PAPAYA Clinical Study Protocol

Study Title:	**PAPAYA -** Phase I study of the anti-PD1 immune checkpoint inhibitor **P**embrolizumab **A**nd **P**latinum in combination with radical radiother**A**p**Y** in cervix c**A**ncer.
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PROTOCOL SIGNATURES

Chief / Principal Investigator Signature:

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

Chief Investigator Name:

Signature:

Date:

Sponsor Signature:

On behalf of Sponsor

RMH Sponsor Representative

Name:

Signature:

Date:

Statistician Signature:

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

Sponsor Representative Name:

Signature:

Date:

TRIAL SUMMARY

Title	Phase I study of the anti-PD1 immune checkpoint inhibitor **P**embrolizumab **A**nd **P**latinum in combination with radical radiother**A**p**Y** in cervix c**A**ncer.
Abbreviated Title	PAPAYA
Trial Phase	I
Clinical Indication	Cervical Cancer
Trial Type	Open Label
Trial Blinding	None
Treatment Groups	**Part A – Dose escalation phase:** Starting dose (Dose Level 1): • 100mg of pembrolizumab in n=3 patients, administered in 8 cycles every 3 weeks for a total of 18 weeks commencing two weeks prior to first fraction of radiotherapy and given in combination with Radical Radiotherapy, Brachytherapy and Cisplatin Chemotherapy. • Increase in cohort by three patients to n=6 patients provided no more than 1/3 patients experience a Dose Limiting Toxicity (DLT). Escalation dose(Dose Level 2) : • Escalation of dose to 200mg of pembrolizumab in a further n=3 patients provided no more than 1/6 patients at starting dose experience a DLT. • Increase in cohort by three patients to n=6 patients provided no more than 1/3 patients experience a Dose Limiting Toxicity (DLT). **Part B – Expansion phase:** • Recruitment of expansion cohort of n=14 patients using Maximum Tolerated Dose (MTD) as determined in the dose escalation phase. MTD to be administered in 8 cycles every 3 weeks for a total of 18 weeks commencing two weeks prior to first fraction of radiotherapy and given in combination with Radical Radiotherapy, Brachytherapy and Cisplatin Chemotherapy.
Number of trial patients / Sites	A total of 20 patients if n=3 at Dose Level 1 + n=3 at Dose Level 2 + n=14 in Expansion phase A total of 23 patients if n=6 at Dose Level 1 + n=3 at Dose Level 2 + n=14 in Expansion phase A total of 26 patients if n=6 at Dose Level 1 + n=6 at Dose level 2 + n=14 in Expansion phase A total of 3 patients if Maximum Administered Dose reached at n=3 (Dose Level 1) A total of 6 patients if Maximum Administered Dose reached at n=6 (Dose Level 1) Single UK investigational site
Estimated duration of trial	24 – 36 months
Duration of Participation	Until progression, intolerance or completion of the study.
Study Objectives	*Primary Objective* • To establish the safety and tolerability of pembrolizumab combined with radiotherapy, cisplatin and brachytherapy in cervix cancer *Secondary Objective* • To evaluate overall response rates by RECIST • To assess cervical HPV status using a cervical smear test for the presence / absence of HPV DNA/RNA. • To ascertain progression free survival and overall survival. *Exploratory Objective*

	• To conduct exploratory translational studies of the effects of pembrolizumab on the immune responses of patients receiving radical chemoradiotherapy for cervix cancer – these studies will include analysis of both peripheral blood mononuclear cells (PBMC) and intratumoural immune infiltrates. • To study the role of measuring circulating free tumour DNA (ctDNA) as a biomarker of tumour clearance and/or recurrence.
Study Endpoints	• *Primary Endpoint* To establish the maximum tolerated dose (MTD) of pembrolizumab that can be safely combined with radiotherapy, brachytherapy and cisplatin in the absence of dose limiting toxicities (DLTs) • *Secondary Endpoints* • To evaluate acute toxicity as measured during treatment by CTCAE v4.0. • To determine response rates by RECIST v1.1 at 12 weeks (week 18), 6 months, 1 year and 2 following radiation treatment • To assess cervical HPV status at 12 weeks following radiation therapy (Week 18) • To assess OS and PFS at 1 and 2 years post treatment. • To evaluate late radiotherapy toxicity as assessed by LENTSOM at 12 weeks (study week 18), 6 months, 1 year and 2 years following radiation therapy *Exploratory Endpoints – Initial Analysis* • Peripheral blood analysis: o Analysis for ctDNA • Tumour biopsies (paraffin embedded and fresh) o Levels of expression of PD1, PDL1/PDL2 expression on tumour cells
Summary of Main Inclusion Criteria	• FIGO stage 1B – IVA carcinoma of the cervix planned to receive radical radiotherapy, cisplatin and brachytherapy. Pelvic lymph node but not para-aortic lymph node involvement is permitted. • Be ≥ 18 years with ECOG PS 0-1 and provide written informed consent. • Have measurable disease based on RECIST 1.1. • Demonstrate adequate organ function. • Negative urine or serum pregnancy within 72 hours prior to confirmation of study eligibility. • Patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. • For concomitant cisplatin GFR>50ml/min, no contraindications to cisplatin
Summary of Main Exclusion Criteria	• Patients requiring para-aortic radiotherapy • Previous pelvic radiotherapy, bowel resection or history of inflammatory bowel disease. • Taking any IMP or using an Investigational device within 4 weeks of the first dose. • Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose. • Prior treatment with monoclonal antibody, chemotherapy, targeted small molecule therapy, or radiation therapy. • Additional malignancy that is progressing or requires active treatment. • Active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.

	• Have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. • Have active tuberculosis. • Active infection requiring systemic therapy. • History or current evidence of any condition, therapy, or laboratory abnormality that might confound trial results, interfere with the patient's participation or is not in the best interest of the patient. • Psychiatric or substance abuse disorders that would interfere with patient's participation. • Pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 120 days after the last dose. • Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137. • History of HIV. HIV 1/2 antibodies, Hepatitis B or Hepatitis C. • Has received a live vaccine within 30 days prior to the first dose of trial treatment.
Treatment / Main Study Procedures	Patients will be registered to receive pembrolizumab in combination with radiotherapy, cisplatin and brachytherapy. A pre-loading dose of 100 or 200mg (dependent on dosing level) of pembrolizumab will be given once the patient has completed the screening period. Patients will then return 2 weeks later to begin week 0 of a regimen of pembrolizumab 3 weekly at a dose of 100 or 200mg (dependent on dosing level) for a total of 8 doses. Patients will continue to receive pembrolizumab every 3 weeks until they have completed a total of 8 doses, suffered disease progression, unacceptable toxicity or discontinued for any other reason. Patients will undergo clinical assessments on the day of each administration of pembrolizumab and all clinical assessments should be completed and reviewed before the administration of the next dose. During radiotherapy weekly assessments for adverse events and radiation toxicities will be undertaken. Patients will begin radiotherapy one (1) day after the week 0 dose of pembrolizumab (Cycle 2 of 8 cycles in total) and will receive 50.4Gy in 28 fractions over 5.5 weeks. Cisplatin will be given weekly for 4 weeks during the same period as the radiotherapy. After completion of radiotherapy patients will then receive brachytherapy. Patients will also undergo tumour assessment using RECIST 1.1 by MRI and PET/CT at screening, on completion of radiotherapy (week 5), on completion of pembrolizumab (cycle 8, week 18). If a patient has not progressed after completing all doses of pembrolizumab they will then have MRI every 3-6 months for 2 years OPTIONAL: Patients can consent to take part in a tumour biopsy and research blood analysis. By consenting patients will be agreeing to give both tumour biopsies and research blood samples. Tumour biopsies and research blood samples will be taken pre and post radiotherapy treatment. If there is an appropriate archival sample of the tumour this will be used as a pre-treatment sample.

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1. INTRODUCTION AND RATIONALE

1.1. Background

Around 3000 patients are diagnosed with cervix cancer in the UK each year (1). Locally advanced cervix cancer (stage 1B-IV) is associated with an overall survival of 60-65% at 5 years when treated with radiotherapy, concomitant cisplatin chemotherapy and brachytherapy (2). Whilst there have been recent advances in the delivery of radiotherapy and brachytherapy, leading to improved local control across all stages of disease, failure to achieve locoregional control (LRC) remains a problem, especially in the setting of stage III/IV disease. More importantly, however, the dominant unresolved problem remains the occurrence of distant metastatic relapse. At present, no therapeutic interventions are available that specifically target this issue.

With the knowledge that 99% of all cervix cancer is associated with human papillomavirus (HPV) infection (3), there is a strong rationale to consider immunomodulatory strategies in the radical management of this disease. This approach will have the potential to enhance both locoregional response to primary chemoradiotherapy and impact on the risk of distant metastatic relapse. The aim of this study is to confirm the feasibility and safety of combining pembrolizumab with radiotherapy and cisplatin in locally advanced cervical cancer patients.

1.2. The PD-1 pathway

The PD-1 pathway represents a major immune control switch which may be engaged by tumour cells to overcome active T-cell immune surveillance (4). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumours (5-8). High expression of PD-L1 on tumour cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC) (9), pancreatic carcinoma (10), hepatocellular carcinoma (11), ovarian carcinoma (12) and non-small cell lung cancer (NSCLC) (13). Furthermore, evidence to implicate a deficient T cell response stems from evidence for over-expression of tumour PD-L1 in cervical cancer leading to T effector cell apoptosis. An association between PD-L1 overexpression and poorer outcome is also seen (14).

1.3. The anti-PD-1 antibody pembrolizumab

Pembrolizumab is 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 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T-cells.

An open-label Phase I trial (Protocol 001) has been conducted to evaluate the safety and clinical activity of single agent MK-3475. 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 tumors. 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 tumor size reduction at all dose levels (1 mg/kg, 3

mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W,is the highest dose tested in PN001. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

1.4. Rationale for the use of pembrolizumab in combination with radiotherapy and cisplatin

The reasons for incorporating immune checkpoint blockade in the treatment of cervix cancer include:

1. Promotion of host immune response to HPV

Most HPV infection does not cause invasive cancer, but in those patients where this does occur, an impaired immune response to infection is strongly implicated (15, 16). This leads to the incorporation and persistence of viral DNA, RNA and protein in cervical tissue. Following radical treatment, the persistence of HPV DNA post-treatment is associated with treatment failure and both local and distant recurrence (17-19). There is evidence that the host immune system is capable of recognizing the presence of HPV-infected tumour cells, but there is a relative deficiency in the effector limb of the immune response that prevents immune-mediated attack and clearance of these cell populations. It is postulated that enhancement of host immune response by adding immune checkpoint blockade at the time of primary radical chemoradiotherapy will lead to HPV clearance and, thus, improve LRC and reduce systemic relapse.

2. Synergistic effects of radiotherapy and brachytherapy with immunotherapy

There is an increasing understanding that ionising radiation acts not only by damaging the DNA of tumour cells, but also by stimulating immune responses in the tumour microenvironment (20). It is postulated that these immune responses can be further activated by combining radiotherapy with an immune checkpoint-modulating drug. The proposed hypothesis is that 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.It has been demonstrated in other tumour types that a large dose per fraction of radiotherapy is required for this effect (21), although it is unknown if prolonged clinical fractionated schedules (eg 50.4 Gy in 28 fractions) may also inducing this effect. Importantly, the use of high dose-rate brachytherapy, as an integral part of the treatment of cervix cancer, provides a unique opportunity to study the effects of both standard fractionation (1.8 Gy daily) and high dose (and high dose-rate) brachytherapy in the same patient population. The brachytherapy component of treatment delivers a highly focal escalated dose of radiation to the primary cervical tumour over a short time.

Therefore, we postulate that the anti-PD1 MAB, pembrolizumab, can be combined safely with the current standard-of-care (radiotherapy, cisplatin chemotherapy and brachytherapy) in the treatment of cervix cancer. Demonstrating this fact will pave the way for a further randomised study of standard-of-care +/- pembrolizumab to assess the role of immune checkpoint blockade in improving LRC and reducing distant relapse in this disease.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Hypothesis

Pembrolizumab can be safely combined with radical radiotherapy, concomitant cisplatin (40mg/m2 weekly) and with brachytherapy in locally advanced cervical cancer.

2.2. Study Objectives

2.2.1. Primary

- To establish the safety and tolerability of pembrolizumab combined with radiotherapy, cisplatin and brachytherapy in cervix cancer

2.2.2. Secondary

- To evaluate overall response rates by RECIST
- To assess cervical HPV status.
- To ascertain progression free survival and overall survival.

2.2.3. Exploratory

- To conduct exploratory translational studies of the effects of pembrolizumab on the immune responses of patients receiving radical chemoradiotherapy for cervix cancer – these studies will include analysis of both peripheral blood mononuclear cells (PBMC) and intratumoural immune infiltrates to assess immune activation.

2.3. Study Endpoints

2.3.1. Primary

- Maximum tolerated dose (MTD) of pembrolizumab that can be safely combined with radiotherapy, brachytherapy and cisplatin in the absence of dose limiting toxicities (DLTs)

2.3.2. Secondary

Acute toxicity as measured during treatment by CTCAE v4.0

- Tumour response rates by RECIST v1.1 at 12 weeks (week 18), 6 months, 1 year and 2 following radiation treatment
- Cervical HPV status at 12 weeks following radiation therapy (Week 18)
- OS and PFS at 1 and 2 years post treatment.
- Late radiotherapy toxicity as assessed by CTCAE v4.0 and LENTSOM at 12 weeks (study week 18), 6 months, 1 year and 2 years following radiation therapy

2.3.3. Exploratory

- Initially the analysis of exploratory markers will be limited to the analysis of circulating tumour DNA (peripheral blood) and PD-1, PD-L1 / PD-L2 expression (tumour biopsies). Research samples obtained will be stored for future analysis of additional markers as follows:
- Peripheral blood analysis:
  - PBMC biomarkers of immune response (T, B, NK, MDSC), markers of T cell activation and T reg function and measurement of T cell reactivity to HPV antigens.
- Tumour biopsies (paraffin embedded and fresh)
  - Immunohistochemical analysis to identify immune infiltrates (T cells [$CD4^+$, $CD8^+$, $CD4^+/CD25^+$, T reg], B cells, macrophages, NK cells)
  - Biomarkers of HPV specific immune response: HPV+ve T cells
  - RNA sequence analysis

3. STUDY DESIGN

3.1. Summary of study design

This is a single centre phase 1 study that will recruit 20-26 patients with locally advanced cervix. All patients will receive pembrolizumab, with radiotherapy, brachytherapy and cisplatin. Patients will continue on the treatment regimen described below until they complete all 8 doses of pembrolizumab or they progress, suffer unacceptable toxicities or withdraw from the trial.

3.2. Treatment Regimens

Each patient will receive treatment with external beam radiotherapy to the pelvis, cisplatin and brachytherapy as per standard care (Appendix 1). A pre-loading dose of pembrolizumab (at the dose level under evaluation (100/200mg)) will be given 2 weeks prior to week 0, after which pembrolizumab will be administered every 3 weeks until a total of 8 doses have been completed or the patient suffers disease progression, presence of unacceptable toxicities or withdrawal. Radiotherapy will begin one (1) day after the week 0 dose of pembrolizumab.

An initial dose of 100mg of pembrolizumab will be implemented. If dose limiting toxicity is not observed at this dose, pembrolizumab will be escalated to 200mg.

A minimum of 3 patients will be required at each dose level. A minimum gap of 1 week should be left between the recruitment of the first and second patient in a new dosing level to mitigate against multiple patients suffering from any acute toxicity.

- If no dose limiting toxicity is observed at a dose level, pembrolizumab will be escalated to the next dosing level.
- If 1 in 3 patients experience a dose limiting toxicity then the cohort will be expanded to 6 patients.
- If 1 in 6 patients experience a DLT then the dose will be escalated to the next dosing level.
- However if ≥ 2 in 6 patients experience a DLT then the maximum administered dose (MAD)will have been reached and the previous dosing level (i.e. Maximum Tolerated Dose, 'MTD') should be used for the expansion phase.

If the MAD is reached at dose level 1 the combination therapy of pembrolizumab, cisplatin and radiotherapy will not be considered possible and the trial discontinued. Once the MTD has been determined the trial enters the expansion cohort whereby a further 14 patients are treated with the determined dosage of pembrolizumab in combination with radiotherapy, brachytherapy and cisplatin.

3.2.1. **Dose levels and Dose Limiting Toxicities**

The rate of entry and escalation to the second dose level will depend upon assessment of the toxicity profile of patients entered at the initial level. Toxicity will be assessed at 6 weeks after the completion of brachytherapy using CTCAE v4.0 criteria for acute toxicity by the pembrolizumab project safety review committee (PPSRC) before recruitment to the next dose level can begin.

For this study the dose limiting toxicities will be assessed by the presence of:

- >=Grade 3 gastrointestinal toxicity
    - Excluding grade 3 toxicity which resolves to grade 2 within 48 hours of medical management

- Haematological toxicity including:
    - Grade 3 thrombocytopenia with bleeding
    - Grade 4 thrombocytopenia
    - Grade 4 neutropenia lasting >7 days in the absence of growth factor support
    - Grade 4 neutropenia of any duration accompanied by fever ≥ 38.5°C and/or systemic infection
    - Any other grade ≥4 haematological toxicity

- Immune system toxicity

- Grade 4 immune toxicity requiring treatment with corticosteroids
- Grade 3 immune toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks. (For patients requiring corticosteroids at week 12 toxicity assessment, the observation period will be continued to monitor for this DLT)

- Radiotherapy treatment interruption > 5 days or failure to complete external beam radiotherapy and brachytherapy due to toxicity
- Any other ≥Grade 3 non-hematologic toxicity (except nausea and vomiting) which in the opinion of the investigator is considered dose-limiting.

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

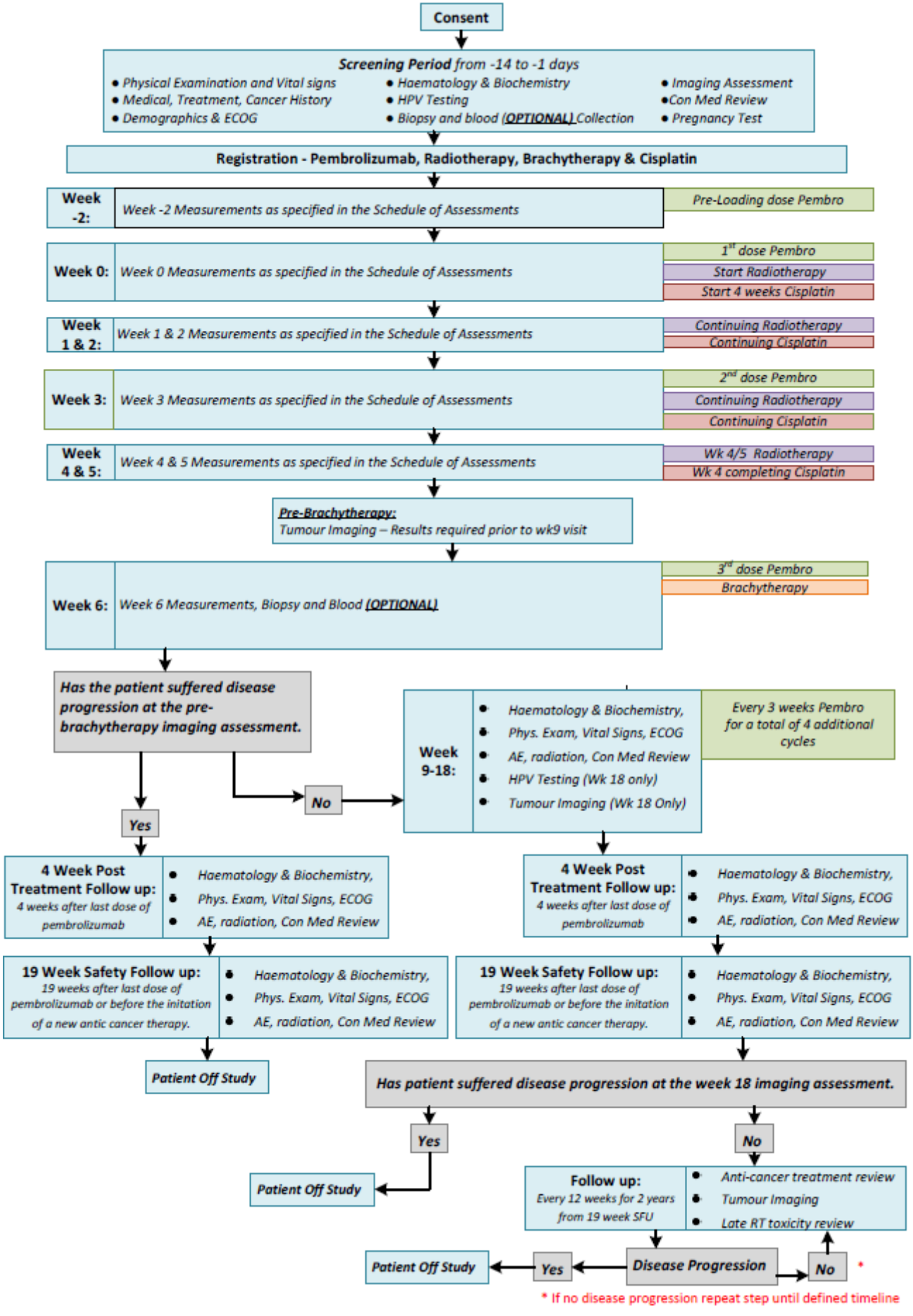
- **If 0/3 patients** experience a DLT escalation to the next dose level can proceed.
- **If 1/3 patients** experiences a DLT a further 3 patients will be recruited at the dose level.
  - If 1/6 patients experience a DLT then escalation to the next dose level can proceed.
  - If ≥ 2/6 patients in a specific dose level experience a DLT, the maximum administered dose will have been reached and all patients in the expansion cohort will be recruited at the previous dose level (i.e. the MTD).
- **If 2/3patients** experience a DLT then the maximum administered dose will have been reached and the expansion cohort phase will begin at the previous dose level.

If the MAD occurs at dose level 1 the expansion cohort will not go ahead and the trial will be stopped.

3.3. Study Flow chart

Refer to Figure 1 below.

Figure 1: Study Flow Chart



3.4. Follow-Up

3.4.1. 4 Week Post Treatment Follow Up

All patients will be required to attend a post treatment follow up visit 4 weeks after their last dose of pembrolizumab where assessments detailed in the study schedule (Table 2) will be performed.

3.4.2. 19 Week Safety Follow Up

In addition all patients will be required to attend a safety follow-up visit at 19 weeks after the last dose of pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. The 19 week safety follow-up time-point is based on the 135 day elimination period of the drug as stipulated by MHRA for Pembrolizumab as [drug half-life multiplied by 5]. All AEs and SAEs that occur prior to the safety follow-up visit should be reported as described in section 7. After the safety follow-up any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the CRF.

3.4.3. Study Follow Up

Patients who have not progressed or discontinued from the study for any cause at the safety follow up visit should be followed for tumour response and review of the initiation of any new anticancer treatment every 12 weeks for 2 years until, progression, initation of a new anti-cancer treatment, death or withdrawal of consent or sponsor's decision to terminate the study.

3.5. Study Termination

The end of the study is defined when the last patient has completed the 2 year follow-up or has discontinued the study for other reasons.

3.5.1. Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients
4. Plans to modify or discontinue the development of the study drug
5. If MTD is seen at dose level 1

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

3.6. Treatment after Study Termination

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

4. SELECTION OF PATIENTS

4.1. Screening and Enrolment

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

4.2. Registration

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

Once all the screening assessments have been completed and the data entered in the CRFs the patient will be assessed for eligibility. If eligible the patient will begin on the trial. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient.

The trial ID will be a unique number that once assigned will become the permanent study identifier for that patient. In the event a patient is registered onto the study but does not begin treatment, then that patient's trial ID will not be reassigned. Treatment will begin within 3 days from the date or registration. To ensure patient confidentiality patients will only be identified on CRFs, other trial specific forms and all communication to RM-CTU using their assigned trial ID. It is the PI's responsibility to maintain a confidential record of the identity i.e. full name, date of birth and hospital number for the patients enrolled in this study and their assigned trial ID. At the end of the study this record should be archived along with the Site File.

4.3. Patient Replacement Strategy

Additional patients may be enrolled in at a specific dose level to ensure that the required number of evaluable patients is achieved. A patient that discontinues the trial for progressive disease or a drug-related AE will not be replaced and will be counted in the evaluable population of patients for the respective cohort. However, patients who do not reach 6 weeks post brachytherapy follow up can be replaced by new patients.

4.4. Entry Criteria

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

4.4.1. **Inclusion criteria**

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

1. Histologically confirmed FIGO stage 1B – IVA carcinoma of the cervix planned to receive radical radiotherapy with concomitant cisplatin and brachytherapy. Pelvic lymph node but not para-aortic lymph node involvement is permitted.
2. ECOG PS 0-1
3. Be willing and able to provide written informed consent for the trial.
4. Be ≥ 18 years of age on day of signing informed consent.
5. Have measurable disease based on RECIST 1.1.
6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days prior to confirmation of study eligibility.

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 patient with creatinine levels > 1.5 X institutional ULN
[a]Creatinine clearance should be calculated per institutional standard.	
Hepatic	
• Serum total bilirubin **OR** • Direct bilirubin	≤ 1.5 X ULN **OR** ≤ ULN for patients with total bilirubin levels > 1.5 ULN
• AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
Prothrombin Time (PT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Table 1: Adequate Organ Function Laboratory Values

7. Female patient of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to confirmation of study eligibility. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
8. 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.
9. For Concomitant cisplatin GFR>50ml/min, no contraindications to cisplatin (pre-existing tinnitus or neuropathy).

4.4.2. **Exclusion criteria**

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

1. has had previous pelvic radiotherapy
2. has a history of previous bowel resection
3. has a history of inflammatory bowel disease or autoimmune condition
4. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
5. 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.
6. Has had a prior monoclonal antibody, chemotherapy, targeted small molecule therapy, or radiation therapy.
   Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. 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.
8. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.
9. Has a history of (non-infectious) pneumonitis that required steroids or current pnuemonitis.
10. Has active tuberculosis.
11. Has an active infection requiring systemic therapy.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive 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.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5. STUDY PLAN AND PROCEDURES

5.1. Study Schedule

Whilst on treatment, patients will be seen in clinic at the pre-loading dose (week -2) and then every 3 weeks at the administration of their next dose of pembrolizumab. In addition weekly assessments for radiation toxicity will be performed during radiotherapy. Patients will remain on this regimen until they complete all 8 doses or they progress, suffer unacceptable toxicities or withdraw from the study.

Patients will also be required to attend a post treatment follow up 4 weeks after their last dose of pembrolizumab and a safety follow up at 19 weeks from their last dose or before the initiation of a new anti-cancer therapy; whichever comes first.

If the patient has completed all 8 doses and has not progressed at the safety follow-up they will be reviewed for tumour progression and initiation of new anti-cancer treatments every 12 weeks for 2 years until progression, initiation of a new anti-cancer therapy, withdrawal or completion of the study.

The schedule of study assessment (Table 2) summarises the trial procedures to be performed at each visit. Individual trial procedures are described in detail below.

Furthermore, additional evaluations/testing may be clinically indicated for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.). Such evaluations/testing will be performed in accordance with local regulations.

Trial Period:	Screening Phase	Pembrolizumab Administration – Every 3 Weeks																				Post-Treatment Follow-up	Safety Follow-up (SFU)	Study Follow-up
Treatment Cycle/Week Title:	Screening	Wk -2 Pre-loading Dose of Pembrolizumab	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	4 wks after last dose of Pembrolizumab	19 wks after last dose of Pembrolizumab or before initiation of new anti-cancer therapy	Every 12 wks for 2 years
Visit Window (Days):	-14 to 1	within 3 days after confirmation of eligibility	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7
Administrative Procedures																								
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demographics, Medical & Cancer History	X																							
Disease Status Review																						X	X	X
New Anti-Cancer Therapy Review																						X	X	X
Clinical Procedures / Assessments																								
Adverse Events Review		X	X			X			X			X			X			X			X	X	X	
Radiation Toxicity Review				X	X	X	X	X	X	X		X			X			X			X	X	X	X[10]
Concomitant Medication Review	X	X	X			X			X			X			X			X			X	X	X	
Full Physical Examination	X	X	X			X			X			X			X			X			X	X	X	
Vital Signs & Weight	X	X	X			X			X			X			X			X			X	X	X	
ECOG Performance Status	X	X	X			X			X			X			X			X			X		X	
Haematology and Biochemistry (inc T4 & TSH)	X		X			X			X			X			X			X			X	X	X	
GFR, PT and aPTT	X																							
Pregnancy Test – Urine / Serum	X																							
Pembrolizumab Administration		X	X[2]			X			X			X			X			X			X			
Radical Radiotherapy			X[3]	X	X	X	X																	
Cisplatin Chemotherapy			X[4]	X	X	X																		
Brachytherapy									X[5]															
HPV testing - Cervical Smear (Cytology)	X								X												X			
Tumour Imaging – MRI/PET-CT	X[6]							X[7]													X			X[8]
Archival Tumour Collection (OPTIONAL)	X																							
New Tumour Biopsies (OPTIONAL)	X								X															
Research Blood Collection (OPTIONAL)	X								X			X[9]												

1. Only required for patients that have not suffered disease progression at the safety follow-up.
2. 1st dose of Pembrolizumab should be given one day before radiotherapy begin and repeated on the same day every 3 weeks until Week 18.
3. Radical Radiotherapy should begin one day after Week 0 dose of Pembrolizumab and last for 5.5 weeks (28 Fractions).
4. Cisplatin Chemotherapy should begin during the same period as radiotherapy and repeated on the same day for a total of 4 weeks during radiotherapy.
5. Brachytherapy should be given after completion of radiotherapy.
6. Imaging – MRI/PET-CT can be up to 6 weeks prior to registration.
7. Pre-Brachytherapy Imaging – MRI/PET-CT should be completed so the results are available at Week 9 Visit.
8. MRI only.
9. Research blood will be collected pre-treatment and at week 6 just prior to brachytherapy, 4 weeks post-brachytherapy and at end of study visit.
10. 3 months, 6 months, 12 months and 24 months from date of start of radiotherapy.

Table 2: Schedule of Study Assessments

5.2. Administrative Procedures/Assessments

5.2.1. Informed Consent

It is the responsibility of the Principal Investigator / designee to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. A minimum of 24 hours will be allowed for the patient to decide on trial entry. Patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrolment. The written patient information is an approved patient information sheet (PIS) according to national guidelines.

The Investigator must obtain documented written informed consent from each potential patient prior to participating in a clinical trial. Consent must be documented by the patient dated signature on a consent form along with the dated signature of the person conducting the consent discussion. If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterwards, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the

informed consent along with the individual who read and discussed the informed consent. Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, having signed the delegation of responsibilities log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol.

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

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

5.2.2. **Inclusion/Exclusion Criteria**

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

5.2.3. **Demographic Data, Medical History**

Demographic data collected will include date of birth and race/ethnicity. A medical history will be obtained by the investigator or designee. Medical history will include all active conditions, and any condition(s) that are considered to be clinically relevant by the Investigator. In addition any abnormal and clinically significant results seen during the screening period should be recorded in the medical history form. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

5.2.4. **Disease Status & Anti-Cancer Therapy Review**

Patients that have completed all 8 doses and not suffered disease progression or discontinued for any other reason will have a follow-up visit every 12 weeks for 2 years. At this visit the investigator should review the patient's recent imaging assessment to assess disease status and any new anti-cancer therapy initiated after the last dose of trial treatment. If the patient progresses or initiates a new anti-cancer therapy during this follow up they will come off the study.

5.2.5. **Prior Medications Review**

The investigator / designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within 14 days before starting the trial. Treatment

for the disease for which the patient has enrolled in this study will be recorded separately and not listed as a prior medication.

5.2.6. **Concomitant Medications Review**

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

5.3. Clinical Procedures/Assessments

5.3.1. **Adverse Event (AE) Monitoring and Radiation Toxicity Assessment**

The investigator or designee will assess each patient to evaluate for potential new or worsening AEs at specified visits as defined in the schedule of study assessment (Table 2) or more frequently if clinically indicated. Adverse events will be graded and recorded from first dose of pembrolizumab until the Safety follow-up. AEs will be graded according to NCI CTCAE Version 4.0. Late radiation toxicity (3 months from the start of radiotherapy treatment) will be assessed with the 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, Appendix 5 and the separate ECI guidance document 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 designee will perform a complete physical exam during the screening period and at each on-treatment visit as defined in the schedule of assessment (Table2). Clinically significant abnormal findings at screening should be recorded as medical history and those occuring on treatment should be recorded as adverse events.

5.3.3. **Vital Signs**

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

5.3.4. **Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or designee will assess ECOG status (Table 3) at screening, prior to the administration of each dose of trial treatment and the safety follow up as specified in the schedule of study assessment (Table 2).

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 23: ECOG Performance Status

5.3.5. **Pregnancy Tests**

Female patients of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to confirmation of study eligibility. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.3.6. **Haematology, Clinical Biochemistry including GFR, PT, aPTT, T4 and TSH**

All Laboratory tests will be performed at screening and then certain assessments at every visit as defined in the schedule of study assessment (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**
• Hemoglobin	• Albumin	• Urine pregnancy test	• PT
• Platelet count	• Alkaline phosphatase		• aPTT
• WBC (total and differential)	• Alanine aminotransferase (ALT)		• Free tyroxine (T4)
• Red Blood Cell Count	• Aspartate aminotransferase (AST)		• Thyroid stimulating hormone (TSH)
• Absolute Neutrophil Count	• Lactate dehydrogenase (LDH)		• GFR
• Mean Cell Volume	• Calcium		
• neutrophils	• Chloride		
• lymphocytes	• Glucose		
• monocytes	• Phosphorus		
• basophils	• Potassium		
• eosinophils	• Sodium		
•	• Magnesium		
	• Total Bilirubin		

- Total protein
- Blood Urea Nitrogen
- Creatinine
- Creatinine Clearance

Laboratory tests for screening should be performed during the screening period. After this all laboratory procedures can be conducted up to 72 hours prior to dosing and if applicable routine results taken for Cisplatin treatment can be used if they fit within this timeline. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Patient 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 CRF. Laboratory values that are considered to be of clinical concern must be recorded as an adverse event (AE) 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.

5.3.7. **Cytology – Human Papillomavirus (HPV) testing**

HPV testing will be performed during the screening period, at week 6 and at week 18 following the last dose of pembrolizumab to assess for clearance of HPV-infected cells.

5.3.8. **Radiological Tumour Assessment**

Tumour response assessments will be performed at screening, pre-brachytherapy (week 5), after the last dose of pembrolizumab (week 18) and then every 3-6 months for 2 years. Assessments can be carried out by physical examination, and tumour imaging by MRI with or without PET/CT. MRI is the preferred imaging technique for evaluation of cervical tumour response unless contraindicated. Tumour response will be assessed based on RECIST v1.1. Progression of disease should be verified in cases where progression is equivocal. If repeat PET/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 patient is considered not to have progressive disease per RECIST v1.1. Confirmation of response is not required.

5.3.9. **Archival Tissue Collection and Tumour Biopsy Research**

5.3.9.1. Archival Tumour tissue samples - OPTIONAL

Archival tissue samples will only be collected from patients who consent to the tumour biopsy research section and have an appropriate sample available. An FFPE tumour block 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 patient's clinical management. Cut sections will be retained by the study team. These are archived samples and as such participating patients will not need to attend extra visits or undergo extra procedures.

All collected archival samples will be classed as pre-treatment samples and used as such in the immunological evaluation as described below.

5.3.10. **Research Blood Samples - OPTIONAL**

For consenting patients, research blood samples will be obtained pre-treatment and at week 6 just prior to brachytherapy, 4 weeks post-brachytherapy and at end of study visit. Initial / future analysis methods will include:

1) Serum will be collected to measure antibodies to HPV E6/E7 antigens. IgG responses will be evaluated by ELISA and change over time documented. We are currently expressing E2 protein for ELISA assays, and if successful, evaluation of anti-E2 titers will be included.

2) PBMC will be collected and cryopreserved for evaluation of T, B, MDSC and NK cells in the blood pre-, during and after aPD1 treatment. Specifically, markers of T-cell activation and Treg function will be evaluated and followed over time (such as HLA-DR, ICOS, PD1, TIM3, CD69, CTLA4, CD25, FoxP3).

3) PBMC will be evaluated for T-cell reactivity to HPV antigens (E6 and E7). We will focus on HPV16 and HPV18, which account for ~80% of HPV infections in cervical cancer. HLA testing (Class I and class II) will be undertaken to guide the evaluation of HPV E6/E7 specific T-cell reactivities by tetramer staining. Currently, in the Southampton ECMC, HLA A2-restricted tetramers for E6 and E7 (n=6) are available and are being developed for other class I and for class II genotypes. If the presence of HPV16/HPV18 is demonstrated, ELISPOT will be used to evaluate the breadth and distribution of T-cell reactivities to E6/E7 at baseline and over time during/following treatment, using pools of 15mer peptides (technology established using HPV16 E6/E7 peptide pools). For HPV18, overlapping peptide pools will be purchased from JPT Technologies for E6/E7.

5.3.11. **Analysis of levels of circulating tumour DNA tumour biopsies (OPTIONAL) – Immunological evaluation**

For consenting patients, tumour/cervix biopsies will be obtained prior to commencing treatment (and at week 6 at the time of brachytherapy). These samples will be used for:

Immunohistochemical analysis to identify immune infiltrates (T-cells [CD4+, CD8+, CD4+/CD25+Treg], B-cells, macrophages, NK cells), levels of expression of PD1, TIM3, LAG3, ICOS, (and other immune activation/exhaustion markers) on immune cells, levels of PDL1/PDL2 expression on tumour/stromal cells and presence of MDSC and CAF in the stroma.

An aliquot of fresh tissue will be used for subsequent analyses by RNAseq from 1) whole tumour and 2) from disaggregated tumour. This will yield key information about immunological pathways that determine the outcome of immune responses and will allow us to probe the changes that are induced in the tissue by chemo/radiotherapy. A small aliquot of tissue will be snap frozen immediately post-biopsy. Further fresh tumour samples will be collected according to defined and established SOP, and transferred to the laboratory in Southampton for processing. The tissue will be enzymatically dispersed to generate single cell suspension of

tumour, stromal and infiltrating immune cells. CD4/CD8/B-cells will be sorted and lysed in RNAzol for downstream RNAseq analysis.

5.3.12. **Chain of Custody of Biological Samples**

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

RM-CTU will keep overall oversight of the entire lifecycle through internal procedures and monitoring of study sites.

5.3.13. **Total Blood Volume**

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

	Sample volume (mL)	No. of samples	Total volume (mL)
Routine Haematology	6[1]	10	60
Routine Clinical chemistry	8[1]	10	80
		Total:	140
Research Blood Samples – OPTIONAL	20	3	60
		Study Total	200

Table 3: Volume of blood to be drawn from each trial patient for the duration of the trial; calculations based on 8 administrations of pembrolizumab, a screening visit and post treatment visit and a safety follow up visit.

[1] *Blood volumes for haematology and clinical chemistry may vary according to local practice*

6. TREATMENTS

Patients will be given pembrolizumab in addition to radiotherapy and brachytherapy and chemotherapy if clinically appropriate

6.1. Standard Treatment

6.1.1. **External Beam radiotherapy**

Radiotherapy should commence the day after the second infusion of pembrolizumab. It is advisable to start radiotherapy planning as soon as the patient has been recruited into the study to ensure the timely delivery of radiotherapy.

External beam radiotherapy should be CT planned using IMRT (or a conformal technique) as per institutional standard. The initial phase of treatment to the pelvis is to a total dose of 50.4Gy in 28 fractions of 1.8Gy per fraction. A concomitant or sequential boost can be utilised for involved pelvic lymph nodes.

6.1.2. **Brachytherapy**

Following completion of external beam radiotherapy or during the final week of treatment, intrauterine brachytherapy will be performed. The aim is to deliver at least 80Gy to the residual tumour and cervix. HDR Brachytherapy will be delivered in 3 fractions over 24 hours.

6.1.3. **Chemotherapy**

Cisplatin will be delivered at a dose of 40mg/m2 weekly for a maximum of 4 weeks during external beam radiotherapy.

For detailed radiotherapy and chemotherapy procedure see Appendix 1.

6.2. Trial Treatment - Pembrolizumab

6.2.1. Investigational Product

The Investigational Medicinal Product (IMP) for this study is Pembrolizumab. A potent and highly-selective 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 nonspecifically 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 4. Additional information about the investigational product can be found in the current Summary of Product Characteristics (SmPC).

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

Table 4: Product Description

6.2.2. Product Preparation

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

6.2.3. Storage and Handling

6.2.3.1. Storage

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

Prepared infusion solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, reconstituted vials and/or IV bags may

be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

6.2.3.2. Handling

Infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or 5% Dextrose Injection, USP (5% dextrose) and the final concentration of pembrolizumab in the infusion solutions should be between 1.0 mg/mL and 10.0 mg/mL. Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Pembrolizumab should **NOT** be mixed with other diluents.

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.

Please **DO NOT**:

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

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

At each site the Investigator / designee e.g. pharmacist at each participating site 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.

6.2.4. **Supply, Packaging and Labelling information**

Pembrolizumab will be supplied by Merck, Sharp and Dohme (MSD) as solution for injection. Pembrolizumab will be packaged, labelled and delivered to the participating sites free of charge by MSD. The IMP will be supplied

specifically for the trial and should not be used for any other purpose than that stated in this protocol. The drug will be labelled in accordance to Good Manufacturing Practice Annex 13.

6.2.5. **Returns and Reconciliation**

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

6.2.6. **Doses and treatment regimens**

All patients will receive pembrolizumab administered as per standard procedures following manufacturer's instructions intravenously as a pre-loading dose and then from week 0 every 3 weeks until 8 doses of treatment have been completed. Treatment should be coordinated so that cisplatin and pembrolizumab are NOT delivered on the same day and an attempt made to either avoid steroid antiemtic or to deliver pembrolizumab once steroid antiemetic is complete (in week 4) Two dose levels of pembrolizumab will be studied to ensure tolerability of combining therapy with radiotherapy and cisplatin

Initially a dose of 100mg will be given every 3 weeks, escalating to 200mg every 3 weeks as per dose escalation protocol.

6.2.7. **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 assessment (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

6.2.8. **Dose modifications and treatment discontinuation**

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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/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

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

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

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

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

Table 5: 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. Patients with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see section 7.

Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

Radiotherapy-related adverse events will be managed as per institution clinical guidelines.

Events of Clinical interest (ECI) can be potential immune related adverse events and dose modifications for these toxicities should they occur can be found in appendix 5 and as per the MSD guidance document for pembrolizumab ECI version 3.0

6.2.9. **Trial Blinding / Masking**

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

6.3. Concomitant medications

Concomitant medications will be recorded at baseline and at every visit during as defined in the study schedule of assessment (Table 2) in the case report form (CRF) in the concomitant therapy section.

6.3.1. **Prohibited concomitant medication**

Medications specifically prohibited in the exclusion criteria and described below are not allowed during the ongoing trial. If there is a clinical indication for one of these or other prohibited medications or vaccinations to be used during the trial then patient should discontinue trial therapy. The Investigator should discuss any questions regarding this with the CI (or delegate).

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

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

- Biological therapy
- Immunotherapy not specified in this protocol (except to treat a drug related AE)
- Chemotherapy 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 as an antiemetic therapy with cisplatin and 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.

Patients may receive other medications that the investigator deems to be medically necessary. The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.3.2. **Acceptable concomitant medication**

All other treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescriptions, over-the-counter (OTC), herbal supplements, and IV medications and fluids. All concomitant medications received within 14 days before the first dose until the patient's safety follow-up should be recorded.

Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10mg/day prednisolone equivalents. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions is permitted.

6.4. Rescue Medications & Supportive Care

6.4.1. **Supportive Care Guidelines**

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

6.4.1.1. Diarrhoea:

Patients should be carefully monitored for signs and symptoms of:

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

Bowel perforation (peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

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

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

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

6.4.1.2. Nausea/vomiting:

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

6.4.1.3. Anti-infectives:

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

6.4.1.4. Immune-related adverse events:

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

6.4.1.5. Management of Infusion Reactions:

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

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

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until investigator deems the patient is medically stable.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids);	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
prophylactic medications indicated for < =24 hrs	• NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until investigator deems the patient is medically stable. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	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 investigator deems the patient is medically stable. Hospitalisation may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Table 6: Infusion Reaction Treatment Guidelines

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

Immune-related Adverse events (IrAEs) may be defined as an adverse event of unknown 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. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the CI/designee.

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

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.**

Table 7: General Approach to Handling irAEs

Details for managing specific irAEs are summarised below:

Immune-mediated pneumonitis

Monitor patients 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 patients 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 patients 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 patients 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 patients 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) signs and for life-threatening (Grade 4) hypophysitis.

Monitor patients 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 patients receiving pembrolizumab and can occur at any time during treatment; therefore, monitor patients 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, andpermanently 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 patients 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 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: 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 and Table 5 in section 15. Patients with symptomatic irECIs should immediately stop receiving pembrolizumab and be evaluated to rule out non treatment related causes of the event. All irECIs irrespective of relationship to the study drug should be reported within 24 hours of the investigator being aware to the Sponsor who will in turn notify MSD. If the irECI is determined to be associated please refer to ECI guidance document and Appendix 5 for the recommendations on the management of these irECIs. If the event is not considered to be associated with the study drug the physician should exercise individual clinical judgment on the event management based on the patient. Any additional questions of the collection or information on management of irECIs should be directed to the Sponsor.

6.6. Diet/Activity/Other Considerations

6.6.1. **Diet**

Patients 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. Patients should start using birth control from study Visit 1 throughout the study period up to 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 estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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

6.6.3. **Use in Pregnancy**

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to MSD without delay and within 24 hours if the outcome is a serious adverse event (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the RM-CTU.

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, patients who are breast-feeding are not eligible for enrolment.

6.6.5. **Treatment of Overdose of IMP**

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20%. Please see section 7.6 for definitions and reporting procedures.

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

6.7.1. **Permanent Discontinuation of Trial Medication**

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

- The patient) 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
- Intercurrent illness that prevents further administration of treatment
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Completion of 8 doses of pembrolizumab

Trial patients will not be replaced or enrolled more than once. The primary reason for discontinuation should be recorded on the eCRF.

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

- If a patient **progress during or at the end of the on treatment period** they will be required to:
  - Attend a post treatment follow-up 4 weeks after their last dose of pembrolizumab,
  - Attend a safety follow up 19 weeks after their last dose of pembrolizumab.

- If a patient completes all 8 doses of pembrolizumab without disease progression or discontinuing for any other reason they will be required to:
  - Attend a post treatment follow-up 4 weeks after their last dose of pembrolizumab,
  - Attend a safety follow-up 19 weeks after their last dose of pembrolizumab.
  - Attend 12 weekly follow up visits for 2 yrs, until progression, initiating a non study cancer therapy, withdrawing consent or becoming lost to follow up.

- If a patient discontinues for reasons other than progression during or at the end of the on treatment period they will be required to:
  - Attend a post treatment follow-up 4 weeks after their last dose of pembrolizumab,
  - Attend a safety follow up 19 weeks after their last dose of pembrolizumab.

- If a patient **progress follow up period** no other assessments will be required.

6.8. Withdrawal from the Study

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

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

Patients may withdraw consent at any time for any reason or 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.

7. PHARMACOVIGILANCE

7.1. Adverse events

7.1.1. Adverse Event Definition:

An AE is defined as any untoward, undesired or unplanned occurrence (including deterioration of a pre-existing medical condition) in a patient administered a pharmaceutical product or undertaking a protocol-specified procedure.

An AE can be an unfavourable and unintended sign, symptom, disease, and/or laboratory or physiological observation associated with the use of a medicinal product of protocol-specified procedure but does not necessarily have to have a causal relationship to this treatment or procedure.

Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of 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.

7.1.2. **Adverse Reaction Definition:**

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

7.1.3. **Disease Progression**

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

7.1.4. **New Cancers**

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

7.1.5. **Abnormal Laboratory Test Results**

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

7.1.6. **Pregnancy and Lactation**

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

7.2. Assessing and Recording Adverse Events

All adverse events will be recorded from the time of the first dose of pembrolizumab until 19 weeks after the date of the administration of the last dose of Pembrolizumab. They will be followed up according to local practice until the event has stabilised or resolved, or the follow-up visit has taken place, whichever is the sooner. Serious Adverse Events (SAEs) will also be recorded throughout the study. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.4.

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

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

The following details will be collected in the 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

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

7.3. Evaluating Adverse Events

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

7.3.1. Determining AE Severity and Grade

AE severity and grade will be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0 and LENT SOMA radiation toxicity grading system. Any adverse event which changes CTCAE grade indicative of worsening toxicity 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. CTCAE grades which change indicating an improvement in toxicity are not reported as AEs.

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

7.3.2. Determining AE Causality

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

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

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

7.4. Serious adverse events (SAEs)

A 'serious adverse event' is defined as follows:

Any untoward medical occurrence or effect that at any dose that:

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

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

7.4.1. **Reporting SAEs**

All SAEs regardless of causality, pregnancy or overdose that occur from the time of the first dose of pembrolizumab until the safety follow-up or the initiation of a new anticancer therapy, whichever is earlier, must be reported on the SAE report form within 24 hours of the investigator / designee becoming aware of the event. The SAE form should be sent to the RM-CTU by Fax 02089156762 who will in turn notify MSD of the event.

The SAE form must be completed, assessed for causality and expectedness against section 4.8 of the current version of the Summary of Product Characteristics (SmPC), then signed and dated by the Principal Investigator or an appropriately qualified designated individual identified on the delegation log. The report will then be reviewed by the Chief Investigator (or a nominated representative) to confirm relatedness and expectedness. The NCI CTCAE Version 4 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 RM-CTU on a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. The RM-CTU will in turn submit the updated report to MSD. Please refer to the SAE completion guidelines for further information.

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

7.4.2. **Events exempt from being reported as SAEs**

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the 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 such as pharmacokinetic sampling according to the trial protocol, is also exempt from being reported as an SAE.
3. Progressive disease and death due to disease are not considered SAE's but should be reported in the eCRFs

7.5. Events of Clinical Interest

7.5.1. **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 below.

Events of clinical interest for this trial include:

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

   AND / OR

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

   AND / OR

   An alkaline phosphatase lab value that is greater than or equal to 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
3. Any AEs identified in the below table can be classified as immune-related events of clinical interest. A detailed narrative of the event should be reported as an ECI as described below:

Table 8: Events of Clinical Interest

<u>Pneumonitis - (reported as ECI if ≥ Grade 2)</u>		
Acute interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis
<u>Colitis</u> - ***(reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotising colitis	Diarrhoea	
<u>Endocrine</u> - ***(reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)***		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine *(reported as ECI)*		
Type 1 diabetes mellitus (if new onset)		

Hematologic - *(reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)*		
Autoimmune haemolytic anaemia	Aplastic anaemia	Thrombotic thrombocytopenic purpura
Idiopathic thrombocytopenia purpura	Disseminated intravascular coagulation	Haemolytic uraemic syndrome
Any grade 4 anaemia regardless of underlying mechanism		
Hepatic - *(reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)*		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALTand/or AST)
Infusion reactions - *(reported as ECI for any grade)*		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic - *(reported as ECI for any grade)*		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenicsyndromw		
Ocular - *(reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)*		
Uveitis	Iritis	
Renal - *(reported as ECI for ≥ Grade 2)*		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations - (report as ECI if ***≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***	
Skin - *(reported as ECI for any grade)*		
Dermatitis exfoliate	Erythema multiforme	Stevens-Johnson Syndrome
Toxic epidermal necrolysis		
Skin - *(reported as ECI for ≥ Grade 3)*		
Pruritus	Rash	Rash generalised
Rash maculo-papular	Any rash clinical significant in the physicians judgement.	
Other - *(reported as ECI for any grade)*		
Myocarditis	Pancreatitis	Percarditis
Any other grade 3 event which is considered immune-related by the physician.		

Further information is provided in Section 12.2 Appendix 2 titled identification, evaluation and management of irECIs. Any additional ECIs identified in this appendix information should also be reported as described below.

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

7.5.2. **Reporting of ECIs**

Any ECIs whether or not related to the Pembrolizumab, occurring from the first dose until 19 weeks following the last treatment dose, or the initiation of a new anticancer therapy, whichever is earlier, must be recorded on the AE e-case report forms and reported using the SAE/ECI report form within 1 working day of the PI/designee

becoming aware of the event to the RM-CTU by fax 02089156762 who will in turn notify who will inform the Sponsor and MSD.

7.6. Definition of an Overdose for This Protocol and Reporting of Overdose

At present no specific information is available on the treatment of overdose of pembrolizumab. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20%. In the event of overdose, pembrolizumab should be discontinued and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) should be recorded on the AE CRF and reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose either SAE or ECI must be reported within 1 working day of the PI or designee becoming aware of the event to the RM-CTU by Fax 0208 915 6762 who will inform MSD.

7.7. 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), that occurs during the trial or within 120 days of completing the trial, or 12 weeks following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported with the parents' consent.
Such events must be reported within 1 working day to RM-CTU by Fax 0208 915 6762 who will inform MSD

7.8. Definition of a Serious Adverse Reaction (SAR)

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

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

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

7.10. Reporting of SUSARs

All SUSARs must be reported using the SAE report form within 24 hours of the PI/designee becoming aware of the event to the RM-CTU by fax 02089156762. The RM-CTU will in turn notify the Sponsor, MSD, relevant Independent Ethics Committee (IEC) / Institutional review, appropriate regulatory authorities and the participating Principal Investigators in accordance with regulatory requirements and within the timelines as defined below:

- For fatal and life-threatening SUSARs the sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case. In addition, follow-up reports for fatal and life-threatening SUSARs will be provided within 8 days of the date of the initial report.

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

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

7.11. Annual Reporting of Serious Adverse Events

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

7.12. Urgent safety measures

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

USMs may be taken without prior notification from the competent authority. However the CI/DI must notify the Medicines and Healthcare Products Regulations (MHRA) the Research Ethics Committee (REC) and the Sponsor of the new events and the measures taken and the plan for further action immediately by telephone and writing within 3 days of the measure being implemented.

Should the site initiate a USM, the Investigator must inform the RM-CTU immediately either by:

- Email: Linda Wedlake
- Telephone: 020 8642 6767
- Fax: 020 8915 6762

The notification must include:

- the date of the USM;
- who took the decision; and

- why action was taken.

RM-CTU will then inform the Sponsor, the MHRA and the REC as detailed above. RM-CTU will distribute the response and any subsequent amendments to the trial sites.

CI Contact Details:

Name: Dr Susan Lalondrelle
Address: The Royal Marsden NHS Foundation Trust
Downs Rd
Sutton SM2 5Pt
Email: susan.lalondrelle@rmh.nhs.uk

8. STATISTICAL DESIGN

8.1. Endpoints

8.1.1. Primary

The maximum tolerated dose of pembrolizumab in combination with radiotherapy and brachytherapy and cisplatin.

8.1.2. Secondary

- To evaluate acute toxicity as measured during treatment by CTCAE v4.0 during radiotherapy treatment.
- To evaluate late radiotherapy toxicity as assessed by LENTSOMA at 12 weeks (study week 18), 6 months, 1 year and 2 years
- To determine response rates by RECIST v1.1 using Partial and Complete Response ('PR' and 'CR') at 12 weeks (week 18) 6 months, 1 year and 2 following radiation treatment as defined in Section 12.5, Appendix 4.
- To assess cervical HPV status at 12 weeks following radiation therapy (Week 18), assessed using a cervical smear test for the presence / absence of HPV DNA/RNA.
- To assess OS and PFS at 1 and 2 years post treatment. Note where these values exceed two years, patients will be followed-up until time of death.

8.1.3. Exploratory

Exploratory Endpoints

Peripheral blood samples and tumour biopsies (embedded and fresh) will be collected from patients consenting to collection of research samples and stored for future analysis of exploratory markers. The initial analysis of exploratory markers will include circulating tumour 'ct' DNA (blood) and expression of immune markers PD-1, PD-L1 and PD-L2 (biopsies of tumour cells). The collection of research samples (where consent is given) for exploratory end-points, will be as shown in the Schedule of Assessments, see section 5.1.

8.2. Sample Size

The sample size for this phase 1 trial is not based on a formal sample size calculation, as no formal statistical hypothesis is being tested. A traditional 3+3 design is used and the total number of patients has been based on

the desire to obtain adequate tolerability and safety. The total number of patients required will depend upon the toxicities encountered and the number of dose cohorts required.

With a minimum of 6 and a maximum of 12 patients required during the dose determination phase and 14 additional patients in the expansion phase, an estimated minimum number of 20 patients will be required. However a maximum of 26 may be needed (i.e. 12 in the dose determination phase and 14 in the expansion phase. It is estimated that 1-2 patients can be accrued per month therefore the study should take 18- 26 months to accrue plus additional time to evaluate toxicities. The end of the trial is defined as the last follow-up appointment of the last patient.

8.3. Statistical Analysis

All quantitative data will be presented as number of observations, median, minimum and maximum values. Qualitative data will be presented as number of observations and percentages. When appropriate, data will be presented together with 95% confidence intervals. All statistical tests will be two-tailed and a p-value <0.05 (5%) will be considered as statistically significant.

- Baseline characteristics will be summarized using descriptive statistics.
- Dose limiting toxicity is defined as any toxicity ≥G3 thought to be related to study drug or treatment interruptions >5 days or persistence of radiotherapy related G3 toxicity at 3 months and will be summarized using overall frequencies.
- Incidence and prevalence (highest grade) of side effects of radiotherapy (CTCAE scale v 4.0, for acute side effects and LENT SOMA for late radiotherapy scoring systems) will be reported at 12 weeks (study week 18), 6 months, 1 year and 2 years.
- Incidence and prevalence (highest grade) of acute toxicities measured by CTCAE v4.0 during treatment will be reported.
- Tumour response (Partial and Complete Response – see summarized definition below) as measured by the RECIST criteria at at 12 weeks (week 18) 6 months, 1 year and 2 years will be presented as proportions and 95% confidence intervals will be reported if appropriate.
- Cervical HPV status at 12 weeks following radiotherapy will also be presented as proportions.
- Progression free survival and overall survival will be determined using Kaplan-Meier analysis and specified as median survival (i.e. the median of all available data). Data will be presented as survival plots. Overall survival will be measured from date of first administration of Pembolizumab (two weeks prior to radiotherapy treatment) to date of death from any cause; surviving patients will be censored at date last known to be alive. Progression free survival will be measured from the same starting point to date of first appearance of disease progression, relapse or death from any cause. Patients alive without progression or relapse will be censored at date last known to be alive.
- Time to significant toxicities will be estimated by Kaplan-Meier method. Time to toxicity will be measured from the date of first administration of Pembrolizumab (i.e. two weeks prior to radiotherapy treatment) to the date of first appearance of grade 3 or above toxicity. The change in level / expression of initial

exploratory end points which include ctDNA, PD-1, PD-L1 and PD-L2 expression will be summarized using descriptive statistics and where appropriate summary statistics.

The definitions of Complete Response (CR) and Partial Response (PR) are summarised as follows and described in full in section 12.5, Appendix 4:

For **Target** lesions the following definitions apply*:

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

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

For **non-Target** lesions the following definitions apply:

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

8.4. End of study and interim analysis

The end of the study for analysis purposes is defined by the 2 years follow-up assessment of the last patient. In the event of survivors with overall or progression free survival exceeding two years, data in respect of these two end-points for these patients will continue to be collected and the end of study analysis will need to take account of this. No formal stopping rules are planned either for efficacy, futility or toxicity since this study is similar to routine standard of care. No interim analysis will be performed except for Dose Limiting Toxicity (DLT) assessment for dose escalation. See section 3.2.1 for a definition of DLT. The end-of-study report will be sent to the MHRA and applicable REC within 12 months of the date of end of trial.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1. Good Clinical Practice

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

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

9.2.1. Initial Approval

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

Prior to the shipment of IMP and the enrolling any patients the Investigator at each site is responsible for any site specific assessments and obtaining local R&D approval for the study

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

9.2.2. **Approval of Amendments**

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

9.2.3. **Annual Safety Reports and End of Trial Notification**

It is the responsibility of the sponsor to submit the Development Safety Update Report annually to the MHRA / REC on the anniversary of the studies MHRA/REC approval. This will facilitate the authorities continuing review of the study. These authorities will also be informed of the end of the study by the sponsor within 90 days of the trial completion. Copies of these reports will also be held within the main trial master file.

9.3. Regulatory Authority Approval

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

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

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

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

b. The protocol.

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

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

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

b. The scientific integrity of the trial.

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

9.5. Insurance and Liability

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

9.6. Contact with General Practitioner (GP)

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

9.7. Patient Confidentiality

9.7.1. Patient Confidentiality and Data Sharing

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

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

9.7.2. Pharmacogenetics Confidentiality

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

9.8. Data collection and documentation

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

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

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

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

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

9.9. End of Trial

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

10. 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

Case Report Forms (CRFs) which are required for specification of the trial database will be in English. The trial database will be developed in Macro (V4). In the case that the database is not ready for data entry, paper CRFs will be used for data collection. This will be regarded as an interim measure only. 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 allow 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 database or in the case of late database availability, paper CRFs.

10.4. Recording of Data

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

The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data captured within the trial database . 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 database. All protocol required investigations must be reported and captured within the trial database. . The Investigators must retain all original reports, traces and images from these investigations for future reference. If a patient withdraws from the study, the reason must be captured and the patient asked as to whether they will allow data captured up to the point of withdrawal to be used in subsequent analysis. .

Study specific information will be entered into the MACRO database by visit. Data that are derived should be consistent with the source documents or the discrepancies should be explained. All data should be anonymous, *i.e.* identified by study patient number only.

Once the patient is 'off study' and the patient's record fully completed, the Investigator must provide a signature to authorise that the patient's data is complete.

10.5. Data Management

Data management will be carried out by RM-CTU using MACRO (v4) in accordance with the data management plan agreed by the RM-CTU and RDSU. Data entry will be carried out by appropriately trained personnel at participating centres. Queries will be raised centrally by the trial manager / trial monitor and sent to the participating centre for resolution.

10.6. Study Management Structure

10.6.1. **Delegations of Responsibilities**

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

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
- raising and resolving queries with local investigators
- keeping records of all serious adverse events (SAEs), overdose incidents, pregnancies and ECI's reported by investigators
- notifying the Main REC, MHRA and Investigators of related Serious Adverse Events

10.6.1.2. MSD

- Provision of pembrolizumab

10.6.1.3. Participating Sites

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

10.7. Protocol compliance and amendments

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

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

10.8. Trial Management

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

Once all relevant trial approvals are in place an initiation (visit or teleconference) will be conducted. In addition, training and ongoing advice will be provided by trial training workshop(s), site initiation and ongoing site support to each participating site by Trial Management Group (TMG).

10.8.1. **Trial Management Group**

A Trial Management Group (TMG) will be set up and membership will include Chief Investigator, Co-Investigators, Trial Statistician and Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG has operational responsibility for the conduct of the trial. The TMG is bound to act on the advice of the Pembrolizumab Project Safety Review Committee (PPSRC) but is also responsible for monitoring recruitment, safety and governance of the trial as well as collaborating with subsequent translational sub-studies. The TMG will also review any safety concerns and can convene a meeting of the PPSRC if significant concerns exist.10.8.2 Pembrolizumab Project Safety Review Committee (PPSRC)

PPSRC has been established to coordinate the management and governance of 4 phase 1 trials evaluating Pembrolizumab in combination with standard of care radiotherapy in different tumour types (bladder, cervix, head and neck, or lung). The PPSRC will include the chief investigators of all 4 Pembrolizumab trials (Dr Tree, Professor Harrington, Dr Lalondrelle and Dr Ahmed), Dr James Larkin, Representative from RM-Clinical Trials Unit, Senior Statistician and be chaired by a clinician independent of study investigators. The PPSRC will meet monthly and at every dose escalation point, the meeting frequency maybe decreased during the expansion phases of all the studies if considered safe to do so. The role of the PPSRC is:

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

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

10.9. Monitoring

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

The trial statistician will periodically examine the data for anomalies and outliers, such as too few or too many events. Queries will be raised by the trial coordinators in such situations and communication with the clinical

teams will take place. In addition statistical monitoring of unusual dates and inconsistent data will take place. 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 circulated to the relevant parties to allow sufficient time for review prior to submission. There will be a fifteen (15) day period to review abstracts or posters and a thirty (30) day period to review slides and manuscripts and respond to the author with any revisions.

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12. APPENDICES

12.1. Appendix 1 – Standard therapy details

12.1.1. External beam radiotherapy

General information

- Patients undergoing radical radiotherapy for SCC cervix are managed in accordance with the guidelines of the RCR regarding prolongation of treatment. This guidance classifies this patient group as category 1 for which there is very strong evidence that prolongation of treatment affects outcome.
- The gap between the end of external beam to commencement of brachytherapy should be minimised in order to fulfil the desired aim of completing total treatment within 47 days and up to a maximum of 50 days. In general the gap should not be more than one week.
- Ideally intracavitary brachytherapy should be given in the last week of external beam radiotherapy or the first week after completion.
- If treatment is missed due to bank holidays, patient illness or non-attendance for other reasons the missing day can usually be added into the time between external beam completion and prior to brachytherapy which reduces the requirement forhyperfractionation.

Scanning and Treatment position

Patients should be treated supine, with hands on chest and using the indexed combi fix system. If the perineum is to be included in the treatment volume the legs should be apart to minimise skin folds.

If there is residual vaginal disease then a marker may be positioned for scanning to enable visualisation of the inferior extent of the tumour or to indicate the position of introitus. The marker should be positioned by the clinical team who should be available at the time of CT planning.

Patients should be planned and treated with the bladder moderately full as per Gynae bladder filling instructions (empty bladder, drink 350ml in 10minutes, wait 45minutes)

Volumes and outlining

PTV for Pelvis irradiation (primary treatment):

- The Clinical target volume **(CTVp)** should be the primary tumour, cervix, uterus, parametrium, proximal uterosacral ligaments, upper half of the vagina. Macroscopic vaginal disease tumour should be covered with a 3cm margin inferiorly.
- CTV of the pelvic nodes **(CTVn)** may be delineated using the blood vessels as a surrogate target. The vessels (common, internal and external iliacs) and obturator region are outlined separately with 7mm added around the vessel except where this encroaches on bone.
- The distal external iliac nodes (where the ext iliac arteries become the femoral arteries) and the inguinal nodes are not included in the volume unless abnormal on biopsy or imaging or there is disease in the lower third of the vagina.

The **Planning Target Volume (PTV)** is designed to encompass the CTV with a suitable margin

Primary PTV (PTVp) = CTVp + 1-1.5cm anterior and posterior

1cm laterally

1.5-2cm superior and inferior

Nodal PTV (PTVn) = CTVn + 7mm

PTVp and PTVn are combined to create the final PTV (PTV).

Planning technique

Pelvic lymph nodes and primary target should be planned using IMRT or arc.Patients with involved pelvic lymph nodes may be planned with concomitant boost IMRT.

Dose constraints

Organ	Dose level Gy	Max volume (%)
RECTUM and SIGMOID	30	80
	40	70
	50	60
	60	50
	Care should be taken to ensure that there are no hot spots in the rectum or sigmoid >100%.	
BLADDER	50	50
	60	25
BOWEL		Aim for (or accept) cc
	45	139 (158)
	50	110 (122)
	55	28 (105)
	60	6 (84)
	65	0 (26)
FEMORAL HEADS	50	50%

	D50(each kidney)	<18Gy

12.1.2. **BRACHYTHERAPY**

Pre-brachytherapy procedures

- Patients should have a diagnostic MRI scan of the pelvis in the week before brachytherapy applicator insertion if an intrauterine tube is to be used.
- FBC, differential, U&Es, serum Ca should be done as late as possible in the week before brachytherapy and the results reviewed. Particular attention should be paid to platelet count (>75k) and neutrophils (>1k).
- The applicator to be used should be chosen prior to BT if possible

Intracavitary doses

- All patients will have MRI and CT image guided brachytherapy unless otherwise contraindicated.
- Following MR/CT fusion the following volumes are defined (on MRI):
    - High risk CTV (HR-CTV):to include GTV (at time of BT), whole cervix and extra-cervical extension as assessed clinically, grey zones on BT MRI in parametrium, uterus and vagina
    - Bladder
    - Rectum
    - Sigmoid
    - Other bowel
    - Intermediate risk CTV (IR-CTV)

- Image guided brachytherapy prescribes to volumes and is described by dose/volume parameters. GEC-ESTRO guidelines are followed with dose constraints calculated for EQD2 values added to external beam dose delivered.

OAR/PTV	**EQD2 (including EBRT component)**
D2cc Bladder	90Gy
D2cc Rectum	70Gy – 75Gy
D2cc Sigmoid	70Gy – 75Gy
HR-CTV D90	**≥ 80 Gy.**

- Standard tube and ovoid weightings will be optimised to meet the dose volume constraints for HRCTV and OAR although the prescription point for intra-uterine brachytherapy will continue to be to the mean Point A as defined by the Manchester system. In the case of image guided intrauterine tube and vaginal dobbie, the prescription point is to 100%.
- Three fractions of brachytherapy will be delivered over 24hours (min 6 hour gap between fractions). The nominal dose is 16.5Gy in 3# to Point A (21Gy in 3# if 45Gy to pelvis). Doses may be revised due to dose constraints or individual clinical considerations. BT distributions and doses are always approved and prescribed by a consultant clinical oncologist or delegated trained clinician.
- If it is not possible to perform intracavitary brachytherapy (e.g. cervical os cannot be located or is stenosed) then an external beam radiotherapy phase II volume should be conformally planned to encompass the CTV (plus a 1.5 cm margin) to a total dose of 63Gy to 68Gy.

12.1.3. **Cisplatin chemotherapy**

- Chemoradiation has been accepted as standard treatment for cervical cancer following publication of a meta-analysis confirming improved survival. Chemotherapy has largely been standardised in the UK as cisplatin 40mg/m^2 weekly (max 75mg).
- Exclusion criteria for concomitant cisplatin are GFR < 50 ml/min or severe co-morbidities.
- The site will follow local protocols for the preparation and administration of cisplatin, including use of supportive medication. The protocol requires the patient to have had an initial EDTA clearance, surface area calculation and weekly FBC, U+E, and LFTs. Chemotherapy should start within the first week of radiotherapy.
- No more than 4 cycles of concomitant chemotherapy are delivered.
- On the day of chemotherapy, RT to be given after chemotherapy

12.2. Appendix 2: Identification, Evaluation and Management of irECIs

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	• methylprednisolone 125mg IV followed by prednisone 1 to 2 mg/kg/day or dexamethasone 4mg every 4 hours.

		• Rule out bowel perforation • Recommend gastroenterologist consult &biopsy with endoscopy	• 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 • Rule out infection and sepsis.	• IV methylprednisone 1-2mg/kg followed by prednisone 1-2mg/kg per day. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. Replacement of appropriate hormones may be required. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4 Hyperthyroidism	• Report 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.	• 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

		• 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.	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 3-4hyperglycaemia 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).	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Report as ECI within 24 hours	• 0.5-1mg/kg/day methlyprednisone 125mg or oral equivalent.

Please refer to ECI guidance for definitions of (DILI)		• 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	• 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	• 1-2mg/kg of prednisone daily. • Symptoms grade 1 or less initiate steroid

		• Evaluation by ophthalmologist recommended • Withhold pembrolizumab & consider discontinuation.	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 • 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, erytemamulitforme, Stevens Johnson syndrome, toxic epidermal	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 with oral steroids at PIs discretion

necrolysis.	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.

12.3. Appendix 3: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

12.4. Appendix 4: 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 LENT SOMA scoring system.

12.5. Appendix 5: 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 MRI or PET-CT may be utilized, as per RECIST 1.1, MRI is the preferred imaging technique in this study.

For **Target** lesions the following definitions apply*:

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

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

For **non-Target** lesions the following definitions apply:

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

* 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.

12.6. Appendix 6: Table of revisions

Document/ Version/ Page/ Section **E.g.** PIS, v1.0 24-05-17, Page 3, Section 9	Previous Wording	New Wording (Tracked)	Comments/ Explanation/rationale for substantial amendment