients' data will be documented on a trial specific e-CRF designed by RM-CTU. Should the eCRF not be available before the study is ready to begin paper CRFs will be used until the switch can be made. Upon signing the informed consent form, the patient is assigned to the next sequential Patient screening number available. Following confirmation of eligibility patient will be randomized and assigned a randomization number.

The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the e-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 e-CRFs. All protocol required investigations must be reported in the e-CRF. The Investigators must retain all original reports, traces and images from these investigations for future reference. The data will be entered in a clinical trials database (Macro V4). If a patient withdraws from the study, the reason must be noted on the e-CRF.

Authorised site personnel must not enter study-specific data directly into e-CRFs and ensure all results are appropriately documented in the patients' medical records. The e-CRF will be signed electronically by the Investigator or by an authorised staff member. Study specific information will be entered into an e-CRF visit by visit. Data that are derived should be consistent with the source documents or the discrepancies should be explained. All e-CRF data should be anonymous, *i.e.* identified by study patient number only.

10.5. Data Management

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

10.6. Study Management Structure

10.6.1. Delegations of Responsibilities

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

10.6.1.1. RM-CTU

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

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

- ensuring an appropriate ethics opinion has been sought, and any amendments have been approved
- giving notice of amendments to protocol, make representations about amendments to the Main REC and MHRA as applicable
- notifying sites and Sponsor that the trial has ended
- randomising patients
- raising and resolving queries with local investigators
- keeping records of all serious adverse events (SAEs), overdose incidents, pregnancies and ECI's reported by investigators (as outlined in section 7.4 above)
- notifying the Main REC, MHRA and Investigators of related Serious Adverse Events

10.6.1.2. Merck, Sharp & Dohme Corp.

Provision of pembrolizumab.

10.6.1.3. Participating Sites

Responsibilities are defined in an agreement between an individual participating sites and the sponsor, which must be signed and in place prior to recruitment commencement. Also (but not limited to);

- 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) in an Investigator Site and Pharmacy File and ensuring appropriate archiving of all essential documentation once the trial has ended
- taking appropriate urgent safety measures
- Sites wishing to participate in this study will be required to provide evidence that they can are equipped to deliver the protocol treatment for the duration of the study.

10.7. Protocol compliance and amendments

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

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

10.8. Trial Management

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

10.8.1. Trial Management Group

A Trial Management Group (TMG) will be set up and membership will include Chief Investigator, Chief Co Investigator, Trial Statistician and Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG have operational responsibility for the conduct of the trial.

10.8.1.1. Safety Review Meetings

At the beginning of the study the TMG will meet every 2 weeks until the first 6 patients randomised to receive both pembrolizumab and radiotherapy have completed 12 weeks of treatment to review any safety aspects relating to the trial.

Once all 6 patients have completed 12 weeks of treatment a safety assessment will be conducted reviewing all AE's, SAE's and radiation toxicities occurring in this population.

10.8.2. Trial Steering Committee (TSC)

A trial steering committee (TSC) will be established at the start of the trial. The TSC will be chaired by an independent chair and include the Co-chief investigators (Dr Larkin and Dr Nathan). Other independent

members (1-2 including a melanoma expert and statistician) will be appointed prior to the start of the study. The TSC will also take on the role of IDMC as part of a closed session without Drs Larkin and Nathan.

The role of the TSC is to monitor trial progress and to ensure the protocol and GCP principles are adhered to. The TSC's terms of reference, roles and responsibilities will be defined in a charter. Further internal or external experts may be consulted by the TSC as necessary.

10.9. Monitoring

During the trial RM-CTU is responsible for monitoring data quality in accordance with relevant standard operating procedures (SOPs). Incoming data will be monitored for protocol compliance and if any inconsistent or missing data is identified queries will be sent to the site for resolution. Any systematic inconsistencies may trigger an onsite monitoring visit.

The trial statistician will periodically examine the data for anomalies and outliers, such as too few or too many events. Queries will be raised by the trial coordinators in such situations and communication with the clinical teams will take place. In addition statistical monitoring of unusual dates and inconsistent data will take place. Again these will raise queries via the trial coordinators.

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

10.10. Quality Control and Quality Assurance

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

10.11. Clinical study report

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

10.12. Record retention

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

RM-CTU will maintain essential documents to facilitate the management of the trial, audit and inspection in accordance with RM G-SOPs and in compliance with the clinical trial regulatory requirements. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. All medical records and TMF documentation will be retained for a minimum of 5 years after the study has concluded.

10.13. Reporting and publication

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

Draft publications (manuscripts, abstracts, slides and posters) should be submitted to the RM-CTU for circulation 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.

10.14. Ethical considerations

Before starting the trial, the protocol, patient information sheet and consent form must be approved by the RM/ICR joint Committee for Clinical Research. Once approved, the study may then be submitted to the relevant regulatory authorities.

It is the Chief and Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief and Principal Investigator must ensure this is documented in the patient's medical records and the patient is re-consented, where appropriate.

The Sponsor and Chief and Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended) and The Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/).

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APPENDICES

APPENDIX 1 - Common Terminology Criteria For Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilised for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

APPENDIX 2: LENT SOMA Scales for all Anatomical Sites

This study will utilize the LENT SOMA radiation toxicity grading system (Int. J. Radiation Oncology Biol. Phys., Vol. 31, No. 5, 1049-1091, 1995).

All appropriate treatment areas should have access to a copy of the current LENT SOMA scoring system.

APPENDIX 3: Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 Criteria for Evaluating

Response in Solid Tumours

RECIST version 1.1* will be used in this study for assessment of tumour response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX 4: Identification, evaluation and management of ECIs

ECI	Grade	Action to be taken	Supportive Care
Pneumonitis –	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Report as ECI within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Consider bronchoscopy and biopsy/BAL, ID Consult and frequent chest x-ray for monitoring. • Conduct in person evaluation twice a week	• 1-2mg/kg/day prednisone or equivalent. • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg prednisone or less or equivalent per day within 12 weeks.
	Grade 3 and 4	• Report as ECI within 24 hours • Discontinue pembrolizumab • Hospitalize 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 ECI guidance document v5.0.
• **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 as ECI within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Symptomatic treatment • Consider GI consult & endoscopy to rule out colitis	• Prednisone 1-2mg/kg/day or equivalent • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg or less of prednisone or equivalent per days within 12 weeks. • If symptoms worsen or persist >1 week treat as grade 3.
	Grade 3	• Report as ECI within 24 hours • Withhold pembrolizumab • Rule out bowel perforation • Recommend gastroenterologist consult & biopsy with endoscopy	• methylprednisolone 125mg IV followed by prednisone 1 to 2 mg/kg/day or dexamethasone 4mg every 4 hours. • Symptoms grade 1 or less initiate steroid taper for no less that 4 weeks. • Taper 6-8 weeks in patients with diffuse or severe ulceration and/or bleeding • If IV steroids do not reduce initial symptoms within 48-72 hours treat with additional anti-inflammatory measures. At symptom relief discontinue anti-inflammatory and initiate steroid taper over 45-60 days. If symptoms worsen during this period refer to ECI guidance document v5.0.
	Grade 4	• Report as ECI within 24 hours • Discontinue pembrolizumab	• Manage as per grade 3
Endocrine – Hypo and hyperthyroidism	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 Hyperthyroidism and Grade 2- 4 Hypothyroidism	• Report as ECI if appropriate - see ECI v5 guidance. • Monitor thyroid function until returned to baseline. • Consider consultation with endocrinologist. • Pembrolizumab can continue while on this treatment.	• Thyroid hormone and/or steroid replacement therapy. • Hyper – non-selective beta blockers for initial therapy • Hypo – thyroid hormone replacement therapy as per standard of care.
	Grade 3 Hyperthyroidism	• Report as ECI within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks	• IV methylprednisone 1-2mg/kg followed by prednisone 1-2mg/kg per day. • Symptoms grade 1 or less initiate steroid taper for no

		• Rule out infection and sepsis.	less than 4 weeks. Replacement of appropriate hormones may be required. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4 Hyperthyroidism	• Report as ECI within 24 hours • Discontinue pembrolizumab	• Manage as per grade 3
Endocrine – Hypophysitis or other symptomatic endocrinopathy	Grade 1 (Asymptomatic)	• No action	Intervention not indicated
	Grade 2 – 4	• Report as ECI if appropriate - see ECI v5 guidance. • Withhold pembrolizumab • Rule out infection and sepsis. • Monitor thyroid function until returned to baseline. • Consider pituitary gland imaging • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. • Consider endocrinologist consult.	• Prednisone 40mg p.o. or equivalent per day. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. Replacement of appropriate hormones may be required. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
Type 1 Diabetes Mellitus and ≥ Grade 3 hyperglycaemia	Type 1 Diabetes Mellitus and ≥ grade 3 hyperglycaemia	• Report as ECI if appropriate see Table 11 • 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 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria. • Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.
Hematologic	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Report as ECI within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Consider Haematology consultation	• Prednisone 1-2mg/kg daily • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 3	• Report as ECI within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Recommend Haematology consultation	• IV methlyprednisone 125mg or Prednisone 1-2mg/kg p.o. (or equivalent) as appropriate. • Permanently discontinue pembrolizumab is if corticosteroid dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• Report as ECI within 24 hours • Discontinue pembrolizumab • Recommend Haematology consultation	• IV methlyprednisone 125mg or Prednisone 1-2mg/kg p.o. (or equivalent) as appropriate.
Hepatic – Drug induced Liver Injury (DILI). ***Please refer to ECI guidance for definitions of (DILI)***	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Report as ECI within 24 hours • Withhold Pembrolizumab if AST or ALT >3.0 to 5.0 X ULN and/or total bilirubin is >1.5to 3.0 X ULN • Monitoring Liver function until values return to baseline	• 0.5-1mg/kg/day methlyprednisone 125mg or oral equivalent. • LFT grade 1 or less initiate steroid taper for no less than 4 weeks. Consider prophylactic antibiotics and resume pembrolizumab. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks. • Permanently discontinue pembrolizumab for patients with liver mets who begin treatment with grade 2 elevation of AST or ALT and AST or ALT increase ≥50% relative to baseline and lasts ≥ 1 week.
	Grade 3	• Report as ECI within 24 hours • Discontinue pembrolizumabif AST or ALT > 5.0 X ULN and/or total bilirubin is >3.0 X ULN • Consider consultation and biopsy to establish etiology	• 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 additional guidance in the ECI guidance document.

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

syndrome, toxic epidermal necrolysis		• Withhold pembrolizumab	with oral steroids at PIs discretion
	Grade 3	• Report as ECI within 24 hours • Withhold Pembrolizumab • Consider dermatology consultation and biopsy for diagnosis.	• 1mg/kg/day prednisone or equivalent or dexamethasone 4mg 4xday. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• Report as ECI within 24 hours • Discontinue pembrolizumab • Dermatology consultation • Consider biopsy for diagnosis & clinical photographs	• Initiate steroids starting with 1-2mg/kg prednisone or equivalent.. • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks.
Other: **Myocarditis** **Pericarditis** **Pancreatitis** **Any additional Grade 3 or higher event which the physician considers to be immune related**	Grade 2 or Grade 1 that do not improve with symptomatic treatment.	• Report as ECI within 24 hours • Withhold Pembrolizumab • Consider biopsy for confirmation of diagnosis.	• Systemic corticosteroids may be indicated. If so: • Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol
	Grade 3	• Report as ECI within 24 hours • Withhold Pembrolizumab	• Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol
	Grade 4	• Report as ECI within 24 hours • Discontinue Pembrolizumab	• Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.

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