Clinical Study Protocol

Study Title:	**PEACH** - Phase I dose-escalation study of **PE**mbrolizumab (MK3475) **A**nti-PD1 immune checkpoint inhibitor combined with radical **C**hemoradiotherapy in patients with stage IV squamous cell carcinoma of the **H**ead and neck
CCR Number:	CCR 4325
Product:	Pembrolizumab
Co-Sponsor:	Royal Marsden NHS Foundation Trust and The Institute of Cancer Research
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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:

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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 dose-escalation study of **PE**mbrolizumab (MK3475) Anti-PD1 immune checkpoint inhibitor combined with radical Chemoradiotherapy in patients with stage IV squamous cell carcinoma of the Head and neck
Abbreviated Title	PEACH
Trial Phase	Phase I
Clinical Indication	Stage IV squamous cell cancer of the head and neck cancer (SCCHN)
Trial Type	Single arm, phase I dose escalation study
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	Group 1 – HPV-ve stage IVA/IVB SCCHN Group 2 – HPV+ve stage IVA/IVB SCCHN
Number of trial patient patients / Sites	6 - 36 (maximally 18 HPV-ve, 18 HPV+ve) / 1 UK investigational site
Estimated duration of trial	30 months
Duration of Participation	15-18 months
Study Objectives	*Primary Objective* • To assess the safety and tolerability of combining platin-based chemoradiotherapy with pembrolizumab in patients with HPV-ve and HPV+ve; stage IV squamous cell head and neck cancer. *Secondary Objective* • To assess progression free and overall survival. • To assess overall responses rates as per RECIST v1.1. *Exploratory Objective* • To assess the effects of pembrolizumab on the immune responses of patients receiving radical chemoradiotherapy for high- and intermediate-risk HPV-ve and HPV+ve LA-SCCHN. • To study the role of measuring circulating free tumour DNA (ctDNA) as a biomarker of tumour clearance and/or recurrence.
Study Endpoints	*Primary Endpoint* • A: To establish the maximum tolerated dose that can safely be combined with platin-based chemoradiotherapy in patients with HPV-ve and HPV+ve LA-SCCHN. • B: To evaluate acute toxicity as measured during treatment by CTCAE v4.0. *Secondary Endpoint* • To measure the PFS and overall survival at 6 months, 1 year and 2 years. • To measure the duration of clinical benefit as defined by CR, PR and SD using RECIST at 6 months, 1 year and 2 years. *Exploratory Endpoint* *Peripheral blood analysis* • PBMC biomarkers of immune response: Quantitative assays of CD4, CD8, T regulatory cell (CD4/CD25, FOXP3), B cells and NK cells will be performed. In addition, where feasible, functional assays of cytokine release will be performed.

	Analysis of circulating free tumour DNA – pre, per- and post-treatment. *Tumour Biopsy samples* • Immunohistochemical analysis to identify immune infiltrates (T cells [$CD4^+$, $CD8^+$, $CD4^+/CD25^+$ Treg], B cells, macrophages, NK cells), levels of expression of PD1 (and other immune exhaustion markers) on immune cells, levels of PDL1 expression on tumour cells.
Summary of Main Inclusion Criteria	• Have treatment naive histologically confirmed high-/intermediate-risk LA-SCCHN • Be ≥ 18 years of age and willing and able to provide written informed consent for the trial. • Have measurable disease based on RECIST 1.1. • Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion. • Be fit for definitive platin-based chemoradiation therapy. • Demonstrate adequate organ function and a performance status of 0 or 1 • Female patient of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to confirmation of study eligibility. • Patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.
Summary of Main Exclusion Criteria	• Taking any IMP or using an Investigational device within 4 weeks of the first dose. • Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose. • Prior use of a monoclonal antibody, chemotherapy, targeted small molecule therapy, or radiation therapy. • Previous radiotherapy to the head and neck region • Additional malignancy that is progressing or requires active treatment. • Active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable, have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. • Active 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. • Evidence of interstitial lung disease or active, non-infectious pneumonitis. • Have active tuberculosis • Has known hypersensitivity to pembrolizumab or any of its excipients. • History or current evidence of any condition, therapy, or laboratory abnormality that might confound trial results, interfere with the patient's participation or is not in the best interest of the patient. • Psychiatric or substance abuse disorders that would interfere with patients participation. • Pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 120 days after the last dose. • Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or

	checkpoint pathways). • History of HIV. HIV 1/2 antibodies, Hepatitis B or Hepatitis C. • Has received a live vaccine within 30 days prior to the first dose of trial treatment. • Has an active infection requiring systemic therapy.
Treatment / Main Study Procedures	Patients will be registered to receive pembrolizumab in combination with platin-based chemoradiotherapy. 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 cycle 1 of a regimen of pembrolizumab 3 weekly at a dose of 100 or 200mg (dependent on dosing level) for a total of 7 cycles (3 during chemoradiotherapy and 4 after chemoradiotherapy). Clinical assessments will be undertaken at the pre-loading dose and then every 3 weeks on the day on which the drug is administered. Patients will continue on this regimen until they complete all 8 doses of pembrolizumab, suffer disease progression, unacceptable toxicities, discontinue the study medication for any other reason or withdraw from the study. Chemoradiotherapy will begin with the cycle 1 dose of pembrolizumab and will continue for 35 fractions over a period of 7 weeks. After the last dose of pembrolizumab patients will be expected to attend post-treatment follow-up visits as described below and/or safety follow-up (SFU) at 12 weeks or earlier if initiating a new anti-cancer treatment. Follow up requirements for patients are as follows: • If a patient completes all 8 doses of pembrolizuamb without disease progression or unacceptable toxicities they will be seen at 4 weeks and 8 weeks after the last dose of pembrolizumab for the post treatment follow up. They will then return at 12 weeks for the SFU and after this be followed up every 4 weeks for 9 months to assess for disease status and the initiation of a new anti-cancer treatment. If the patient progresses or begins a new treatment during this time then they will move into the survival follow up every 12 weeks by telephone for overall survival until death, withdrawal of consent, or the end of the study • If a patient discontinues for reasons other than disease progression they will be seen at 8 weeks after the last dose of pembrolizumab for the post treatment follow up. They will then return at 12 weeks for the SFU and after this be followed up every 8 weeks for 9 months to assess disease status until progression, initiating a non-study cancer treatment or withdrawal. If a patient progresses or begins a new anticancer therapy patients will be followed every 12 weeks by telephone for overall survival until death, withdrawal of consent, or the end of the study. • If a patients progresses at any time in the study they would be expected to complete a SFU visit at 12 weeks after their last dose of pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. They will then move into survival follow up and will be followed every 12 weeks by telephone for overall survival until death, withdrawal of consent, or the end of the study. Patients will also undergo tumour assessment by RECIST 1.1 at screening, 8 weeks post chemoradiotherapy (cycle6) and then every 12 weeks for 12 months (irrespective of delays

	in treatment) to establish disease response. OPTIONAL: Patients will be asked to consent to the collection of pre, per- and post-treatment research bloods and an additional tissue biopsy after the pre-loading dose and before chemoradiotherapy for translational endpoints.

CONTENTS

1.0 BACKGROUND & RATIONALE

1.1 Background

Stage III-IV locoregionally advanced squamous cell cancer of the head and neck (LA-SCCHN) accounts for over 50% of patients diagnosed with head and neck cancer [1]. Following radical non-surgical treatment, five-year overall survival (OS) rates for LA-SCCHN vary from 10% to 75% depending on tumour stage, the site of the primary tumour, the association with human papillomavirus (HPV) and other known risk factors [2]–[6]. For oropharyngeal squamous cell carcinoma, specific risk groups have been clearly defined: high-risk patients are those with locally advanced disease, with HPV-negative tumours who either have a ≤10 pack-year smoking history with T4 tumours or have a >10 pack-year smoking history irrespective of T stage [7], [8]. Patients with HPV-positive tumours and a >10 pack-year smoking history also have a worse prognosis and are defined as being at an intermediate risk of death. Overall survival (OS) in patients with high-risk locally advanced oropharynx cancer is low (3-year OS 46.2% following concurrent chemoradiotherapy (CRT)), compared with 70.8% in the intermediate-risk and 93% in the low-risk groups [7]. Locally advanced laryngeal and hypopharyngeal cancers behave as high- to intermediate-risk tumours. Both locoregional failure and systemic metastatic relapse represent major causes of disease persistence/recurrence and account for significant morbidity and mortality in high-risk disease. In patients with intermediate-risk disease, systemic metastasis represents a particular problem [9]. Meta-analysis data have failed to show a role for adjuvant chemotherapy as a means of reducing the risk of locoregional or systemic failure in LA-SCCHN [10]. Therefore, there is a significant unmet need for novel therapies to improve outcomes in patients with high- and intermediate-risk disease and, currently, the only ongoing studies involve small molecule inhibitors of c-erbB signaling pathways. Data presented in abstract form at ASCO 2014 have recently shown that use of the EGFR/HER2 dual tyrosine kinase inhibitor, lapatinib, during and after post-operative adjuvant cisplatin-based chemoradiotherapy is not associated with improved progression-free or overall survival [11].

LA-SCCHN is an attractive model in which to test immune checkpoint blockade because of the documented efficacy of anti-PD1 monoclonal antibody (MAB) therapy in non-small-cell lung cancers (including squamous cell cancers). In addition, pembrolizumab has been reported to have single-agent activity in patients with relapsed head and neck cancers, with activity in both HPV-ve and HPV+ve disease [12]. Furthermore, the existence of both HPV-ve and HPV+ve forms of the disease affords the opportunity to study the relative importance of targetable self and non-self tumour antigens (HPV E6 and E7) in LA-SCCHN. In addition, there exists the potential to develop parallel studies in cervix cancer (>95% HPV+ve) which may shed further light on both HPV+ve and HPV-ve contexts in LA-SCCHN. Therefore, we propose to test immune checkpoint blockade in patients with high- and intermediate-risk LA-SCCHN.

It is increasingly recognized that ionising radiation may stimulate immune responses in the tumour microenvironment [13]. We seek to test the hypothesis that these immune responses can be further activated by combining radical cytotoxic chemoradiotherapy with an immune checkpoint-modulating drug. We postulate that pembrolizumab can be combined safely with the current standard-of-care (70 Gy in 35 fractions with concomitant cisplatin 100 mg/m^2 on three occasions) in the treatment of high- and intermediate-risk LA-SCCHN. This study will aim to demonstrate safety and feasibility of this approach prior to subsequent testing in randomized phase II trial.

1.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [14]. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies [15]–[19]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) [20], [21]. The structure of murine PD-1 has been resolved [22]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade [20], [22]–[24]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signalling proteins [25], [26]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [27], [28]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [29]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours [25], [30]–[32]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signalling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the

T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [25]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumour-specific T-cell expansion in patient s with melanoma (MEL) [33]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and should be considered as an attractive target for therapeutic intervention.

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

1.1.2 Preclinical and Clinical Trial Data

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

1.2 Rationale

1.2.1 Rationale for the Trial and Selected Patient Population

The outcomes with radiation alone for advanced (stage III and IV) head and neck cancer are disappointing. In recent years, systemic chemotherapy has increasingly been incorporated into the treatment plan. As part of primary treatment, systemic chemotherapy can be administered before (induction or neo-adjuvant chemotherapy) or during (concomitant chemotherapy) radiotherapy. Using chemotherapy concomitantly with radiation (CRT) has been shown to improve survival and rates of organ preservation [10], [34]. Cisplatin is considered the gold standard for concomitant treatment in head and neck cancers [35]. CRT is now the standard-of-care as an organ-sparing approach in the treatment of stage III and IV squamous cell carcinomas of the larynx and the hypopharynx [34], [36], [37].

However, the addition of concomitant chemotherapy results in an increased incidence and exacerbation of acute radiation toxicity [38], [39]. In a meta-analyses of chemotherapy trials, the relative risk of acute mucositis was nearly three times that of treatment with radiation alone [40]. The late radiation-induced toxicity includes xerostomia [41] (60-90% incidence), grade 3 dysphagia [38], [41](15-30%), osteoradionecrosis (ORN) of the mandible [42] (5-15%), sensori-neural hearing loss [43] (40-60%), skin fibrosis and laryngeal cartilage necrosis.

The addition of chemotherapy to radical radiotherapy also results in a significant increase in the risk of radiation-induced late toxicity [44], [45]. Hey et al compared the normal tissue complication probability parameter, D50 (dose at which 50% complication probability is expected) for the parotid salivary glands for patients having RT alone and CRT. The D50 was higher for patients receiving RT alone (39.6 vs. 32.6) [46]. Studies using chemo-radiation (CRT) or altered radiation fractionation strategies have reported rates of 12-50%

significant late dysphagia i.e. feeding tube dependency at 1 year which significantly affects patient's QOL [47]–[52].

Taking these data into consideration, it is important to appreciate that further intensification of treatment by adding additional chemotherapy drugs or agents that directly or indirectly enhance DNA damage may lead to unacceptable toxicities in patients with LA-SCCHN. Therefore, an alternative approach, such as systemic immunotherapy, which is less likely to have a toxicity profile that overlaps with that of concomitant chemoradiotherapy, represents an attractive new paradigm for the treatment of LA-SCCHN. This approach will be relevant both to HPV-ve and HPV+ve disease, although the tumour-specific immune effects are likely to be different in each disease sub-type.

1.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being 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 patient s 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. 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.

It has therefore been decided to use a dosage of pembrolizumab that will be based on a total dose and not defined by weight. This will be either 100 mg (dose level 1) or 200 mg (dose level 2). The decision to include dose level 1 (100 mg q 3 weeks) is based on the fact that this therapeutic combination has never been tested in patients with newly diagnosed LA-SCCHN who are receiving curative chemoradiotherapy. In such patients, any interruptions or delays to chemoradiotherapy can have a negative impact on treatment outcomes. For this reason, we have chosen to be cautious in treating an initial cohort at 100 mg q 3 weeks – rather than the usual single-agent dose of 200 mg q 3 weeks.

1.2.3 Rationale for Endpoints

This study aims to establish whether the combination of pembrolizumab (MK-3475) and conventional cisplatin-based chemoradiotherapy is tolerable and results in acceptable levels of acute and late toxicity in patients with stage IV LA-SCCHN. In particular, the study will provide data on the levels of mucosal and cutaneous toxicity within the radiation fields, as these are the primary acute toxicities associated with this treatment regimen. In addition, toxicity outside the radiation portals (which may theoretically be exacerbated by radiation) will be studied. However, all toxicity will be monitored. This study will also give an indication of the activity of pembrolizumab in LA-SCCHN because we are deliberately selecting a group of patients with high- and intermediate-risk disease who have a significant chance of experiencing loco-regional or systemic failure.

1.2.3.1 Efficacy Endpoints

Acute and late toxicity assessed by CTCAEv4 will be used to judge the tolerability of a combination of pembrolizumab and chemoradiotherapy to ensure that the treatment does not cause excess toxicity.

Flexible nasendoscopy and standard ENT examination will be performed to support the measurement the clinical response of disease. These findings will be augmented by imaging investigations performed according to the schedule of study assessment (in Section 5.0).

1.2.3.2 Biomarker Research

This protocol provides an excellent opportunity to obtain tumour tissue for translational studies. All patients will have baseline tumour biopsies available for study (in many cases these will include both fresh and formalin-fixed paraffin-embedded specimens). Patients that consent have serial blood samples drawn for analysis of circulating free tumour DNA – pre, per- and post-treatment. Patients with node-positive disease will undergo neck dissection at 12 weeks post-chemoradiotherapy.

If the patient consents, tumour biopsies will be obtained prior to commencing treatment (week 0) and, where feasible, at week 3 of treatment. We have experience of such procedures, with a high degree of successful tissue acquisition 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 (and other immune exhaustion markers) on immune cells, levels of PDL1 expression on tumour cells.

In addition research blood samples will be used to assess PBMC biomarkers of immune response using quantitative assays of CD4, CD8, T regulatory cell (CD4/CD25, FOXP3), B cells and NK cells will be performed. In addition, where feasible, functional assays of cytokine release will be performed.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

Objective: To assess the safety and tolerability of combining platin-based chemoradiotherapy (70 Gy in 35 fractions plus cisplatin (100 mg/m^2) on days 1, 22 and 43) with pembrolizumab anti-PD1 monoclonal antibody in patients with HPV-ve and HPV +ve disease.

Hypothesis: It is hypothesised that pembrolizumab can be safely dosed at 200 mg every 3 weeks during cisplatin-based chemoradiotherapy in patients with locally advanced head and neck cancer.

2.1.2 Secondary Objectives

Objective: To assess progression free and overall survival.

Hypothesis: Combining pembrolizumab with chemoradiotherapy and continued use of pembrolizumab alone could lead to prolonged responses in patients.

Objective: To assess duration of clinical benefit defined as SD, PR or CR response using RECIST v1.1 by imaging and clinical examinations.

Hypothesis: High- and intermediate-risk disease have a significant chance of experiencing loco-regional or systemic failure.

2.1.3 Exploratory Objectives

Objective: To conduct exploratory translational studies of the effects of pembrolizumab on the immune responses of patients receiving radical chemoradiotherapy for high- and intermediate-risk HPV-ve and HPV+ve LA-SCCHN – these studies will include analysis of both peripheral blood mononuclear cells (PBMC) and intratumoural immune infiltrates.

Hypothesis: It is hypothesised that pembrolizumab will favourably alter the anti-tumour immune response in patients receiving cisplatin-based chemoradiotherapy for locally advanced head and neck cancer**.**

Objective: To study the role of measuring circulating free tumour DNA (ctDNA) as a biomarker of tumour clearance and/or recurrence.

Hypothesis: It is hypothesised that pembrolizumab will favourably alter the kinetics of ctDNA clearance in patients receiving cisplatin-based chemoradiotherapy for locally advanced head and neck cancer (in comparison with a historical control dataset that we are currently generating).

2.2 Study Endpoints

2.2.1 Primary Endpoint

1. A: To establish the maximum tolerated dose that can safely be combined with platin-based chemoradiotherapy in patients with HPV-ve and HPV+ve LA-SCCHN.
   B: To evaluate acute toxicity as measured during treatment by CTCAE v4.0.

2.2.2 Secondary Endpoints

1. To measure the PFS and overall survival at 6 months, 1 year and 2 years.
2. To measure the duration of clinical benefit using RECIST at 6 months, 1 year and 2 years.
3. To evaluate late radiotherapy toxicities as measured during treatment by LENT SOMA 52 weeks from the end of radiation therapy (week 7).

2.2.3 Exploratory Endpoints

A. Peripheral blood analysis

1. PBMC biomarkers of immune response: Quantitative assays of CD4, CD8, T regulatory cell (CD4/CD25, FOXP3), B cells and NK cells will be performed. In addition, where feasible, functional assays of cytokine release will be performed.
2. Analysis of circulating free tumour DNA – pre, per- and post-treatment.

B. Tumour Biopsy samples

1. Immunohistochemical analysis to identify immune infiltrates (T cells [$CD4^+$, $CD8^+$, $CD4^+/CD25^+$ Treg], B cells, macrophages, NK cells), levels of expression of PD1 (and other immune exhaustion markers) on immune cells, levels of PDL1 expression on tumour cells.

3.0 STUDY DESIGN

3.1 Overall Study Design

This will be a single centre phase 1 dose-escalation study to confirm the safety of combining pembrolizumab with standard platin-based chemoradiotherapy in patients with stage IV high- and intermediate-risk locally-

advanced squamous cell carcinoma of the head and neck (LA-SCCHN). 6-36 patients (18 HPV+ve and 18 HPV-ve) will be recruited in a standard 3+3 dose-escalation trial design with an expansion cohort at the maximum tolerated dose (or 200 mg, if no DLT is defined). 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 cycle 1 of a regimen of pembrolizumab 3 weekly at a dose of 100 or 200mg (dependent on dosing level) for a total of 7 cycles (3 during chemoradiotherapy and 4 after chemoradiotherapy).

Parallel studies in HPV-ve and HPV +ve disease will be conducted (note these patients may have different patterns of co-morbidity and, hence, different treatment-related toxicities). The primary endpoint of the study will be safety and tolerability. Dose-limiting acute toxicity will be assessed during administration of study drug according to CTCAEv4.0. The maximum tolerated dose of study drug (or 200 mg in the absence of DLT) will be used in a subsequent randomised phase 2 study comparing standard-of-care therapy with standard-of-care therapy plus study drug.

3.2 Treatment Regimen

All patients will receive radical platin-based chemoradiotherapy (70 Gy in 35 fractions plus cisplatin 100 mg/m2 or carboplatin Area under the curve (AUC) = 5) on days 1, 22, 43 in combination with Pembrolizumab.

Pembrolizumab (at the dose level under current evaluation –100/200mg) will be administered as a pre-loading dose after the completion of the screening period, cycle 1 which will be 2 weeks after the pre-loading dose and then every 3 weeks for a total of 7 cycles (3 during chemoradiotherapy and 4 after chemoradiotherapy) or until disease progression, presence of unacceptable toxicities or withdrawal. Both the HPV-ve and HPV+ve arms will run simultaneously.

A minimum of 3 patients will be required per HPV cohort 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 in the first 3 patients at a dose level, pembrolizumab will be escalated to the next dosing level. If 1 in 3 patients experience a 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 administereddose (MAD) will have been reached and the previous dosing level, the MTD, should be used for the expansion phase. If 2/3 patients experience a DLT the MTD will have been reached and the previous dosing level should be used for the expansion phase, if this occurs at dose level 1 the study would be stopped.

Once the MTD has been determined the trial enters the expansion cohort whereby a further 6 are treated in each HPV cohort with the determined dosage of pembrolizumab in combination with platin-based chemoradiotherapy.

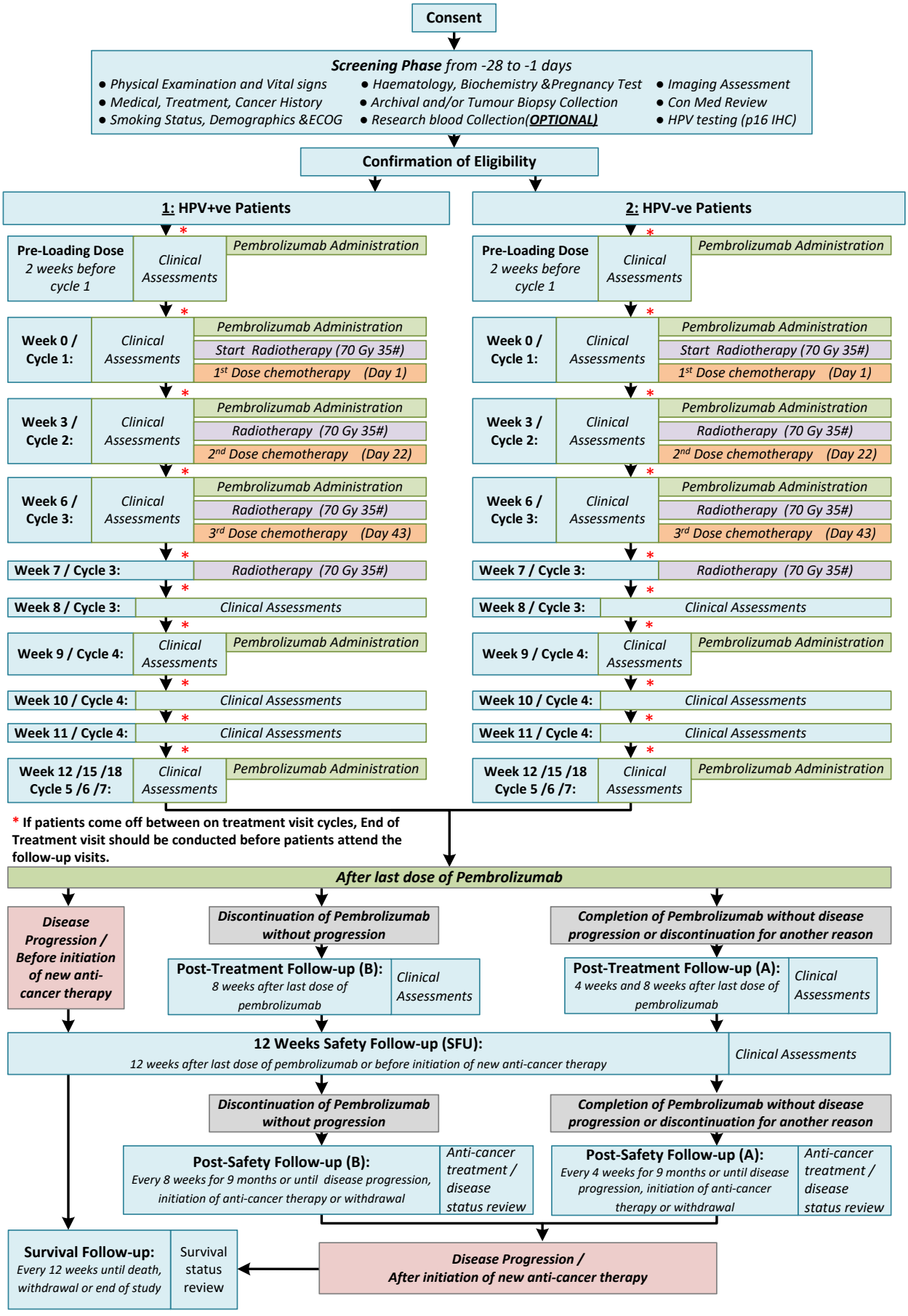
3.3 Dose Levels

This study has 2 dosing levels. The rate of entry and escalation to the next dose level will depend upon assessment of the toxicity profile of patients entered at the previous level. Toxicity and assessment for DLT period will be assessed during treatment and up until 6weeks after the completion of chemoradiotherapy. The DLTs for this study will be defined as: Grade 4 thrombocytopenia (or Grade 3 with haemorrhage); Grade 4 neutropenia lasting >7 days (or Grade 3 with fever); Grade 4 anemia; Grade 4 mucositis (or Grade 3 with confluent lesions lasting >6 weeks after the end of radiotherapy); >2 weeks toxicity-related treatment delay; or any other ≥Grade 3 non-hematologic toxicity (except nausea and vomiting) which in the opinion of the investigator is considered dose-limiting. The results of each dosing level will be reviewed by the safety review committee (SRC) before recruitment to the next dose level can begin.

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

- **If 0/3 patients** experience any of the above mentioned DLT's escalation to the next dose level can proceed.
- **If 1/3 patients** experiences any of the above mentioned DLT's the dose level will be expanded to a total of 6 patients.
    - If 1/6 patients experience any of the above mentioned DLT's then escalation to the next dose level can proceed.
    - If ≥ 2/6 patients in a specific dose level experience any of the above mentioned DLT's the maximum tolerated dose will have been reached and all subsequent patients will be recruited at the previous dose level.
- **If 2/3 patients** experience any of the above mentioned DLT's then the maximum tolerated dose will have been reached and the expansion cohort phase will begin at the previous dose level. If the MTD is reached at dose level 1 the study will be stopped.

3.4 Study Flow Chart



3.5 Follow-up Visits

3.5.1 Post-Chemoradiotherapy Follow-up Visits

Patients will be seen weekly for 4 weeks after completion of chemoradiotherapy. After this they will then be seen 3 weekly at the administration of the next cycles of pembrolizumab.

3.5.2 Post-Treatment Follow-up (A) Visit – Patients who complete all cycles of pembrolizumab

Patients who complete all cycles of pembrolizumab without disease progression or suffering unacceptable toxicities will be seen at 4 weeks and 8 weeks after the last dose of pembrolizumab. Procedures and assessments will be performed as defined in the schedule of study assessment (Table 2).

3.5.3 Post-Treatment Follow-up (B) Visit – Patients who discontinue without progression.

Patients who discontinue pembrolizumab for any reason other than disease progression will be seen 8 weeks after the last dose of pembrolizumab. Procedures and assessments will be performed as defined in the schedule of study assessment (Table 2).

3.5.4 12 Weeks Safety Follow-up (SFU) Visit

In addition to the above follow up all patients are expected to attend a mandatory safety follow-up visit conducted at 12 weeks after the last dose of pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the safety follow-up visit should be recorded as described in section 7.0. 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.

3.5.5 Post-Safety Follow-up (A) Visits – Patients who complete all cycles of pembrolizumab.

Patients who complete all cycles of pembrolizumab without disease progression or suffering unacceptable toxicities will move into the post-safety follow-up (A) phase. These patients will be assessed every 4 weeks from SFU for 9 months or until the patient suffers disease progression, they begin a new anti-cancer treatment or they withdraw. Each follow up visit will monitor disease status and assess for any new anti-cancer therapies. If a patient progresses or begins a new anti-cancer therapy they will move to the survival follow-up phase.

3.5.6 Post-Safety Follow-up (B) Visits – Patients who discontinue without progression.

Patients who discontinue pembrolizumab for any reason other than disease progression will move into the post-safety follow-up (B) phase. These patients will be assessed every 8 weeks from SFU for 9 months or until the patient suffers disease progression, they begin a new anti-cancer treatment or they withdraw. Each follow-up visits will monitor disease status and assess for any new anti-cancer therapies initiated. If a patient progresses or begins a new anti-cancer therapy they will move to the survival follow-up phase.

3.5.7 Survival Follow-up – Patients who have disease progression

Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy, the patient moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. If a patient progresses on treatment they will also be required to attend a SFU at 12 weeks or before the initiation of a new anti-cancer treatment; whichever comes first.

3.6 Study Termination

The end of the study is defined when the last patient has completed post-safety follow-up phase (A)/(B) or discontinued the study for other reasons.

3.6.1 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. MTD is seen at dose level 1

In accordance with the conditions of supply agreement with Merck 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.

3.7 Treatment after Study Termination

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

4.0 PATIENT SELECTION AND ENROLMENT

4.1 Screening and Enrolment

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

4.2 Registration

When the patient signs the consent form they will be allocated a trial identification number that will be used to identify the patient throughout the trial. Once all the screening assessments have been completed and the data entered on the CRFs; the patient will be assessed for eligibility. If eligible the patient will begin on the trial. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient.

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

4.3 Stratification

Patients will be stratified in to each arm according to the HPV status of their tumour.

4.4 Patient Replacement Strategy

Additional patients may be enrolled in a given cohort to ensure that the required number of evaluable patients in each cohort is achieved. A patient that discontinues the trial for progressive disease or a drug-related AE will not be replaced. Patients receiving at least one radiotherapy fraction and one dose of pembrolizumab will also be counted in the evaluable population for the primary endpoint of treatment-related toxicity of patients for the respective cohort.

Patients found to be ineligible during screening or do not continue onto treatment or do not reach the visit 6 weeks post chemoradiotherapy can be replaced by new patients in that cohort to ensure there is a minimum of 3 (or 6 if required) patients in each cohort.

All other patients will be assessed for toxicity and secondary endpoints.

4.5 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.

4.5.1 Inclusion Criteria

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

1. Have treatment naive and histologically confirmed high-/intermediate-risk LA-SCCHN
2. Be willing and able to provide written informed consent for the trial.
3. Be ≥ 18 years of age on day of signing informed consent.
4. Have measurable disease based on RECIST 1.1.
5. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Be fit for definitive platin-based chemoradiation therapy.
8. Demonstrate adequate organ function as defined in table 1, all screening labs should be performed within 10 days of confirmation of study eligibility.

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

Table 1: Adequate Organ Function Laboratory Values

9. 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.
10. Female patient s 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 (Reference Section 6.7.2). Patient s of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
11. Male patient s should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

4.5.2 Patient Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Has received prior radiotherapy to the head and neck region.
3. 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.
4. Has had a prior monoclonal antibody, chemotherapy, targeted small molecule therapy, or radiation therapy.
5. 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.
6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patient s with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
7. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patient s 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. Patient s with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.
8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
9. Has an active infection requiring systemic therapy.
10. Has active tuberculosis.

11. Has known hypersensitivity to pembrolizumab or any of its excipients.
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 or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
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.

5.0 STUDY PLAN AND PROCEDURES

5.1 Study Schedule

Whilst on this treatment patients will be assessed at the administration of the pre-loading dose and then every 3 weeks at the administration of their next dose of pembrolizumab for a total of 8 doses or until they progress, suffer unacceptable toxicities, withdraw or the study ends. After the last dose of pembrolizumab patients will be required to attend post-treatment follow-up visits as described below and/or safety follow-up (SFU) visit at 12 weeks or before the initiation of a new anti-cancer therapy, whichever comes first.

If the patient has completed all 8 doses of pembrolizumab and has not progressed or discontinued treatment for any other reason they will be seen at 4 weeks and 8 weeks after the last dose of pembrolizumab for the post treatment follow up visit. They will then return at 12 weeks for the SFU and after this be followed up every 4 weeks for 9 months or until disease progression, initiation of a new anti-cancer therapy death, withdrawal, end of the study.

If the patient has not progressed but discontinued treatment for another reason they will be seen 8 weeks after the last dose of pembrolizumab for the post treatment follow up. They will then return at 12 weeks for the SFU and after this be followed up every 8 weeks for 9 months until disease progression, initiation of a new anti-cancer therapy, death, withdrawal or end of the study.

Patients that have progressed or initiated a new anti-cancer therapy during treatment or follow-up phase will enter into the survival follow-up phase and will be contacted every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Patients that progress during treatment will be required to have a SFU at 12 weeks or before the initiation of a new anti-cancer therapy; whichever comes first.

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. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

Trial Period:		Treatment Cycles – Every 3 Weeks													Post-Treatment					
Treatment Cycle/Week Title:	Screening Phase	Pre-Loading Dose	C 1 *Wk 0*	C 2 *Wk 3*	C 3 *Wk 6*	C3 *Wk 7*[8]	C 3 *Wk 8*	C 4 *Wk 9*	C 4 *Wk 10*	C 4 *Wk 11*	C 5 *Wk 12*	C 6 *Wk 15*	C 7 *Wk 18*	End of Treatment - At time of discontinuation of treatment[4]	Post-Treatment Follow-up (A)[1]	Post-Treatment Follow-up (B)[2]	Safety Follow-up (SFU)	Post-Safety Follow-up (A)[1]	Post-Safety Follow-up (B)[2]	Survival Follow-up
Scheduling Window (Days):	-28 to -1	wihtin 3 days after confirmation of eligibility	2 wks after pre-loading dose (± 3)	± 3	± 3	N/A	± 1	± 3	± 1	± 1	± 3	± 3	± 3		4 wks and 8 wks from last dose of Pembrolizumab	8 wks from last dose of Pembrolizumab	12 wks from last dose of Pembrolizumab[3]	Every 4 wks from SFU for 9 months	Every 8 wks from SFU for 9 months	Every 12 wks from progression / initiation of anti-cancer treatment
Administrative Procedures																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X																			
Demographics, Medical & Treatment History, Smoking Status	X																			
Anti-cancer therapy Review															X	X	X	X	X	
Survival / Disease Status															X	X	X	X	X	X
Clinical Procedures / Assessments																				
Review Adverse Events		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Radiation Toxicity Review				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medication Review	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Full Physical Exam	X																			
Directed Physical Exam		X	X	X	X		X	X	X	X	X	X	X	X			X			
Vital Signs, Weight & ECOG	X	X	X	X	X		X	X	X	X	X	X	X	X			X			
Height	X																			
Pregnancy Test – Urine/Serum	X																			
T3, T4, TSH, PT and aPTT	X		X		X			X		X		X					X			
Haematology & Biochemistry	X	X	X	X	X		X	X	X	X	X	X	X	X			X			
Urinalysis	X																			
Admin of Pembrolizumab		X	X	X	X			X			X	X	X							
Admin of Radiotherapy			X	X	X	X														
Admin of Chemotherapy			X	X	X															
Tumour Imaging	X											X[7]								
Clinical disease assessment	X		X	X	X			X			X	X								
Archival collection or new tumour biopsy	X		X[5]	X[5]																
HPV testing (p16 Immunohistochemistry)	X																			
Research Blood Collection (OPTIONAL)	X			X				X				X								
Neck dissection													X[6]							

1. For patients who have completed 8 doses of pembrolizumab and have not progressed or discontinued from unacceptable toxicities.
2. For patients that have discontinued treatment for any reason other than progression and have not withdrawn consent for participation.
3. Or before the initiation of a new anti-cancer therapy whichever comes first.
4. Only applicable if patients come off between on treatment visit cycles.
5. Where feasible and if the patient has consented OPTIONAL post-treatment research tumour biopsies will be taken at week 0 and week 3.
6. In patients with N+ Disease.
7. CT / MRI Imaging should be completed at screening, Week 15 (Cycle 6) and then every 12 weeks for 12 months or until disease progression, discontinuation or initiation of another anti-cancer treatment.
8. C3 Wk 7 is not a clinic visit. Patient will continue to receive radiotherapy only.

Table 2: Schedule of Study Assessment

5.2 Administrative Procedures/Assessments

5.2.1 Informed Consent

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

The Investigator must obtain documented written informed consent from each potential patient prior to participating in a clinical trial. Consent must be documented by the patients' 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 and Treatment History

Demographic data collected will include date of birth and race/ethnicity. A medical history will be obtained by the investigator /designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. In addition any abnormal and clinically significant results seen during the screening period should be recorded in the medical history form. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

In addition to the medical history the investigator or qualified designee will obtain details the patient's current disease status and treatment history including:

- Prior and current details regarding disease status
- Review all prior cancer treatments including systemic treatments, radiation and surgeries
- Smoking status

5.2.4 Anti-Cancer Therapy Review

Anti-cancer therapy review will be performed at all follow-up visits as defined in the schedule of study assessment (Table 2). The investigator should review all new anti-cancer therapy initiated after the last dose of trial treatment. If a patient initiates a new anti-cancer therapy after the last dose of trial treatment, the 12 Weeks Safety Follow-up (SFU) visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the patient will move into survival follow-up.

5.2.5 Survival / Disease Status

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

5.2.6 Prior and Concomitant Medications Review

5.2.6.1 Prior Medications

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

5.2.6.2 Concomitant Medications

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

5.3 Clinical Procedures/Assessments

5.3.1 Adverse Event (AE) Monitoring

The investigator / designee will assess each patient for potential new or worsening AEs as specified in the schedule of study assessment (Table 2) and more frequently if clinically indicated. Adverse events will be graded and recorded from the first dose of pembrolizumab until the patients 12 weeks safety follow-up visit according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

5.3.2 Radiation Toxicity Assessment

Radiotherapy toxicity will be documented using the LENT SOMA radiation toxicity grading system (Appendix 3). Assessments will take place at each visit as defined by the study's schedule of assessment (Table 2)

5.3.3 Full Physical Exam

The investigator / designee will perform a complete physical exam at screening period and ther time points as defined in the study schedule of assessment (Table 2). Clinically significant abnormal findings should be recorded as adverse events during the trial.

5.3.4 Directed Physical Exam

For cycles that do not require a full physical exam as described in the schedule of assessment (Table 2), the investigator / designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

5.3.5 Vital Signs

The investigator /designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the schedule of study assessment (Table 2) Vital

signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

5.3.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator / designee will assess ECOG status (Table 3)at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the study schedule of 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 ClinOncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Table 3: ECOG Performance Status

5.3.7 Pregnancy Tests

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

5.3.8 Haematology, Clinical Biochemistry and Urinalysis, PT, aPTT, FT3, FT4 and TSH

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

Haematology	Chemistry	Urinalysis	Other
Haematocrit	Albumin	Blood	PT
Haemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	FTotal triiodothyronine (FT3)
WBC (total and differential)	Aspartate aminotransferase	Specific gravity	Free tyroxine (FT4)

	(AST)		
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If results are abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Uric Acid	Urine pregnancy test †	
	Calcium Corrected		
	Chloride		
	Glucose		
	Phosphate		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	Creatinine Clearance		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

Table 4: Required Laboratory Assessments

Laboratory tests for screening should be performed within 10 days of confirmation of study eligibility. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator / designee and found to be acceptable prior to each dose of trial treatment.

5.3.9 Tumour Imaging and Assessment of Disease

5.3.9.1 Clinical Assessment.

Patients will be assessed clinically for disease resolution at screening and then every 3 weeks until 8 weeks post-chemoradiotherapy. These clinical assessments will include direct visualisation of the upper aerodigestive tract (including flexible nasendoscopy) and clinical examination of the neck.

5.3.9.2 Baseline tumour imaging

Imaging should confirm that the patient has a lesion is measurable using RECIST v1.1 to be eligible for the trial.

5.3.9.3 Timing and Assessment of Disease

Tumour imaging may be performed by CT or magnetic resonance imaging (MRI), but the same imaging technique should be used in a patient throughout the trial. The initial tumour imaging will be performed no more than 28 days prior to confirmation of eligibility. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within the correct time window.

On-study imaging will be performed at screening then at cycle 6 to assess disease response. After cycle 6 imaging will be performed every 12 weeks for 12 months and should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies.

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

Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

5.3.9.4 Confirmation of Disease Response

Per RECIST v1.1 (Appendix 4), response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

5.3.9.5 Confirmation of Disease Progression

Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable patients. Patients who have unconfirmed disease progression may continue on treatment until progression is confirmed.

Clinically stable is defined by the following criteria:

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

5.3.10 Human Papillomavirus (HPV) testing via p16 Immunohistochemistry

Archival or new tumour biopsy collected at screening will be used for HPV testing via standard p16 immunohistochemistry. Sample will be analysed by the local study site laboratory using standard method for routine test. Patients will be stratified into two cohorts according to the HPV status of their tumour. The first cohort containing patients with HPV+ve disease and the second cohort containing patients with HPV-ve disease. Both cohorts will receive pembrolizumab in combination with chemoradiotherapy.

5.3.11 Tumour Tissue Collection and Correlative Studies Blood Sampling

5.3.11.1 Archival Tumour tissue samples

For patients where a baseline biopsy is not feasible, archival tumour material must be provided. All collected archival samples will be classed as pre-treatment samples and used as such in the immunological evaluation as described below.

5.3.12 Tumour Biopsies and Research Blood Samples

For patients without archived samples tumour biopsies will be obtained during the screening period and if the patient consents additional biopsies at week 0 and week 3 where feasible. Patients with node positive disease will also where feasible receive a neck dissection 12 weeks after completing chemoradiotherapy. In addition to the tumour biopsies if a patient has consented they will also provide a series of research blood samples for analysis of circulating free tumour DNA – pre, per- and post-treatment and serum for pharmacokenetic / pharmacodynamic evaluations.

Tumour and blood samples from this study may undergo proteomic, genomic and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and radiotherapy. Assays may include, but are not limited to:

- **Characterization of TILs and tumour antigens**

  Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within tumour tissue before and where feasible (at week 0 and week 3, and for N+ 12 weeks after chemoradiotherapy) after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: T cells [$CD4^+$, $CD8^+$, $CD4^+/CD25^+$ Treg], B cells, macrophages, NK cells), levels of expression of PD1 (and other immune exhaustion markers) on immune cells, levels of PDL1 expression on tumour cells.

- **Immunophenotyping**

  The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in peripheral blood mononuclear cell (PBMC) preparations will be analysed. Analyses may include, but not necessarily be limited to; CD4, CD8, T regulatory cell (CD4/CD25, FOXP3), B cells and NK cells will be performed. In addition where it is feasible, functional assays of cytokine release will be performed.

Assays will be performed in accordance with the standard operating procedures (SOPs) of the research laboratory headed by Prof Christian Ottensmeier. Please refer to laboratory manual for details on sample collection and processing.

5.3.13 Chain of Custody of Biological Samples

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle. The Investigator at each site is responsible

for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Anyone with custody of the samples e.g. sub-contracted service provider will have to keep full traceability of samples from receipt to further shipment or disposal (as appropriate).

RM-CTU will keep overall oversight of the entire lifecycle through internal procedures and monitoring of study sites. Samples retained for further use will be registered with the Prof Christian Ottensmeier and Prof Gareth Thomas at the University of Southampton.

5.4 Total Blood Volume

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

	Sample volume (mL)	No. of samples	Totalvolume (mL)
Routine Haematology	6[1]	14	84
Routine Clinical chemistry	8[1]	14	112
		Total:	196
Research Blood Samples – OPTIONAL	30	4	120
		Study Total	316

Table 5: Volume of blood to be drawn from each trial patient for the duration of the trial; calculations based on 8 administrations of pembrolizumab (1 pre-loading dose and 7 cycles on study), 3 post chemoradiotherapy toxicity visits, a screening visit and 30 days post end of treatment safety visit.

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

6.0 TREATMENTS

Patients will be given pembrolizumab in addition to platin based chemoradiotherapy.

6.1 Standard Treatment - Radiotherapy

6.1.1 Radiotherapy

Intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT)/RapidArc planning will be used in all patients. Detailed outlining and planning guidelines are detailed in the ISO accredited standard operating procedures (SOPs) of the Royal Marsden Radiotherapy Department..

6.1.2 Radiotherapy Dose

Patients will receive a dose of 70Gy in 35 fractions.

6.1.3 Patient Immobilisation and Image Acquisition

All patients will be immobilised in a custom-made thermoplastic shell supine with the neck in the extended position. All patients will undergo a planning CT scan with intravenous contrast. The scans (from vertex of skull to carina) will be taken at intervals of 2.5 mm throughout.

6.1.4 Outlining process (Gross Tumour Volume (GTV) and Clinical Target Volume (CTV) definition)

The gross tumour volume of the primary site (**GTV-p**) is defined as all known gross disease before any treatment as defined by the staging CT and or MRI scans, operative findings and clinical information. The gross tumour volume of the lymph nodes (**GTV-n**) is defined by the physician as all known gross disease before any treatment as defined by the staging CT and or MRI scan, and clinical information.

CTVs for macroscopic disease (GTV-p and GTV-n) and areas at risk of harbouring microscopic disease will be outlined on each CT slice, as will critical structures. MRI scans, clinical information and operative findings may be used to assist the delineation of target volumes. The margins used in the expansion from GTVs to CTVs will be defined in the SOPs. The spinal cord, brain stem, and bilateral parotid glands will be outlined. Primary and elective nodal irradiation volumes will be outlined as in the EORTC, GORTEC and RTOG-endorsed consensus guidelines and target volume definition PARSPORT guidelines for the delineation of the CTV in the node negative and node positive neck for patients with head and neck squamous cell carcinoma.

6.1.5 Radiotherapy Planning

The margin for planning target volume (PTV) and organs-at-risk (planning risk volume, PRV) will be pre-determined based on the known set-up error. Radiotherapy will be performed using the local treatment planning system. A 5- to 9-field technique will be used to obtain a uniform coverage of the PTV and satisfy the dose constraints to the organs-at-risk (OAR). Dose distributions should be calculated and corrected for inhomogeneities and deliverable beams.

The prescription will be to the median dose point on the dose volume histograms (DVH) such that the prescription dose (70 Gy) is received by 50% of the PTV1. The minimum and maximum doses to the PTV should be within 90 –110% of the prescription dose (see table below). Less than 2% of the volume outside the PTV should receive >107% of the prescription dose.

% PTV	% Dose
99%	at least 90%
95%	>95%
<5%	105%
<2%	107%

Table 6: Dose limits for PTV

The dose limits for radiosensitive organs are given below and should be assessed from dose-volume histograms (DVH) of 3D volumes:

Spinal cord	Absolute Maximum dose 48 Gy to PRV spinal cord for all patients
Brain Stem	Absolute Maximum dose 55 Gy to PRV brainstem for all patients
Parotid	Mean <24 Gy (where feasible)

Table 7: Dose constraints for OAR

6.1.6 Radiotherapy delays

Delays in radiotherapy should be avoided. If a treatment gap occurs, two fractions per day should be given with an inter-fraction interval of at least 8 hours. Alternatively the patient could be treated on a weekend.

6.2 Standard Treatment – Chemotherapy

6.2.1 Chemotherapy Dose

Cisplatin (or carboplatin) will be administered on day 1, day 22 and day 43 to the patient at a dose of 100 mg/m^2 with pre- and post-hydration as an in-patient. Cisplatin (or carboplatin) will be prepared, administered and handled as per local practice. BSA calculations, dose banding and dose capping should all be done as per local practice. Additional information regarding dose modification for chemotherapy can be found in appendix 1.

6.3 Trial Treatment - Pembrolizumab

6.3.1 Investigational Product

The Investigational Medicinal Product (IMP) for this study is Pembrolizumab. A potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T-cells.

Pembrolizumab will be manufactured by MSD according to Good Manufacturing Practice and will be provided in the formulation as described in the table below. Additional information about the investigational product can be found in the Investigator's Brochure (IB).

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

Table 8: Product Description

6.3.2 Product Preparation

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

6.3.3 Storage and Handling

6.3.3.1 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.

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

6.3.3.2 Handling

Infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or 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. Administer infusion solution through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

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.

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**.

Further details on the preparation of the drug product can be found in the MSD pharmacy manual.

At each site the Investigator / designee e.g pharmacist at each participating site is responsible for ensuring that all trial Medication must be stored in a secure, limited-access location under the storage conditions specified

on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Trial medication may not be used for any purpose other than that stated in the protocol.

6.3.4 Packaging and Labelling Information

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

6.3.5 Returns and Reconciliation

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

Upon completion or termination of the study, partially used trial medication will be destroyed at the site per institutional policy. It is the Investigator's/designees responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Upon completion or termination of the study, all unused trial medication will be returned to MSD or destroyed at the site per institutional policy. It is the Investigator's/designees responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.3.6 Doses and treatment regimens

All patients will receive pembrolizumab administered as per standard procedures following manufacturer's instructions. Two dose levels of pembrolizumab will be studied to ensure tolerability of combining therapy with chemoradiotherapy. The treatment regimen to be used at each dosing level is outlined in the table below.

Drug	Dose Level	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	1	100 mg	3-weekly	IV infusion	8 doses (pre treatment & 7 cycles)	Experimental
Pembrolizumab	2	200 mg	3-weekly	IV infusion	8 doses (pre treatment & 7 cycles)	Experimental
The pembrolizumab dosing interval may be increased due to toxicity as described in Section 6.3.9.2						

Table 9: Pembrolizumab treatment regimens for each dosing level.

6.3.7 Timing of Dose Administration

Trial treatment should be administered at the pre-loading dose and then on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the Study Flow Chart (Section 3.4) and on the schedule of study assessment (Table 2). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Cisplatin will be administered to the patient at a dose of 100 mg/m^2 with pre- and post-hydration as an in-patient. Therefore, the first 3 cycles of pembrolizumab will also be administered as an in-patient. Thereafter, all trial treatments will be administered on an outpatient basis. If the patient receives concomitant carboplatin (AUC = 5) rather than cisplatin, concomitant chemotherapy and study medication can be given as an outpatient.

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section6.3.9.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

6.3.8 Trial Blinding/Masking

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

6.3.9 Dose Selection/Modification

6.3.9.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 1.2.2 – Background and Rationale.

6.3.9.2 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities (except for toxicities, such as mucositis, skin reaction, pain) that are commonly encountered during chemoradiotherapy for LA-SCCHN), and severe or life-threatening AEs as per the below table.

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 prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue

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

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

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

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

Table 10: Dose Modification guidelines for drug-related adverse events.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued. Patient's 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.

Patient's 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.

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

6.4 Concomitant medications

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

6.4.1 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria and described below are not allowed during the ongoing trial. If there is a clinical indication for these or other medications or vaccinations to be used during the trial, then the patient should discontinue trial therapy. The investigator should discuss any questions regarding this with the CI (or delegate). Please refer to the corresponding SmPC for further recommendations on co-administration.

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, and the patient.

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemoradiotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in the protocol, Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or to manage nausea and vomiting during cisplatin treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Patient's 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.

6.4.2 Acceptable Concomitant Medications

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

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

6.5 Rescue Medications & Supportive Care

6.5.1 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:

6.5.1.1 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.

6.5.1.2 Nausea/vomiting:

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

6.5.1.3 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.

6.5.1.4 Immune-related adverse events:

Please see Section 6.6 below regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

6.5.1.5 Management of Infusion Reactions:

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

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 the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS,	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids	Patient may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be pre-medicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at <u>http://ctep.cancer.gov</u>		

Table 11: Infusion Reaction Treatment Guidelines

6.6 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 cancer, infectious, metabolic, toxin or other etiologic causes prior to labelling an adverse event as an irAE.

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

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. Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

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

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

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) and for life-threatening (Grade 4) hypophysitis.

Monitor patients for hyperglycemia or other signs and symptoms of type 1 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, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hyperthyroidism. Treat symptoms of hyperthyroidism as appropriate. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. For 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, Guillain-Barre syndrome, 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 Appendix 5. Patients with symptomatic irECIs should immediately stop receiving pembrolizumab and be evaluated to rule out non treatment related causes of the event. Overdose and liver tocicity irECIs irrespective of relationship to the study drug should be reported within 24 hours of the investigator being aware to the Sponsor who will in turn notify MSD. If the irECI is determined to be associated please refer to Appendix 5 for the recommendations on the management of these irECIs. If the event is not considered to be associated with the study drug the physician should exercise individual clinical judgment on the event management based on the patient. Any additional questions of the collection or information on management of irECIs should be directed to the Sponsor.

6.7 Diet/Activity/Other Considerations

6.7.1 Diet

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

6.7.2 Contraception

Pembrolizumab may have adverse effects on a foetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either, two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. Male patients with partners of child bearing potential will also be required to agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

Patients should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If

there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.7.3 Use in Pregnancy

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

6.7.4 Use in Nursing Women

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

6.8 Treatment of Overdose of IMP

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

6.9 Permanent Discontinuation of Trial Medication and Withdrawal from the Study

6.9.1 Permanent Discontinuation of Trial Medication

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

- The subject withdraws consent.
- Confirmed radiographic disease progression

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

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

After the last dose of pembrolizumab patient will be required to complete post-treatment follow-up visits as described below and/or safety follow-up visit in 12 weeks of that dose or before initiating another anti-cancer treatment, whichever comes first.

Follow-up actions for patients are as follows:

- If a patient has **not progressed** and has completed all 8 doses of pembrolizumab they will be required to:
    - Attend follow-up assessments at 4 weeks and 8 weeks after the last dose of pembrolizumab;
    - Attend SFU visit at 12 weeks after the last dose of pembrolizumab.
    - Attend follow-up assessments every 4 weeks from safety follow-up visit for 9 months or until they progress, initiate a new anti-cancer treatment or withdraw.

- If a patient discontinues treatment and does not complete all 8 doses of pembrolizumab for reasons other than progression during treatment and **does not withdraw their consent to follow up** they will be required to:
    - Attend follow-up assessments at 8 weeks after the last dose of pembrolizumab;
    - Attend SFU visit at 12 weeks after the last dose of pembrolizumab
    - Attend follow-up assessments every 8 weeks from safety follow-up visit for 9 months or until disease progression, initiation of a new anti-cancer treatment or withdrawal. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

- If a patient **progress or initiates a new antic-cancer treatment** at any point in the trial they will be required to:
    - Undertake survival status assessments every 12 weeks until death, withdrawal of consent, lost to follow up or the end of the study.
    - ***Please Note:*** Patients that progress on treatment will be required to attend a SFU at 12 weeks or before the initiation of a new anti-cancer therapy; whichever comes first.

6.10 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 or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. When a patient discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation, these are listed in the schedule of study assessment (Table 2). Any adverse events which are present at that time should be followed in accordance with the safety requirements outlined in Section 7.

Patients who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria. After discontinuing treatment following assessment of CR, these patients should return to the site for post-treatment follow-up visits and/or 12 weeks safety follow-up visit and then proceed to the follow-up period of the study.

7.0 PHARMACOVIGILANCE

7.1 Adverse events

7.1.1 Adverse Event Definition:

An adverse event is defined as any untoward undesired or unplanned occurrence (including deterioration of a pre-existing medical condition) in a patient administered a pharmaceutical product or undertaking a protocol-specified procedure. An AE can therefore be any unfavourable and unintended sign, symptom or disease and/or laboratory or physiological observation associated with the use of a medicinal product or protocol-specified procedure but does not necessarily have to have a causal relationship to this treatment or procedure.

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered 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 7.4

7.2 Assessing and Recording Adverse Events

All adverse events will be recorded from the first dose until the safety follow-up in the CRF. They will be followed up according to local practice until the event has stabilised or resolved, or the follow-up visit has taken place, whichever is the sooner. 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.

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

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

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

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

For the pre-registration period 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 medical physician.

7.3.1 Determining AE Severity and Grade

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

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

7.3.2 Determining AE Causality

The Principal Investigator must endeavour to obtain sufficient information to assess the causality of the AE and must provide his/her opinion whether the event has any relationship to the administered study treatment / procedure. This may require instituting supplementary investigations of significant AEs based on their clinical

judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

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

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

7.4 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, 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, foetal 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 24 hrs to RM-CTU by Fax 0208 915 6762 or e-mail to Peach.Trial@rmh.nhs.uk who will inform MSD.

7.5 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 new cancer
- is a congenital anomaly or birth defect;
- Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event.
- is any other medically important event.[3]

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

7.5.1 Reporting SAEs

All SAEs regardless of causality, pregnancy or overdose that occur from the first dose until the 12 weeks 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 or e-mail to Peach.Trial@rmh.nhs.uk who will in turn notify the sponsor and MSD of the event.

The SAE form must be completed, assessed for causality and expectedness against the current version of the Investigator Brochure (Reference Safety Information Appendices), 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 the sponsor and 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 the Sponsor and MSD.

7.5.2 Events exempt from being reported as SAEs

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

1. Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting.
2. Hospitalisation for administration of the IMP, or to facilitate study procedures such as pharmacokinetic sampling according to the trial protocol, is also exempt from being reported as an SAE.
3. Progressive disease and death due to disease are not considered SAE's but should be reported in the CRFs

7.5.3 Determining SAE Causality and Expectedness

Assessment of causality for all SAEs will be made by the PI/designee and Chief Investigator or delegate. Thereafter, assessment of expectedness for all SAEs will be made by the PI/designee and Chief Investigator or delegate against the current version of the Investigator Brochure (Reference Safety Information Appendices). If updated versions of the investigator brochure are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.

7.6 Events of Clinical Interest

7.6.1 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 overdose and liver toxicity ECIs must be reported as described in section 7.5.2.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 7.7 that is not associated with clinical symptoms or abnormal laboratory results.
2. A Drug induced liver injury (DILI) defined as elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal

   AND / OR

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

   AND / OR

   An alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
3. Any AEs identified in the below table 13 can be classified as immune-related events of clinical interest. A detailed narrative of overdose and liver toxicity ECIs should be reported as described in section 7.5.2:

Pneumonitis - ***(classified as ECI if ≥ Grade 2)***

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

Table 13: Immune related AEs considered ECIs

Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or

symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.6.2 Reporting of ECIs

Overdose and liver toxicity ECIs whether or not related to the Pembrolizumab, occurring from the first dose until 12 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 24 hrs of the PI/designee becoming aware of the event to the RM-CTU by fax 02089156762 or e-mail Peach.Trial@rmh.nhs.uk who will in turn notify who will inform the Sponsor and MSD.

7.7 Definition of an Overdose for This Protocol and Reporting of Overdose

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

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

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

All reports of overdose either SAE or ECI must be reported within 24hrs of the PI or designee becoming aware of the event to the RM-CTU by Fax 0208 915 6762 or e-mail to Peach.Trial@rmh.nhs.uk who will inform MSD.

7.8 Definition of a Serious Adverse Reaction (SAR)

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

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

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

contained in the Investigator's Brochure. The Investigator's Brochure will be used for assessing the expectedness of all adverse reactions.

7.10 Reporting of SUSARs

All SUSARs must be reported using the SAE report form within 24hrs of the PI/designee becoming aware of the event to the RM-CTU by fax 02089156762 or e-mail to Peach.Trial@rmh.nhs.uk. 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.
- SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

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

7.11 Annual Reporting of Serious Adverse Events

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

7.12 Urgent safety measures

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

USMs may be taken without prior notification from the competent authority. The CI / DI must notify the Medicines and Healthcare Products Regulations (MHRA), Research Ethics Committee (REC) and Sponsor immediately and in any event, within 3 days of the measures taken and the plan for further action. The initial notification to the MHRA will be by telephone, and then a written notice will be sent out within 3 days. Should the site initiate a USM, the Investigator must inform the RM-CTU immediately either by:

- Email: Peach.Trial@rmh.nhs.uk
- Telephone: 020 8915 6667
- Fax: 020 8915 6762

The notification must include:

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

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

CI Contact Details:

Name: Prof Kevin Harrington

Address: The Royal Marsden NHS Foundation Trust
Downs Rd
Sutton SM2 5Pt

Email: kevin.harrington@icr.ac.uk

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

8.2 Endpoints

8.2.1 Primary Endpoint

A: To establish the maximum tolerated dose that can safely be combined with platin-based chemoradiotherapy in patients with HPV-ve and with HPV+ve LA-SCCHN, respectively.

B: To evaluate acute toxicity in each HPV group as measured during treatment by CTCAE v4.0.

8.2.2 Secondary Endpoints

1. To measure the PFS and overall survival at 6 months , 1 year and 2 years, respectively.
2. To measure the duration of clinical benefit using RECIST at 6 months, 1 year and 2 years, respectively.
3. To evaluate late radiotherapy toxicities as measured during treatment by LENT SOMA 52 weeks from the end of radiation therapy (week 7).

8.2.3 Exploratory Endpoints

A. Peripheral blood analysis

1. PBMC biomarkers of immune response: Quantitative assays of CD4, CD8, T regulatory cell (CD4/CD25, FOXP3), B cells and NK cells will be performed. In addition, where feasible, functional assays of cytokine release will be performed.
2. Analysis of circulating free tumour DNA – pre, per- and post-treatment.

B. Tumour Biopsy samples

1. Immunohistochemical analysis to identify immune infiltrates (T cells [$CD4^+$, $CD8^+$, $CD4^+/CD25^+$ Treg], B cells, macrophages, NK cells), levels of expression of PD1 (and other immune exhaustion markers) on immune cells, levels of PDL1 expression on tumour cells.

8.2.4 Sample Size

With a minimum of 3 patients in each HPV cohort at dose level 1, a minimum of 6 patients are required. With a maximum of 6 patients in each of the 2 dose levels and a further 6 in the expansion phase, a maximum of 18 patients are required in each HPV cohort, respectively. This gives a minimum of 6 to a maximum of 36 patients, respectively, are required for the trial.

8.2.5 Data analysis

All quantitative data will be presented as number of observations, means and SDs for normally distributed data or as median and interquartile ranges for data that appear to be non-normally distributed. Qualitative data will be presented as number of observations and frequencies. 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 achieving statistical significance. The analysis will be performed separately in HPV-ve and HPV+ve cohorts, respectively.

- Baseline characteristics will be summarized using descriptive statistics. Dose limiting toxicity will be summarized using overall frequencies. Incidence (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.

- Duration of clinical benefit will be calculated as the number of patients who had a best overall response of CR, PR, or SD according to the RECIST criteria until the first date of recurrence or progressive disease (PD) and will be measured at the landmark points in the study 6 months, 1 year and 2 years, respectively. They will be presented as proportions and 95% confidence intervals will be reported if appropriate.

- Progression free and overall survival will be determined using Kaplan-Meier methods presenting the median survival times, and survival rates will be reported at 6 months, 1 and 2 years, respectively. Overall survival will be measured from date of 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 start of treatment 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. Survival curves will be estimated for each HPV cohort and compared using the log-rank test.

- The levels of CD4, CD8, T regulatory cell (CD4/CD25, FOXP3), B cells, NK cells and Circulating free tumour DNA pre RT , during RT and post RT will be presented as descriptive statistics according to their HPV status. The expression of PD1 (and other immune exhaustion markers) on immune cells and PDL1 on tumour cells will be presented as descriptive statistics.

8.2.6 Timing of analysis

For the primary end point, the results of each dosing level will be reviewed by the safety review committee (SRC) before recruitment to the next dose level can begin and once the MTD has been determined the trial enters the expansion cohort. Analysis of the secondary endpoints will take place 1 year after the enrolment of the last patient. Analysis of the exploratory endpoints will be reported once all the relevant samples have been collected and analysed.

9.0 REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

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 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 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.

9.5 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.

9.6 Patient Confidentiality

9.6.1 Patient Confidentiality and Data Sharing

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

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

9.6.2 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.

9.7 Data collection and documentation

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

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

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

9.8 End of Trial

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

10.0 DATA AND STUDY MANAGEMENT

10.1 Source Data

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

10.2 Language

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

10.3 Data Collection

The medical records/medical notes should be clearly marked and 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 CRF.

10.4 Recording of Data

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

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

The CRF will be signed by the Investigator or by an authorised staff member. Study specific information will be entered into an CRF visit by visit. Data that are derived should be consistent with the source documents or the

discrepancies should be explained. All CRF data should be anonymous, *i.e.* identified by study patient number only.

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

10.5 Data Management

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

10.6 Study Management Structure

10.6.1 Delegations of Responsibilities

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

10.6.1.1 RM-CTU

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

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

- ensuring an appropriate ethics opinion has been sought, and any amendments have been approved
- giving notice of amendments to protocol, make representations about amendments to the Main REC and MHRA as applicable
- notifying sites and Sponsor that the trial has ended
- randomising patients
- raising and resolving queries with local investigators
- keeping records of all serious adverse events (SAEs), overdose incidents, pregnancies and overdose and liver toxicity 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
- .

10.7 Protocol compliance and amendments

All participating sites will be required to sign and adhere to the trial protocol.

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

10.8 Trial Management

The RM-CTU will be responsible for the day-to-day coordination and management of the trial. This includes all duties relating to safety reporting. 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 (1 per study)

A Trial Management Group (TMG) will be set up and membership will include Chief Investigator, Co-Investigators, Trial Statistician and Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG has operational responsibility for the conduct of the trial. The TMG is bound to act on the advice of the 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), Representative from RM-Clinical Trials Unit, Senior Statistician and be chaired by Dr James Larkin,. The PPSRC will meet monthly and at every dose escalation point, the meeting frequency maybe decreased during the expansion phases of all the studies if considered safe to do so. The role of the PPSRC is:

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

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

10.9 Monitoring

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

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

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

10.10 Quality Control and Quality Assurance

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

10.11 Clinical study report

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

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.

The Chief investigator 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 15 years after the study has concluded.

10.13 Reporting and publication

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

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

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12.0 APPENDICES

12.1 Appendix 1: Dose-Modification Guidelines for Chemotherapy

Toxicities are to be assessed according to the CTCAE version 4.0. Patients should be monitored closely for toxicities, and the cisplatin dosing should be withheld or reduced according to degrees of toxicity.

The guiding principle for dose modifications in patients receiving therapy with MK-3475, cisplatin, and radiotherapy is to modify only the treatment responsible for the toxicity in question, if the toxicity is entirely consistent with 1 of the 3 treatments. Therapy with the other treatment may continue while treatment with the presumptive causative agent is interrupted or modified. In contrast, if the toxicity in question cannot be easily attributed to 1 of 3 treatments, then further treatment with each of the agents may need to be discontinued, interrupted, or modified. Treatment modifications will, however, take into account that radiation therapy is the foundation therapy being employed, and adjustments to the radiotherapy regimen will only be made if unavoidable due to the toxicity observed.

12.1.1 Dose Limiting Toxicity for Cisplatin

12.1.1.1 Haematological Toxicity

Hematologic Toxicity	Cisplatin Modifications of Dose and Regimen
ANC < 1200/mm^3	Withhold cisplatin therapy until toxicity resolves. When toxicity resolves (ANC≥1200) reinitiate cisplatin at same dose.
Neutropenic fever	Permanently reduce cisplatin dose by 25%.
Platelet count is <75,000 /mm^3	Withhold cisplatin therapy until toxicity resolves. When toxicity resolves (> 75,000 per cu. mm) reinitiate cisplatin at

	same dose.
Thrombocytopenia with bleeding	Permanently reduce cisplatin dose by 25%.

12.1.1.2 Neurotoxicity

If any signs of ≥ Grade 3 neurotoxicity occur, cisplatin use should be discontinued. In this instance, cisplatin should be replaced with carboplatin at a dose of 5 AUC (carboplatin dose = 5 x [GFR+25]).

12.1.1.3 Renal Toxicity

Cisplatin should be administered on the scheduled day of treatment using the following guidelines.

Creatinine Clearance	Cisplatin Dose
> 60 mL/min	100 mg/m^2*
50-60 mL/min	50 mg/m^2
< 50 mL/min	Discontinue and notify Medical Monitor Switch to carboplatin AUC = 5

In the event that GFR <50 mL/min, substitute carboplatin 5 AUC for cisplatin. Carboplatin is contraindicated if GFR < 30mL/min.

12.1.1.4 Mucositis

Grade 4 mucositis will require a permanent 25% dose reduction of cisplatin.

12.1.1.5 Ototoxicity

Ototoxicities, including clinical hearing loss not requiring a hearing aid or tinnitus that interferes with activities of daily living, should lead to discontinuation of cisplatin and substitution with carboplatin at a dose of AUC = 5.

12.1.2 Dose Modifications for Carboplatin

ANC/µL	Platelet/µL	Neurotoxicity, Grade	% Dose Administered
>2000	100,000	0, 1	100
1000 to 1999	75 000 to100 000	2	50
<1000	<75 000	3, 4	hold for 1 week

12.1.3 Criteria for Retreatment

Following the first dose of cisplatin and the first dose of MK-3475, 2 further doses of cisplatin or carboplatin and 6 additional doses of MK-3475 will be given. Cisplatin or carboplatin will be given concurrently with radiation to a total of 70 Gy. These subsequent doses are at the discretion of the investigator and consent from the patient. If the patient meets any of the following criteria, treatment will be delayed 1 week and the patient will be re-evaluated.

- Neutrophils ≤1,500/mm^3
- Platelets ≤75,000/mm^3
- Grade 3 - 4 hematologic toxicities

- Grade 3 - 4 non-hematologic toxicities

Initiation of cisplatin or carboplatin re-treatment may be delayed for a maximum of 14 days to allow recovery from any toxicity. If the toxicity has not resolved within 14 days of the planned treatment date, re-treatment may occur if the patient is responding to treatment and there is agreement with the Trial Steering Committee.

12.1.4 Dose-Limiting Toxicity of Chemoradiotherapy

The definition of DLT will follow the generally accepted parameters in published phase I trials and will aim to identify any amplification of the expected toxicities of standard chemoradiotherapy by addition of pembrolizumab. The DLT period will be up until 6 weeks after the end of chemoradiotherapy. Therefore, DLT will be defined as: Grade 4 thrombocytopenia (or Grade 3 with haemorrhage); Grade 4 neutropenia lasting >7 days (or Grade 3 with fever); Grade 4 anemia; Grade 4 mucositis (or Grade 3 with confluent lesions lasting >6 weeks after the end of radiotherapy); >2 weeks toxicity-related treatment delay; or any other ≥Grade 3 non-hematologic toxicity (except nausea and vomiting) which in the opinion of the investigator is considered dose-limiting.

12.2 APPENDIX 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

12.3 APPENDIX 3: LENT SOMA Scales for all Anatomical Sites

This study will 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.

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

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

* As published in the European Journal of Cancer:

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

12.5 APPENDIX 5: Identification, evaluation and management of ECIs

ECI	Grade	Action to be taken	Supportive Care
Pneumonitis –	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Withhold pembrolizumab, may restart if Grade 1 or	• 1-2mg/kg/day prednisone or equivalent. • Symptoms grade 1 or less, initiate steroid

		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	taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg prednisone or less or equivalent per day within 12 weeks.
	Grade 3 and 4	• Discontinue pembrolizumab • 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 o 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 tosection 6 and 7.
• 1st episode - May increase dosing interval by one week in subsequent cycles • 2nd episode of - Pneumonitis Permanently discontinue pembrolizumab if upon re-challenge patient develops Pneumonitis ≥ Grade 2			
Colitis	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 (For grade 2 diarrhoea that persists > 3 days)	• Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Symptomatic treatment o Consider GI consult & endoscopy to rule out colitis	• Prednisone 1-2mg/kg/day or equivalent • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg or less of prednisone or equivalent per days within 12 weeks. • If symptoms worsen or persist >1 week treat as grade 3.
	Grade 3	• Withhold pembrolizumab • Rule out bowel perforation • Recommend gastroenterologist consult & biopsy with endoscopy	• methylprednisolone 125mg IV followed by prednisone 1 to 2 mg/kg/day or dexamethasone 4mg every 4 hours. • Symptoms grade 1 or less initiate steroid taper for no less that 4 weeks. • Taper 6-8 weeks in patients with diffuse or severe ulceration and/or bleeding • If IV steroids do not reduce initial symptoms within 48-72 hours treat with additional anti-inflammatory measures. At symptom relief discontinue anti-inflammatory and initiate steroid taper over 45-60 days. If symptoms worsen during this period refer to Section 6 and 7.
	Grade 4	• Discontinue pembrolizumab	• Manage as per grade 3
Endocrine –	Grade 1	• No action	• Intervention not indicated

Hypo and hyperthyroidism	(Asymptomatic)		
	Grade 2 Hyperthyroidism and Grade 2- 4 Hypothyroidism	• Monitor thyroid function until returned to baseline. • Consider consultation with endocrinologist. • Pembrolizumab can continue while on this treatment.	• Thyroid hormone and/or steroid replacement therapy. • Hyper – non-selective beta blockers for initial therapy • Hypo – thyroid hormone replacement therapy as per standard of care.
	Grade 3 Hyperthyroidism	• Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Rule out infection and sepsis.	• IV methylprednisone 1-2mg/kg followed by prednisone 1-2mg/kg per day. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. Replacement of appropriate hormones may be required. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4 Hyperthyroidism	• Discontinue pembrolizumab	• Manage as per grade 3
Endocrine – Hypophysitis or other symptomatic endocrinopathy	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 – 4	• Withhold pembrolizumab • Rule out infection and sepsis. • Monitor thyroid function until returned to baseline. • Consider pituitary gland imaging • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. • Consider endocrinologist consult.	• Prednisone 40mg p.o. or equivalent per day. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. Replacement of appropriate hormones may be required. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
Type 1 Diabetes Mellitus and ≥ grade 3 hyperglycaemia	Type 1 Diabetes Mellitus and ≥ grade 3 hyperglycaemia	• Hold pembrolizumab if new onset of diabetes or grade 3-4 hyperglycaemia with evidence of beta cell failure. • Consultation with endocrinologist • Consider islet cell antibodies and antibodies	• Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria. • Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.

		to GAD, IA-2 ZnT8 and insulin.	
Hematologic	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Consider Haematology consultation	• Prednisone 1-2mg/kg daily • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 3	• Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Recommend Haematology consultation	• IV methlyprednisone 125mg or Prednisone 1-2mg/kg p.o. (or equivalent) as appropriate. • Permanently discontinue pembrolizumab is if corticosteroid dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• Discontinue pembrolizumab • Recommend Haematology consultation	• IV methlyprednisone 125mg or Prednisone 1-2mg/kg p.o. (or equivalent) as appropriate.
Hepatic – Drug induced Liver Injury (DILI). *Please refer to sections 6 and 7 for definitions of (DILI)*	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Report liver toxicity ECIs within 24 hours, as detailed in section 7.6.2. • Withhold Pembrolizumab if AST or ALT >3.0 to 5.0 X ULN and/or total bilirubin is >1.5to 3.0 X ULN • Monitoring Liver function until values return to baseline	• 0.5-1mg/kg/day methlyprednisone 125mg or oral equivalent. • LFT grade 1 or less initiate steroid taper for no less than 4 weeks. Consider prophylactic antibiotics and resume pembrolizumab. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks. • Permanently discontinue pembrolizumab for patients with liver mets who begin treatment with grade 2 elevation of AST or ALT and AST or ALT increase ≥50% relative to baseline and lasts ≥ 1 week.
	Grade 3	• Report liver toxicity ECIs within 24 hours, as detailed in section 7.6.2. • 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 section 6 and 7. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• Report liver toxicity ECIs within 24 hours, as detailed in section 7.6.2.	• Manage as per grade 3

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

	Grade 3	• Withhold Pembrolizumab • Consider dermatology consult & biopsy for diagnosis.	• 1mg/kg/day prednisone or equivalent or dexamethasone 4mg 4xdaily • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• Discontinue pembrolizumab • Dermatology consultation • Consider biopsy for diagnosis & clinical photographs	• Initiate steroids starting with 1-2mg/kg prednisone or equivalent.. • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks.
Skin – Dermatitis exfoliative, erytema mulitforme, Stevens Johnson syndrome, toxic epidermal necrolysis.	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	• Withhold Pembrolizumab • Consider dermatology consultation and biopsy for diagnosis.	• 1mg/kg/day prednisone or equivalent or dexamethasone 4mg 4xday. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• Discontinue pembrolizumab • Dermatology consultation • Consider biopsy for diagnosis & clinical photographs	• Initiate steroids starting with 1-2mg/kg prednisone or equivalent.. • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks.