Title: Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer

NCT02635360

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Study Title	A randomized Phase II study of chemoradiation and pembrolizumab for locally advanced cervical cancer
Test Article	**Pembrolizumab** (MK-3475)
Protocol Number	UVA-LACC-PD201
Phase of Study	Phase II
Sponsor-Investigator	**Linda Duska, MD**
Drug Source:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
GCP Statement	This study is to be performed in full compliance with acceptable Good Clinical Practices (GCP) and applicable regulations. All required study documentation will be archived as required by regulatory authorities.
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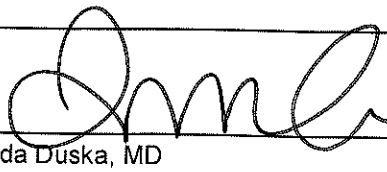
Signature: 

Linda Duska, MD
Study Chair

25Apr2018
Date

INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol and agree to conduct the study as outlined herein. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices as outlined in ICH E6 and the applicable laws and regulations.

Investigator: _____ Signature _____ Date

_____ Name

Instructions to the Investigator: Please sign and date this signature page. File the original signature page in the study file at the site and send a copy of the signed and dated page to the Study Chair or designee.

TABLE OF CONTENTS

List of Abbreviations

Abbreviation or specialist term	Explanation
AE	Adverse Event
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code Of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CRT	Chemoradiation Treatment
CTCAE	Common Terminology Criteria For Adverse Events
DSMC	University of Virginia Cancer Center Data and Safety Monitoring Committee
ECG	Electrocardiogram
FDA	Food And Drug Administration
GCP	Good Clinical Practices
HCG	Beta-Human Chorionic Gonadotropin
HR	Heart Rate
I/E	Inclusion Exclusion Criteria
ICH	International Conference On Harmonization
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
iULN	Institutional Upper Limit Of Normal
IV	Intravenous
OS	Overall Survival
PFS	Progression Free Survival
RR	Clinical response rate
pCR	Pathological complete response
aPTT	Activated Partial Thromboplastin Time
PT	Prothrombin Time
SAE	Serious Adverse Event
US	United States
UVA	University of Virginia
WOCBP	Women of Childbearing Potential

1.0 TRIAL SUMMARY

Abbreviated Title	Chemoradiation (CRT) with pembrolizumab in Cervical Cancer
Trial Phase	Phase 2
Clinical Indication	Locally advanced cervical cancer (stages IB-IVA, all histologies)
Trial Type	Randomized
Type of control	Active comparator and historical data
Route of administration	IV
Trial Blinding	Unblinded (open label)
Treatment Groups	2 arms
Number of trial subjects	88 evaluable
Estimated enrollment period	24 months
Estimated duration of trial	3 years to analysis of primary endpoint
Duration of Participation	20 weeks active treatment plus 5 years survival follow-up

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, Phase II, open-label multi-center study in which 88 eligible subjects with locally advanced cervical cancer will be treated with standard chemoradiation treatment (CRT) plus the PD-L1 monoclonal antibody pembrolizumab. The primary objectives in the study will be to estimate the safety and immune response to pembrolizumab given either sequentially or concurrently with CRT. Secondary objectives will evaluate the metabolic response and rates of distant metastases following treatment with pembrolizumab given sequentially or concurrently with CRT. The study design also affords the opportunity to characterize the effect of treatment on immune response pathways by estimating the effects of treatment on specific immune markers.

At baseline, subjects will undergo a full medical history and physical examination, vital signs, performance status, and general laboratory evaluations. Baseline imaging assessments will include PET/CT and MRI (MRI is required, unless there are contraindications or at the discretion of the investigator). Eligible subjects (n=88) will be randomized 1:1 to two treatment sequences to receive pembrolizumab after completion of CRT (Arm 1) or to receive pembrolizumab concurrent to CRT (Arm 2). Subjects in both arms will receive identical regimen, as follows:

- Chemotherapy: Weekly Cisplatin (40 mg/m^2) for 5 or 6 weeks
- Radiation: Standard dose IMRT with 4-6 fractions of high-dose-rate (HDR) brachytherapy using standard doses and methods
- Pembrolizumab: 200 mg, 3 cycles (every 21 days)

Subjects will be evaluated for safety by monitoring for adverse events. All subjects will have a PET/CT approximately 12 weeks following completion of all CRT to evaluate for response. Tumor and blood samples will be collected at baseline, during CRT and post-treatment for analysis of immune response markers. All subjects will be followed for disease-free survival and overall survival for up to 5 years.

Figure 1. Study Design

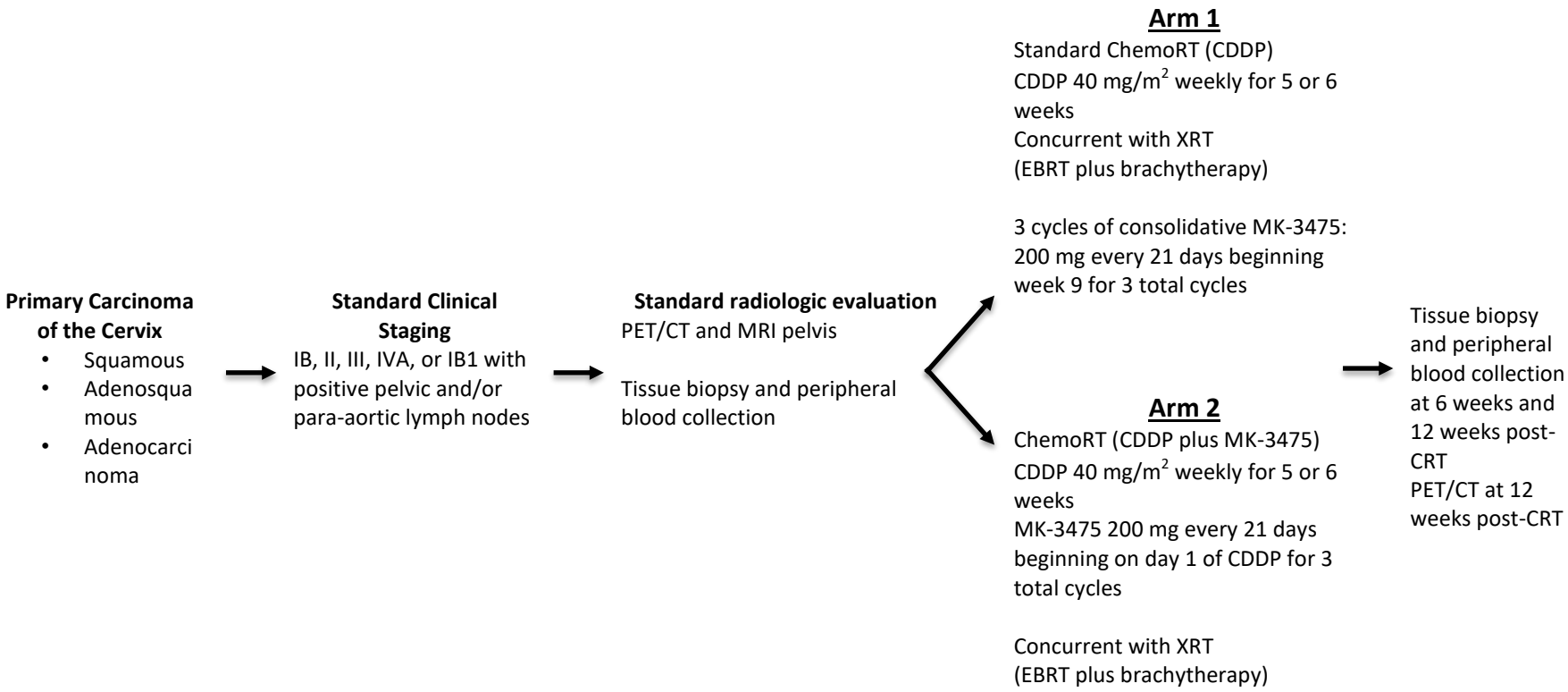
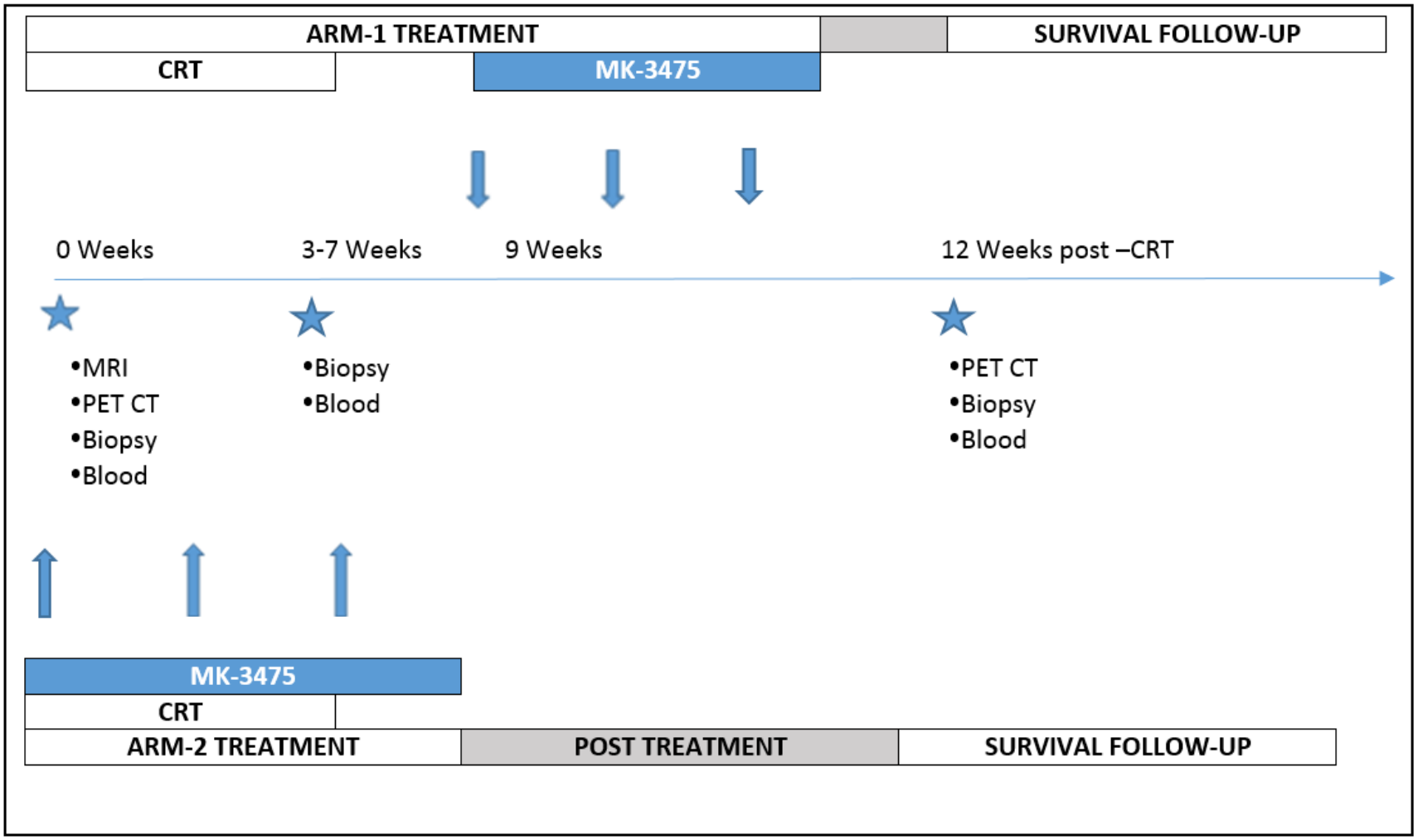


Figure 2. Study Schema



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives

(1) To estimate the immunologic effects, as assessed in the tumor & PBMC, of both sequential and concurrent administration of pembrolizumab to CRT. Change between pre and post measurements of HPV E2, E7 specific CD8+ T cells, regulatory FoxP3+ T cells (Tregs) and the ratio of CD8+ T cells to Tregs are the immune measurements of primary interest.

(2) To determine the safety of concurrent chemoradiation in combination with pembrolizumab for the treatment of locally advanced cervical cancer.

3.2 Secondary Objectives

(1) To estimate rates of complete metabolic response on PET/CT imaging obtained 12 weeks after CRT.

(2) To estimate rates of distant metastasis as the first site of recurrence for patients.

(3) To estimate the influence of concurrent and consolidative MK-3475 on levels of plasminogen activator inhibitor-1 (PAI-1), a marker of immunosuppressive TGF-B.

(4) To estimate the influence of concurrent and consolidative MK-3475 on levels of IDO, an enzyme that depletes tryptophan, which is essential for T-cell function.

(5) To estimate the influence of concurrent and consolidative MK-3475 on levels of MHC class I (CD8+ T cell ligand) and MICA (NK ligand), as measured by MHC.

(6) To estimate the progression free survival (PFS) in subjects with locally advanced cervical cancer treated with sequential and concurrent administration of pembrolizumab in relation to CRT.

(7) To estimate the overall survival (OS) in subjects with locally advanced cervical cancer treated with sequential and concurrent administration of pembrolizumab in relation to CRT.

4.0 BACKGROUND & RATIONALE

4.1 Disease Background

Cervical cancer is the fourth most common cancer among women worldwide, with an estimated 528,000 new cases and 266,000 deaths in 2012.[1] The standard of care (SOC) for patients with locally advanced cervical cancer (LACC) is concurrent chemoradiation therapy (CRT) with weekly cisplatin.[2] Five-year disease OS after contemporary CRT for Stages IB-IVA cervical cancer is only 66%.[2]

Human Papillomavirus (HPV) DNA is detected in virtually all cervical cancers, and HPV specific CD4+ and CD8+ T cells are found in cervical tumors.[3] The failure of the immune system to eradicate HPV DNA integration is due to cancer cells' acquisition of cytotoxic T cells, including down-regulation of HLA class I, down-regulation of MHC class I chain-related molecule A (MICA), production of immune-suppressive cytokines, and induction of FoxP3+ immunosuppressive regulatory T cells.[4] Low ratios of CD8+ T cells: regulatory T cells (Tregs) are associated with poorer survival for cervical cancer patients,[4] suggesting that strategies to enhance immune response would be effective.

Compelling evidence indicates that B7 molecules (i.e., B7-1/CD80, B7-2/CD86, B7-H1/PDL1, B7-H2/LICOS, B7-DC, B7-H3 and B7-H4) and their ligands (i.e., CTLA-4, CD28, PD-1, ICOS) not only provide crucial positive signals to stimulate and support T-cell activation, but also offer negative signals that control and suppress potentially protective T-cell responses against spontaneously arising and virally-induced human tumors.[5] Expression of these molecules on the surface of cervical tumor cells, tumor associated macrophages, and/or dendritic cells (DC), may attenuate or abrogate the ability of the immune system to eliminate strongly antigenic (i.e., virus-infected) tumors such as cervical cancer.[5] Because these negative signals in human solid tumors have been shown to be largely provided by programmed death, blockade of PD- 1/PD-L1 co-inhibitory pathways by novel monoclonal antibodies may represent an innovative and effective approach to reverse immune suppression while inducing tumor-specific immunity in cervical cancer patients.

PD-1 and PD-L1 expression on cervical T cells and DCs, respectively, has been recently reported to be associated with high risk-HPV positivity and to be increased in parallel with increasing CIN grade.[6] Increased expression of PD-1 and PD-L1 correlates with impaired cell-mediated immunity in high-risk HPV related CIN.[7] Finally, in cervical cancer, PD-1 is expressed by the majority of infiltrating CD8 T cells, suggesting that blocking of PD-1 could have therapeutic potential.[7] Taken together, this evidence validates the importance of the PD-1-PD-L1 pathway for the treatment of patients harboring virally-infected tumors such as cervical cancer.

4.2 Pembrolizumab

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

4.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. 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 tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors 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 signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. 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. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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 tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-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. 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 tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.2.2 Preclinical and Clinical Trial Data

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

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Subject Population

We hypothesize that CRT in LACC will be beneficial to the immunostimulatory activity of pembrolizumab compared to single agent use. This hypothesis is based on evidence that platinum-based DNA intercalators and irradiation are highly effective at inducing a form of apoptosis known as immunological cell death (ICD),[8] which can lead to auto-vaccination that is promoted by blocking checkpoint molecules such as PD-1. We anticipate that ICD will not only curtail the immunosuppressive activity of T cells, but will also increase the source of antigen and improve the context of antigen presentation (by activating dendritic cells) that could lead to greater immune cell activation in the cervical cancer environment. However, cisplatin is deleterious to activated effector T cells (our unpublished data), and irradiation and chemotherapy can recruit myeloid cells and regulatory cells with immunosuppressive function.[9, 10] Therefore, the sequencing of SOC with PD-1 blockade deserves considerable attention, with the intent of defining optimal treatment regimens and the development of prognostic and predictive biomarkers. These observations suggest that PD-1 blockade is a potential therapeutic strategy to increase immune responses against cervical cancer. Pembrolizumab (MK-3475) is an PD-1 antibody approved for use in melanoma,[11] and the proposed study focuses on evaluating the influence of the addition of pembrolizumab to standard CRT, and sequencing of pembrolizumab with CRT, on CD8+ infiltrating T cells in subjects with locally advanced cervical cancer.

Secondary objectives of the study will estimate clinical endpoints to obtain preliminary data regarding the potential clinical effect of the combination. We will estimate the rate of complete metabolic response as measured by PET/CT at 12 weeks, as well as the rate of distant (versus local) recurrence.

There is no data available to predict the optimal time point to incorporate immunotherapy into a treatment course. Therefore, this study will evaluate biological endpoints and responses to immunotherapy given at the time of chemotherapy and following completion of chemotherapy.

4.3.2 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 subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 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 MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 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 MK-3475 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. MK-3475 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 MK-3475 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.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.3.2.1 Biomarker Research

The overall rationale for this study is that the addition of pembrolizumab to the standard of care chemoradiation treatment may improve survival for cervical cancer patients by modifying the immune response against the tumor. It is anticipated that pembrolizumab treatment will favorably improve the ratio of effector CD8+ T cells: regulatory T cells in the tumor microenvironment. Biopsies and blood samples to collect peripheral blood mononuclear cells (PBMC) will be collected pre, during and post treatments in both arms. We will determine whether the inclusion of pembrolizumab: 1) alters the quantity and quality of tumor lymphocytic infiltration; 2) increases the systemic immune response against tumor-associated antigens.

Tumor lymphocyte infiltration: PD-1 blockade (pembrolizumab) can support CD8+ T cell function in the periphery, either by promoting TCR signaling or biochemical pathways that support effector activity, or potentially by influencing regulatory T cell development and function. Thus, pembrolizumab

has the potential to synergize with CRT to augment CD8+ T cell responses. Tumor biopsies will be evaluated by IHC and flow cytometry and by transcriptional analysis to provide a broad characterization of the effect of treatment on lymphocyte and myeloid cell composition and immune function.

These studies will provide a direct assessment of the capability of PD-1 blockade to augment T cell responses initiated by CRT-induced ICD and DC activation. Our current trial design will allow us to detect acute effects of these study drugs on the immunological composition of the tumors, but not their independent effect on long term immune responses initiated in CRT-treated subjects. Our goal is to generate preliminary data addressing whether the addition of pembrolizumab to CRT promotes the modulation of cellular subsets that are likely to be involved in controlling tumor outgrowth and whether concomitant treatment alters patterns of adaptive resistance (checkpoint molecules; immunosuppressive cellular populations; inhibitory cytokines) compared to CRT alone. With respect to immunological outcomes, our expectation is that the addition of pembrolizumab will augment the magnitude and the function of intratumoral and systemic tumor-specific CD8+ T cells (as judged by HPV reactivity), and will lead to increased expression of HLA, MICA and PDL1 compared to CRT alone. We will learn whether pembrolizumab can modulate NK and Treg frequencies in tumors in addition to peripheral blood. Furthermore, we anticipate that CRT will initially deplete tumor infiltrating lymphocytes, but that the consolidation regimen of pembrolizumab post CRT will increase the acuteness and magnitude of the response driven by CRT.

Systemic response: Flow cytometry will be used to examine blood for an increase in HLA-DR (a marker of recent T cell activation) expressing CD8+ T cells. ELIspot assays, using overlapping peptide libraries constructed for HPV E2, E5, E6 and E7, will be used to determine whether treatment induces/increases CD8+ T cell responses to defined cervical cancer antigens.

Human Papillomavirus (HPV) and tumor immunogenicity: DNA is detected in virtually all cervical cancers, and HPV specific CD4+ and CD8+ T cells are found in cervical tumors.[3] The failure of the immune system to eradicate HPV DNA integration is due to cancer cells' acquisition of resistance to cytotoxic T cells, including down-regulation of HLA class I, down-regulation of MHC class I chain-related molecule A (MICA), production of immune-suppressive cytokines, and induction of FoxP3+ immunosuppressive regulatory T cells.[4] The presence of CD8+ T cells specific for HPV-antigens in cervical cancer subjects is limited, considering the potential immunogenicity of these antigens. Tumor infiltration by lymphocytes could be limited by antigen availability and weak T cell activation; deficiencies in lymphocyte trafficking into tumor; or poor survival and proliferation in the tumor site. In preclinical models, both cisplatin and irradiation have profound influences on the cellular and cytokine components of the tumor; they can lead to the death of immunosuppressive cell subsets, the release of damage associated molecular patterns that can activate DC resulting in increased T cell activation and presence of lymphocytes within tumors. Whether this occurs in human disease has not been assessed. However, irradiation can induce many negative feedback mechanisms, and has the capacity to induce PD-L1 expression either directly, or as a part of adaptive resistance to the effector activity of infiltrating lymphocytes. Furthermore, it is unknown whether low-dose cisplatin will eradicate both regulatory and effector T cells in the tumor site, and whether any HPV-specific CD8+ T cell response can be elicited subsequent to SOC treatment and whether these cells express PD-1 and other inhibitory molecules.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1. Histologically confirmed cervical cancer

    a. Histologically confirmed invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, stages IB, IIA, IIB, IIIB, and IVA. Stage IB1 with positive pelvic or para-aortic nodes based on imaging is also eligible.
    b. No evidence of distant metastases (based on PET/CT done within 6 weeks of start of treatment).
    c. Recurrent cervical cancer is not eligible.

5.1.2 Subject Inclusion Criteria

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 a performance status of 0-2 on the ECOG Performance Scale.

5. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
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 subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject 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 subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

6. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7. Subjects 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, or until they are no longer of child bearing potential.

5.1.3 Subject Exclusion Criteria

Medical History:

1. Has history of malignancy within the prior 5 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy.

2. Has a diagnosis of immunodeficiency

3. Has a known history of: i) Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies); ii) Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative]); iii) active TB (Bacillus Tuberculosis); or iv) inflammatory bowel disease.

4. Hypersensitivity to pembrolizumab or any of its excipients

5. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

6. Has known history of, or any evidence of active, non-infectious pneumonitis.

7. Has an active infection requiring systemic therapy.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects 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. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

10. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

11. A serious uncontrolled medical disorder that in the opinion of the Investigator would impair the ability of the subject to receive protocol therapy.

Medication History:

12. Has had prior radiation for other diagnoses to the expected treatment field.
13. Has had prior radiation, chemotherapy, targeted therapy, or investigational therapy for cervical cancer.
    - Note: If subject received major surgery for reason other than cervical cancer, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting treatment.
14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

15. Within 7 days prior to the planned start of study treatment:

    a) Is receiving systemic steroid therapy or any other form of immunosuppressive therapy

16. Within 30 days prior to the planned start of study treatment:

    a) Has received a live vaccine. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

    b) Has participated in a study of an investigational agent and received study therapy or used an investigational device.

Subject Characteristics:

17. Is unable or unwilling to participate in a study related procedure.

18. Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of pembrolizumab.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 2. Trial Treatment				
Agent	**Dose**	**Route**	**Schedule**	**Use**
Pembrolizumab	200 mg	IV	Infusion given every 21 (± 3) days for 3 cycles	Experimental
Cisplatin	40 mg/m^2 in 1L (max 70 mg)	IV	One hour infusion, once weekly for 5-6 weeks	Standard of care
Radiation	45 Gy +/- boost doses	IMRT to primary tumor and nodal volumes	25 fractions over a 5-8 week interval	Standard of care (Parametrial or nodal boosts of 5.4-14.4 Gy can be delivered as indicated.) Variations permitted to reflect institutional standards
	25-30 Gy	high-dose-rate (HDR) brachytherapy	4-6 fractions of 5-6 Gy per fraction	Standard of care Variations permitted as described to reflect institutional standards

5.3 Dose Selection/Modification

5.3.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.3.2 Dose Modification

Dose modifications in response to treatment-related adverse events are permitted in order to keep the participant on study drug. Details on the modifications for each study intervention are provided in the sections below. In general:

i. Dose modifications for reasons other than treatment related adverse events are not allowed on this protocol. Relationship to treatment should be determined as outline in Table 7.

ii. Whenever treatment is held pending resolution of toxicity to grade 1 or 0, this criterion may also be met if the toxicity resolves to pre-study baseline grade (if toxicity was present at baseline).

iii. Study drugs and radiation may be held together or separately. Investigator discretion is permitted to determine which drug is the source for a given toxicity and to adjust the dosage of pembrolizumab, cisplatin, or radiation therapies accordingly. If study drugs are held for hematological toxicity, radiation therapy may be continued at the investigator's discretion in order to minimize treatment delays.

5.3.2.1 Pembrolizumab Dose Modification

Modification of the dose of pembrolizumab is not allowed on this study. The dose of pembrolizumab can be delayed or withheld due to adverse events. Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Error! Reference source not found.** below. See Section 5.5.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Pembrolizumab should be administered once every 21 days for 3 cycles. If a delay in dosing is required per the guidelines in **Error! Reference source not found.**, then the dose may be delayed for up to 7 days. In case the toxicity does not resolve to Grade 0-1 or baseline within 7 days, the dosing on either the second or third cycle may be withheld. If the second cycle dose cannot be administered due to unresolved toxicity, then the third dose of pembrolizumab should occur on the scheduled day 1 of the third cycle (if the toxicity has resolved to Grade 0-1 or baseline). If the third dose cannot be administered due to unresolved toxicity within 7 days, then the subject may continue on study without additional pembrolizumab (may continue to receive cisplatin and RT). In general, please follow the following pembrolizumab-specific guidelines:

i. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. This criterion may also be met if the toxicity resolves to pre-study baseline grade (if toxicity was present at baseline).

ii. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

iii. For situations where pembrolizumab has been withheld and the toxicity has not resolved within 7 days, the dose may be skipped. Otherwise, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 (or baseline, as described in “i”) and corticosteroid has been tapered.

Table 3. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

	Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis 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.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)				

5.3.2.2 Dose Modifications of Other Treatments

5.3.2.3 Radiation Dose Modifications

Radiation treatment may be delayed due to toxicities for 1- 7 consecutive days in patients in either treatment arm. Additionally, the start of brachytherapy can be delayed 1-14 days from completion of external beam RT if needed. All radiation treatments must be delivered within a total of 8 weeks, therefore treatment breaks should be kept to a minimum.

If radiation treatment is held, then cisplatin dose should be held until radiation treatment is resumed.

5.3.2.4 Cisplatin Dose Modifications

Toxicity due to cisplatin administration may be managed by symptomatic treatment, dose interruptions and adjustment of cisplatin dose. Recommended dose reductions are provided in Table 3. Dose should only be reduced once and future dosing should continue at the reduced dose. If the reduced dose cannot be tolerated the subject may continue on study without cisplatin (may continue to receive pembrolizumab and RT).

Table 3. Cisplatin Dose Modifications	
DOSE LEVEL	**CISPLATIN**
Dose Level 1	40 mg/m^2 (max = 70 mg*)
Dose Level -1	30 mg/m^2 (max = 52.5 mg*)
* Max doses apply to those with BSA > 1.75 m^2	

5.3.2.4.1 Recommendations for Cisplatin Dose Modifications

Gastrointestinal Adverse Effects

- For nausea and vomiting, anti-emetics should be used prophylactically.
- For Grade 4 nausea and vomiting, reduce Cisplatin by one dose level.

Renal/Genitourinary Adverse Effects

- If creatinine rises to greater than 2.0 mg/dl, hold cisplatin therapy. If creatinine does not recover after a one-week delay, discontinue cisplatin for remainder of regimen.

- Selective renal tubular defects are sometimes observed:
    - Hypocalcemia with hypomagnesemia and hypokalemia are common and potentially severe.
    - Replacement of magnesium, calcium and potassium are usually effective.
    - Severe tubular effects, although rare, may require chronic replacement therapy.
    - Diagnostic tests for alternative mechanisms of hypocalcemia (e.g. GI or metabolic) should be considered.

Neurologic Adverse Effects

- Grade 1 - No change
- Grade 2 - Reduce Cisplatin by one dose level
- Grade 3-4 – Hold cisplatin. Reduce Cisplatin by one dose level after recovery to ≤ Grade 2

Blood/Bone Marrow (Hematologic) Adverse Effects

- Cisplatin should be withheld from patients with an ANC less than 1,000 or platelet count less than 50,000. Therapy should be delayed week-by-week until these levels are exceeded. Any interruption in cisplatin for longer than one week due to toxicity requires a dose reduction of one level.
- External radiation should continue while drug is withheld.

5.3.3 Timing of Dose Administration

The below sections describe the recommended timing of study specific treatments. Treatments may be delayed up to 3 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled).

5.3.3.1 Cisplatin

Cisplatin chemotherapy will consist of weekly administrations of 40 mg/m^2 of cisplatin administered in 1 L of IV fluid (according to local protocol) delivered in 1 hour IV infusion (per institutional guidelines) The maximum dose of cisplatin administered should not exceed 70 mg. Cisplatin will be given on a day that IMRT is scheduled and must be given prior to radiation therapy that day. Cisplatin should be given on a Monday, Tuesday or Wednesday. Cisplatin infusion should proceed after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

5.3.3.2 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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).

Pembrolizumab should be administered on day of treatment after all pretreatment procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled treatment date due to administrative reasons.

Pembrolizumab treatment to subjects in Arm 2 should be given prior to any other chemoradiation treatment (i.e. prior to radiation therapy). It is recommended that subjects receive pembrolizumab on the same day as cisplatin. The pembrolizumab infusion can be administered concurrent to the pre-hydration for the cisplatin treatment.

All trial treatments will be administered on an outpatient basis.

5.3.3.3 Radiation Treatments

Radiation therapy details will be identical for both Arms 1 and 2. This trial will include external beam radiation therapy (EBRT), including intensity modulated radiation therapy (IMRT), and image-guided brachytherapy with three-dimensional (3-D) treatment planning. IMRT is included as it may reduce the acute normal tissue toxicity from cervical cancer radiotherapy[14], and 3-D planned brachytherapy has been shown to improve local tumor control and reduce toxicity compared to two-dimensional planning.[15] Standard doses of external beam radiation therapy and brachytherapy will be delivered, and this radiation therapy section is written with the purpose of including the range of treatment approaches used by each participating institution, as long as the cumulative doses are within the target range. Each institution may follow their specific institutional policies for IMRT, including pseudo-split-field IMRT.[16] Parametrial boosts and nodal boosts may be delivered using either sequential or concomitant-integrated boost methods. Investigators may use both simultaneous and integrated boosts to comply with local institutional policies.[17] All IMRT and brachytherapy treatments must be delivered within a total of 8 weeks.

5.3.3.3.1 External Beam Radiation Therapy

IMRT planning is encouraged in this study. However, three-dimensional conformal radiation therapy is permitted instead of IMRT if cumulative organ-at-risk (OAR) constraints are respected. The EBRT plan will deliver at least 45 Gy, with treatment sites including the primary tumor and nodal volumes. Consensus guidelines are suggested to define target volume definition for IMRT.[18] This may be accompanied by parametrial or nodal boosts of 5.4-18 Gy as indicated (up to total dose of 63 Gy by EBRT). Three-dimensional conformal radiation therapy is permitted instead of IMRT if cumulative organ-at-risk (OAR) constraints are respected.

<u>Simulation and Immobilization</u>

CT simulation is required for the study to permit target delineation and dose calculation. Patients may be simulated in the supine or prone position based on institutional practice. If a four-field, 3D conformal plan is used rather than IMRT, prone positioning with a belly board is recommended.

Target Volume ad Organ-At-Risk Definitions

Target volumes and OARs must be defined on CT scan, and co-registered complementary imaging (i.e., MRI and/or PET imaging) can be used based on institutional practice. OAR volumes should include the entire organ (rather than just the wall of the organ) for ease of reporting. The radiation therapy case report forms will use the following nomenclature, so consistent labeling is suggested. *Investigators may choose to label structures differently according to institutional standards, and the target volume and OAR labeling are suggestions, not protocol requirements*. , When completing the case report forms, investigators are asked to simply report the requested data for their target volume that is most similar to the structures described below. The case report form will request the data using the following labels:

Target Volumes	**Description**
GTV (gross tumor volume) or HR-CTV (high risk CTV)	Gross tumor alone (GTV) or gross tumor and highest risk area at time of brachytherapy (HR-CTV)
GTVnodal	Gross tumor volume for lymph node as identified on imaging or exam. Dose to the nodal volume receiving highest boost dose will be requested.
CTVnodal	Clinical target volume for regional lymph nodes. Prescription dose to at-risk nodal regions will be requested.
OARs	**Description**
Bladder	Entire organ contoured on CT. Cumulative dose from EBRT+brachytherapy will be requested.
Sigmoid	Entire organ contoured on CT. Cumulative dose from EBRT+brachytherapy will be requested.
Rectum	Contoured from ischial tuberosities to sigmoid flexure. Entire organ contoured. Cumulative dose from EBRT+brachytherapy will be requested.
Bowel	May be contoured as bag of bowel or individual loops of bowel. Cumulative dose from EBRT alone will be requested.

CT = computed tomography; CTV = clinical target volume; EBRT = external beam radiation therapy; GTV = gross tumor volume

Treatment Planning

IMRT or 3D conformal RT planning will be used to deliver a total dose of at least 45 Gy to the nodal CTV. Depending on institutional practice, pseudo-split-field IMRT or integrated boost approaches can be used with goal of meeting the planning objectives stated in the table below. The following

objectives are based on a recent RTOG protocol (NCT01672892), published series,[16, 17, 19] and guidelines.[20, 21]

Target Volumes	Planning Objectives
GTV or HR-CTV	D90 EQD2 ≥ 80 Gy (representing dose from brachytherapy + EBRT)
GTVnodal	≥ 59 Gy from EBRT
CTVnodal	≥ 45 Gy from EBRT
OARs	**Planning Objectives**
Bladder	D2cc ≤ 90 Gy EQD2 (representing dose from brachytherapy + EBRT)
Sigmoid	D2cc ≤ 75 Gy EQD2 (representing dose from brachytherapy + EBRT)
Rectum	D2cc ≤ 75 Gy EQD2 (representing dose from brachytherapy + EBRT)
Bowel	D5cc ≤ 55 Gy EQD2 (representing dose from EBRT only); no more than 30% receives 40 Gy

D2cc = dose encompassing the highest exposed 2 cc; D5cc = dose encompassing the most exposed 5 cc; EQD2 = equivalent dose in 2 Gy fractions; HR-CTV = high risk clinical target volume (recommended to comply with GEC-ESTRO definition[21]); EBRT = external beam RT; OARs = organs at risk

Treatment Delivery

Daily imaging is recommended during EBRT to permit verification of target alignment. Imaging and alignment method is to follow institutional practice, and can consist of orthogonal plain films, kV matching or CT imaging.

5.3.3.3.2 Brachytherapy

Brachytherapy will consist of 4-6 fractions of 5-7 Gy per fraction delivered with high-dose-rate (HDR) brachytherapy, based on institutional practice. Brachytherapy is not to be delivered on the same day as cisplatin chemotherapy.

Either CT-based or MRI-based treatment planning will be permitted for brachytherapy. The minimum EQD2Gy for the highest dose encompassing 90% (D90) of the high-risk clinical target volume (HR-CTV) or gross tumor volume (GTV) is 80 Gy, consistent with ABS guidelines.[20] It is recommended that the HR-CTV D90 is ≥ 100% of the prescription dose and the HR-CTV volume encompassing 100% of the target volume (V100) is ≥ 90%.

Cumulative doses to rectum, bladder, sigmoid and bowel will be followed to limit doses below threshold values for dose to the hottest 2 cc (D2cc) as calculated by equivalent dose in 2 Gy fractions (EQD2Gy) using a modified version of the American Brachytherapy Society (ABS) worksheet. The EQD2Gy limits will be 90 Gy for bladder and 75 Gy for rectum and sigmoid. This is consistent with ABS guidelines.[20]

Brachytherapy Target Volume Definitions

It is recommended that the brachytherapy treatment planning include delineation of the GTV or HR-CTV, per institutional practice, as well as the rectum, sigmoid, bladder and bowel.

Dose Reporting

Case report forms will request these doses for each fraction of brachytherapy: estimated D90 and V100 for the HR-CTV or GTV, Point A, and D2cc for sigmoid, rectum, bladder and bowel. Cumulative EQD2Gy doses for D90 of the HRCTV and D2cc for the sigmoid, rectum, bladder and bowel will be requested.

5.4 Concomitant Medications/Vaccinations

Medications or vaccinations specifically prohibited in the exclusion criteria and listed in Section 5.4.2 are not allowed during the Screening and Treatment Phase of this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor-Investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

5.4.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol
- Live vaccines
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor-Investigator.

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are recommended when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.3.2 for guidelines regarding dosing delays and modifications.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. These procedures should be performed at the discretion of the investigator and are not mandated by the protocol. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events,** immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
      For **Grade 3-4 events, or recurrent Grade 2 events**, permanently discontinue Pembrolizumab.
    - Monitor participants for signs and symptoms of pneumonitis
    - Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Myocarditis:**
    - Ensure adequate evaluation to confirm etiology and/or exclude other causes
    - Administer corticosteroids based on severity of event

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

If diarrhea/colitis occurs prior to initiation of pembrolizumab or can be attributed to the CRT treatment, then subjects should be advised to drink liberal quantities of clear fluids and will receive standard management for diarrhea with loperamide, low residue diet and Lomotil if needed. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea where colitis is suspected, consider GI consultation and endoscopy to confirm or rule out colitis.

If diarrhea/colitis occurs after subject has received any administration of pembrolizumab, then it is critically important to evaluate the subject for immune-related diarrhea/colitis. The diarrhea/colitis is likely to be immune-related if it has any of the following characteristics:

- Bloody or mucous stools
- Cramping
- occurs at a timepoint not typical for chemoRT (i.e., in first 2 weeks of treatment or after completion of external beam RT)

If the event meets these criteria, then it should be treated as follows:

- All subjects who experience diarrhea/colitis 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.
- For **Grade 2 diarrhea/colitis** that is felt to be possibly, probably, or likely related to investigational agent, administer oral corticosteroids consistent with the guidelines in the pembrolizumab lab. Current recommendation is to start at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent.
- For **Grade 3 or 4 diarrhea/colitis** that is felt to be possibly, probably, or likely related to investigational agent and that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- Withhold pembrolizumab administration for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue pembrolizumab administration for life-threatening (Grade 4) colitis.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and anti-hyperglycemic in participants for Grade 3-4 hyperglycemia with evidence of Beta-cell failure.
        - Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
        - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2-4** events, monitor with liver function tests (weekly or more frequently until returned to baseline values or is stable.
    - Treat with IV or oral corticosteroids
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:

  - For **Grade 2-4** events, treat with corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.

  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

  - Monitor changes in renal function

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4. Infusion Reaction Treatment Guidelines

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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject 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.		

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

Pembrolizumab may have adverse effects on a fetus 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) sterilized surgically or as a result of radiation treatments, 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. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy, or until they are no longer of childbearing potential.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (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 subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3 Use in Pregnancy

If a subject becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor-Investigator. If the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn), this should be reported within 24 hours to the Sponsor-Investigator.

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor-Investigator.

5.6.4 Use in Nursing Women

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

5.7 Subject Participation and Withdrawal/Discontinuation Criteria

A subject is considered On-Study from the time eligibility is confirmed through the follow-up interval. Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor-Investigator if enrollment into the trial is inappropriate,

the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in the sections below.

5.7.1 Duration of Treatment

Subjects will continue to receive study treatment (defined as chemoradiation and pembrolizumab) until:

- Subject has completed all study treatments
- Disease progression
- Unacceptable adverse event(s)
- Subject withdraws consent for further treatment
- Female subject has a confirmed positive serum pregnancy test
- Subject receives a non-study treatment (not protocol-specified) for their cancer
- Subject non-compliance
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator

If any of the above events occurs, the subject will be considered off treatment and in follow-up. Subjects will be followed for 5 years for PFS and OS, or until the trial is terminated per Section 5.7.4.

5.7.2 Discontinuation/Withdrawal from Study

Subjects may withdraw or be discontinued from the study at any time for any of the following reasons:

- Subject decides to withdraw from the study
- Subject is unable or unwilling to complete the follow-up procedures
- The subject is lost to follow-up
- Death

The primary reason for discontinuation or withdrawal should be entered into OnCore. All subjects that discontinue or withdraw from the study will continue to receive standard of care treatment. Subjects who have withdrawn consent for the study will not be followed for any reason.

A subject's participation is considered completed when the subject has completed the 5 year follow-up interval.

5.7.3 Subject Status Definitions

Enrolled: All subjects who sign an informed consent will be considered enrolled on the study. All subjects consented on the study must be entered into OnCore.

Screen Failure: A subject who is withdrawn or discontinues from the study prior to receiving any treatment is considered a post enrollment screen failure. Post enrollment screen failures are not considered a study accrual and will be replaced. Note: The UVa IRB-HSR defines any individual that has signed an informed consent as an enrollment in this study and so screen failures should be reported to the IRB with enrollment numbers.

On-Study: A subject is considered on-study on the date when the study team has confirmed the subject has met all of the inclusion and none of the exclusion criteria, and the treating physician/surgeon or study PI has signed off on the confirmation.

Randomized: A subject that has been randomized to an arm is considered a randomized subject.

On-Treatment: A subject is considered on-treatment on the date that CRT is initiated

Off-Treatment: A subject is considered off-treatment on the date that they have met any of the criteria listed in Section 5.7.1

On Follow-up: A subject is considered on follow-up on the date that they have met any of the criteria listed in Section 5.7.1.

Off-Study: A subject is considered off-study if they are removed from the study for any of the reasons listed in Section 5.7.2, or if they have completed the follow-up interval.

5.7.4 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 subjects
4. Plans to modify or discontinue the development of the study drug

In the event of a decision by Merck to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.7.5 Trial Blinding/Masking

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

6.1.1 Arm 1

Trial Period:	Pre-Study	Treatment		Post-treatment		Survival Follow-Up[1]
Visit:	Screening	CRT	Pembro	EOT visit[2]	Imaging	
Scheduling Interval:	-42d-1d	W1-W8	W9-W15	35 ± 5d	12w ± 10d post-CRT	
Administrative Procedures						
Informed Consent/ IE	X					
Demographics/Medical History	X					
Concomitant Medication Review	X					
Disease Status						X
Survival Status						X
Study Treatments						
Cisplatin		X				
Radiation		X				
MK-3475 administration			X[3]			
Specimen Collection						
Tissue Collection[4]	X	X[5]			X	
Research Blood Collection	X	X[5]			X	
Clinical Procedures/ Laboratory Assessments						
Pregnancy Test (Urine or Serum)[6]	X					
Review Adverse Events	X	X	X	X		

[1] All subjects should be followed for 5 years following treatment to monitor disease status and overall survival. There are no per protocol assessments, all subjects should be monitored according to the standard of care of the treating physicians.

[2] Each subject should return to the clinic for a visit 30-40 days following the last study treatment (of either pembrolizumab or chemoradiation) for assessment of adverse events

[3] Pembrolizumab treatment should be scheduled for every 21 days (± 3 days) starting on Week 9.

[4] Fresh tissue biopsies are required. If archival tissue is available these may also be submitted to supplement fresh tissue collected at baseline.

[5] Tissue and blood specimen collected during CRT interval should be obtained at 5 ± 2 weeks

[6] Women of childbearing potential must have a negative pregnancy test within 72 hours of first dose of study treatment.

Trial Period:	Pre-Study	Treatment		Post-treatment		Survival Follow-Up[1]
Visit:	Screening	CRT	Pembro	EOT visit[2]	Imaging	
Scheduling Interval:	-42d-1d	W1-W8	W9-W15	35 ± 5d	12w ± 10d post-CRT	
Physical Examination/ECOG	X[7]	X[8]	X[8]	X	X[7]	
Vital Signs	X	X	X	X		
PT/INR and aPTT[14]	X					
CBC with Differential[14]	X	X[9,10,11]	X[11,12]	X		
Serum Chemistry Panel[14]	X	X[9,10,11]	X[11,12]	X		
Thyroid panel[14]	X		X[11,13]	X		
Tumor Imaging/Disease Assessments						
MRI[15]	X					
PET/CT[16]	X				X	

[7] Physical exam at screening and at the time of the post-treatment imaging should include a clinical tumor assessment

[8] Physical exams should be done at a minimum every 3 weeks during study treatment interval

[9] Prior to first day of treatment (Day 1 Week 1), laboratory tests do not need to be repeated if screening labs were performed within 14 days prior to treatment date.

[10] General safety labs (CBC and Basic Serum Chemistry) should be performed once weekly during chemoradiation to evaluate for toxicities.

[11] Labs required prior to treatments do not need to be repeated if labs have been performed within 72 hours prior to dose.

[12] General safety labs (CBC and Complete Chemistry Panel including liver function tests) should be performed prior to pembrolizumab administration on day of dosing to evaluate for toxicities (if not done in previous 72 hours).

[13] Thyroid function tests should include, at a minimum, TSH. If TSH is abnormal, T3 and T4 must be evaluated. Thyroid function tests should be performed prior to pembrolizumab administration on day of dosing (if not done in previous 72 hours).

[14] Screening labs must be obtained within 14 days of start of treatment.

[15] Pelvic MRI is required within 4 weeks of start of treatment unless there are contraindications or at the discretion of investigator.

[16] PET/CT (skull base to thighs) should be performed within 6 weeks of start of treatment and repeated at 12 weeks +/- 10 days after completion of CRT.

6.1.2 Arm 2

Trial Period:	Pre-Study	Treatment	Post-treatment		Survival Follow-Up[1]
Visit:	Screening	CRT + MK-3475	EOT visit[2]	Imaging	
Scheduling Interval:	-42d-1d	W1-W9	(35 ± 5d)	12w ± 10d post-CRT	
Administrative Procedures					
Informed Consent/ IE	X				
Demographics/Medical History	X				
Concomitant Medication Review	X				
Disease Status					X
Survival Status					X
Study Treatments					
Cisplatin		X			
Radiation		X			
MK-3475 administration		X[3]			
Specimen Collection					
Tissue Collection[4]	X	X[5]		X	
Research Blood Collection	X	X[5]		X	
Clinical Procedures/ Laboratory Assessments					
Pregnancy Test (Urine or Serum)[6]	X				
Review Adverse Events	X	X	X		
Physical Examination/ECOG	X[7]	X[8]	X	X[7]	
Vital Signs	X	X	X		

[1] All subjects should be followed for 5 years following treatment to monitor disease status and overall survival. There are no per protocol assessments, all subjects should be monitored according to the standard of care of the treating physicians.

[2] Each subject should return to the clinic for a visit 30-40 days following the last study treatment (of either pembrolizumab or chemoradiation) for assessment of adverse events

[3] Pembrolizumab treatment should be scheduled for every 21 days (± 3 days) starting on Day 1.

[4] Fresh tissue biopsies are required. If archival tissue is available these may also be submitted to supplement fresh tissue collected at baseline.

[5] Tissue and blood specimen collected during CRT interval should be obtained at 5 ± 2 weeks

[6] Women of childbearing potential must have a negative pregnancy test within 72 hours of first dose of study treatment.

[7] Physical exam at screening and at the time of the post-treatment imaging should include a clinical tumor assessment

[8] Physical exams should be done at a minimum every 3 weeks during study treatment interval

Trial Period:	Pre-Study	Treatment	Post-treatment		Survival Follow-Up[1]
Visit:	Screening	CRT + MK-3475	EOT visit[2]	Imaging	
Scheduling Interval:	-42d-1d	W1-W9	(35 ± 5d)	12w ± 10d post-CRT	
PT/INR and aPTT[13]	X				
CBC with Differential[13]	X	X[9,10,11]	X		
Serum Chemistry Panel[13]	X	X[9,10,11]	X		
Thyroid panel[13]	X	X[9,11,12]	X		
Tumor Imaging/Disease Assessments					
MRI[14]	X				
PET/CT[15]	X			X	

[9] Prior to first day of treatment (Day 1 Week 1), laboratory tests do not need to be repeated if screening labs were performed within 14 days prior to treatment date.

[10] General safety labs (CBC and serum chemistry) should be performed once weekly during chemoradiation and should also be performed prior to pembrolizumab administration on day of dosing to evaluate for toxicities (if not done in previous 72 hours). A basic serum chemistry panel is sufficient during chemoradiation, however, a complete chemistry panel including liver function tests should be performed within 72 hours of pembrolizumab treatments.

[11] Labs required prior to treatments do not need to be repeated if labs have been performed within 72 hours prior to dose

[12] Thyroid function tests should include, at a minimum, TSH. If TSH is abnormal, T3 and T4 must be evaluated. Thyroid tests should be completed within 72 hours prior to pembrolizumab administration.

[13] Screening labs must be obtained within 14 days of start of treatment.

[14] Pelvic MRI is required within 4 weeks of start of treatment unless there are contraindications or at the discretion of investigator.

[15] PET/CT (skull base to thighs) should be performed within 6 weeks of start of treatment, and repeated at 12 weeks ± 10 days after completion of CRT.

6.2 TRIAL PROCEDURES

6.3 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes 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 deemed necessary by the Sponsor-Investigator and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.3.1 Administrative Procedures

6.3.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor-Investigator requirements.

6.3.1.2 Registration

Subjects who are consented to the study must be registered in OnCore in accordance with the University of Virginia Cancer Center OnCore SOP, which can be found on the OnCore Resources page (see the Oncore Help tab). General guidelines are provided below for reference, but the procedure should follow the OnCore SOP in case of any discrepancy.

All subjects who have signed an informed consent should have the following information entered into OnCore:

- demographics
- date of signed informed consent

Subject eligibility must be confirmed by the site principal investigator (PI) and the eligibility packet should include at a minimum the informed consent and eligibility worksheet. All sites will submit an eligibility packet for each eligible subject to the study manager for review. The study manager will inform the site if the subject can be put on-study and instruct the site to then enter the following information into OnCore:

- subject number (provided by the study manager)
- on-study date
- disease site
- registering investigator

6.3.2 Randomization or Treatment Allocation

The subject will be randomized by the study manager at UVa using custom randomization software developed at UVa. The software incorporates the randomization scheme generated by the study statistician and assigns the subject to one of the two protocol arms.

6.3.2.1 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.3.2.2 Prior and Concomitant Medications Review

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

6.3.2.3 Disease Details and Treatments

6.3.2.3.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.3.2.3.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

6.3.3 Clinical Procedures/Assessments

6.3.3.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded according to NCI CTCAE Version 4.0. Toxicities will be

characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see separate ECI guidance document regarding the identification, evaluation and management of potential irAEs.

Please refer to Section 6.4 for detailed information regarding the assessment and recording of AEs.

6.3.3.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.

At subsequent visits requiring a physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated. On treatment days the physical exam should be performed prior to trial treatment administration. The physical exam conducted at the time of the post-treatment imaging should include, at a minimum, a clinical tumor assessment.

6.3.3.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.3.3.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.3.4 Laboratory Procedures/Assessments

Labs required prior to treatments do not need to be repeated if labs have been performed within 72 hours prior to dose. Screening labs must be performed within 14 days prior to treatment initiation; prior to first day of treatment (Day 1 Week 1) laboratory tests do not need to be repeated if screening labs were completed in the 14 day window. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase		PT (INR)
Platelet count	Alanine aminotransferase (ALT)		aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)		Total triiodothyronine (T3)
Red Blood Cell Count	Carbon Dioxide ‡		Free thyroxine (T4)
Absolute Neutrophil Count	*(CO_2 or biocarbonate)*		Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Calcium		Blood for correlative studies
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

6.3.4.1 Tumor Imaging and Assessment of Disease

Baseline imaging should be obtained within 6 weeks of the start of treatment and should include MRI and PET/CT. A pelvic MRI is required only at the Pre-Study Assessments unless there are contraindications or at the discretion of investigator.

PET/CT should be inclusive of the skull base to the thigh area ("eyes to thighs") and should be performed during the Pre-Study Assessments for initial staging. PET/CT should be repeated at 12 weeks ± 10 days after completion of CRT for evaluation of disease.

6.3.4.2 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood and tumor tissue should be collected from subjects at the intervals specified in the Trial Flow Chart and sent to the University of Virginia for analysis. All blood and tissue will be stored for research.

Tissue Markers: Tissue samples will be evaluated for tumor infiltrating lymphocytes using flow cytometry (FC) and standard immunohistochemical (IHC) staining techniques. Flow cytometry will be performed using standard techniques as described previously. For immunohistochemistry, tissue microarrays will be prepared using tissue cores from representative tumor areas from the FFPE tissue blocks. The tissue microarray will be incubated with specific antibodies, and positive and negative controls. Staining will be quantitated in quadruplicate by a pathologist blinded to the sample identity. Total cell count will be expressed in cells/mm^2 and density will be expressed as a number of cells per high power field (hpf). Staining will be determined in the five most abundant areas, using the average over the five to determine the percentage.

In addition, gene expression arrays on the resected tumor samples will be performed as a part of this study and may assist in identifying the activation of these receptors and factors.

Circulating Biomarkers: Collected blood will be processed to isolate peripheral blood lymphocytes. ELIspot analyses will be performed on PBMCs isolated from blood samples at each timepoint.

The planned initial analyses of the samples include the markers specified in this protocol; however actual analyses conducted may vary slightly as new information and technology develop.

6.3.4.2.1 Tumor Samples

Tumor tissue samples must be collected at the intervals specified in the Trial Flow Chart, adhering to the following guidelines:

1. Pre-study Tissue sample: Fresh tissue must be collected from an office biopsy performed within the 4 weeks prior to start of treatment. If this biopsy yields insufficient tumor tissue, an archival sample may be requested.

2. CRT Treatment Sample: Fresh tissue must be collected during CRT treatment, at 5 ± 2 weeks. It is recommended that this sample be obtained at the time of brachytherapy delivery, so that biopsy can be performed conveniently.

3. Treatment completion: Fresh tissue must be collected from an office biopsy performed at 12 weeks ± 10 days following completion of CRT.

Fresh tumor tissue should be divided into portions for several preparations including formalin fixed paraffin embedded (FFPE) in blocks, flash freezing and single cell isolations. Detail instructions for tissue processing and shipping will be provided in a separate study manual.

6.3.4.2.2 Blood Samples

Blood samples will be collected from subjects at the intervals specified in the Trial Flow Chart.

At each collection, approximately 70 cc of blood should be collected in heparinized green top tubes. Detail instructions for blood processing and shipping will be provided in a separate study manual.

6.3.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

6.3.5.1 Screening

Prior to the performance of any study-specific procedures, the patient will have the nature of the study explained to them, and will be asked to give written informed consent. Informed consent must be obtained prior to any study-specific procedures that do not form a part of the patient's normal care. However, assessments performed according to standard of care prior to receipt of informed consent may be utilized to fulfill the screening requirement, if completed within the required window for screening.

6.3.5.2 Treatment Period

The treatment period will consist of the duration of chemoradiation and pembrolizumab treatments. Subject should receive study assessments as defined in the Trial Flow Chart.

6.3.5.3 Post-treatment Visits

6.3.5.3.1 Follow-up Visit 1

A follow-up visit should be scheduled within 30 - 40 days following administration of the last study treatment in all subjects to perform the safety assessments defined in the Trial Flow Chart. Any assessments that were performed within 3 days prior to this visit do not need to be repeated.

6.3.5.4 Survival Follow-up

Following completion of treatment, subjects should be followed for 5 years to monitor disease and survival. No assessments are specified for this interval, but it is recommended that surveillance follow NCCN guidelines. Subjects should be contacted by telephone annually to assess for disease and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.4 Assessing and Recording Adverse Events

Adverse events should be collected from the start of treatment through a minimum of 30 days following the last study treatment.

After informed consent has been obtained, and prior to initiation of investigational treatment, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study treatment, all adverse events will be reported according to the guidelines in the following sections. Throughout the study, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to the investigational intervention.

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of pembrolizumab, is also an adverse event.

Adverse events may occur during the course of the use of Pembrolizumab in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

A summary of the adverse event collection and reporting is provided in Table 6.

Table 6. Adverse Event Reporting Overview

Event Type	Collection Timeframe	Reporting Timeframe	Reference
Routine Adverse Events	the start of treatment through at least 30 days following the last study treatment	Within 30 days to UVa	Section 6.4
Serious Adverse Events†		Within 24h to UVa	Section 6.4.4.1
Events of Clinical Interest	the start of treatment through 90 days following the last dose of pembrolizumab (or date subject starts new cancer treatment)	Within 24h to UVa	Section 6.4.4.2
Overdose	On pembrolizumab dosing days	Within 24h to UVa	Section 6.4.2
Pregnancy	the start of treatment through 120 days following the last dose of pembrolizumab (or 30 days following the last dose of pembrolizumab if subjects start new cancer treatment)	Within 24h to UVa	Section 6.4.3
†Serious and unexpected adverse events should also be reported to the site IRB per their institutional guidelines			

6.4.1 Assessment of Adverse Events

All adverse events, whether reported by the subject or noted by study personnel, should be recorded in the subject's medical record. Adverse events should be assessed for seriousness, severity, attribute and expectedness, in relation to Pembrolizumab treatment, by the Principal Investigator or designee. The following sections provide definitions for adverse event characteristics and reporting requirements.

6.4.1.1 Expectedness

The expectedness of the adverse event will be determined by the Investigator based on current literature, the Investigator's Brochure or package insert and the Investigator's experience. Adverse events commonly observed with the standard of care chemoradiation treatment, such as hematological, genitourinary and gastrointestinal, should be expected during the CRT interval.

6.4.1.2 Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

6.4.1.3 Attribution

The Principal Investigator will evaluate all AEs and assess their toxicity and attribution, if any, to pembrolizumab. See Table 8 for further guidance on evaluation of attribute. The following criteria will define the attribution:

Definite: The AE is clearly related to the investigational intervention.
Probable: The AE is likely related to the investigational intervention.
Possible: The AE may be related to the investigational intervention.
Unlikely*:* The AE is doubtfully related to the investigational intervention.
Unrelated*:* The AE is NOT related to the investigational intervention.

6.4.1.4 Seriousness

A serious adverse event is any adverse event that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

*Hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event, except if the hospitalization meets at least one of the following criteria:

- The hospitalization is less than 24 hours without an admission
- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for anticipated or protocol specified procedures such as administration of Intravenous fluids, central line insertion, biopsy procedures)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The subject has not suffered an adverse event.

If the hospitalization meets any of these criteria, then it is not considered a serious adverse event.

Refer to Table 7 for additional details regarding each of the above criteria.

6.4.2 Definition of an Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject 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 a Pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor-Investigator (Fax notification to UVa) using the Safety Reporting Form.

6.4.3 Reporting of Pregnancy and Lactation to the Sponsor-Investigator

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 subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the pembrolizumab treatment, or 30 days following cessation of pembrolizumab treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor-Investigator using the Safety Reporting Form.

6.4.4 Immediate Reporting of Adverse Events to the Sponsor-Investigator

6.4.4.1 Serious Adverse Events

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of start of treatment through 30 days following the last dose of study treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to pembrolizumab, must be reported within 24 hours to the Sponsor-Investigator. Additionally, after informed consent has been obtained, and prior to start of treatment, serious adverse events determined to be caused by a protocol-mandated intervention should also be reported.

Non-serious Events of Clinical Interest (See Section 6.4.4.2) will be forwarded to Sponsor-Investigator and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Pembrolizumab that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor-Investigator.

All subjects with serious adverse events must be followed up for outcome.

6.4.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor-Investigator using the Safety Reporting Form.

Events of clinical interest for this trial include:

1. an overdose of Pembrolizumab, as defined in Section 6.4.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Additional adverse events:

> A separate guidance document has been provided titled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor-Investigator using the Safety Reporting Form.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects 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.

Table 7. Evaluating Adverse Events

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Expectedness	Events included in Pembrolizumab Investigator's Brochure should be considered expected with pembrolizumab treatment for the purposes of assessment for expedited reporting requirements.	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?

6.4.4.3 UVA Cancer Center DSMC Reporting Requirements

All adverse events must be reported into the University of Virginia Cancer Center OnCore database within the time frame specified below:

Table B: Medium Risk Studies
Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected	Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 15 days	OnCore 15 days
Possible Probable Definite	OnCore 30 days	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 15 days	OnCore 15 days	OnCore 15 days	OnCore (24-hrs)* 7 days

*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

6.4.4.4 IRB Reporting Requirements

Serious and unexpected adverse events must be submitted to the site Institutional Review Board according to the participating site institutional policies.

6.4.4.5 Reporting to the FDA

The Sponsor-Investigator for the study (the UVA PI or designee) is responsible for providing safety updates to the FDA per the following guidelines. The reporting times refer to the time the Sponsor-Investigator received knowledge of the AE.

Table 8. FDA Reporting Requirements

UVa PI HELD IND			
Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

6.4.4.6 Reporting to Participating Sites

The Sponsor-Investigator for the study (the UVA PI or designee) is responsible for providing safety updates to all participating sites per the following guidelines:

Table 9. Required Reporting to Participating Sites

UVA PI of MULTI-SITE TRIAL			
Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**

Serious, unexpected and related or possibly related adverse events	All Research Sites	Within 15 calendar days after the Overall PI receives knowledge of the event	IND/IDE Safety Report (Cover letter, copy of MedWatch/narrative)
Unanticipated Problem	All Research Sites	Within 15 calendar days from the time the Overall PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative

6.4.5 Data Safety Monitoring Plan

The Data and Safety Monitoring Board for this study is the UVA Data Safety Monitoring Committee (DSMC).

6.4.5.1 UVA Cancer Center Data Safety Monitoring Committee

The University of Virginia Cancer Center Data and Safety Monitoring Committee (DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC). The DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The CC DSMC will meet every month for aggregate review of AE data. Tracking reports of the meetings are available to the PI for review. Issues of immediate concern by the DSMC are brought to the attention of the PI (and if appropriate to the PRC and IRB) and a formal response from the PI is requested. Per the Cancer Center NIH approved institutional plan this study will be audited approximately every 6 or 12 months.

7.0 STATISTICAL CONSIDERATIONS

This is a randomized phase II study to assess the safety of CRT in combination with pembrolizumab given as consolidation therapy or current with CRT, and to obtain preliminary estimates of the immunologic effect of the addition of pembrolizumab to CRT in this patient population. Eligible participants will be randomized 1:1 between the two arms. All participants receiving any protocol treatment will be evaluated for safety and the primary immunologic endpoint which is the ratio of the phenotype of HPV-specific CD8+ T cells to regulatory T cells (CD8+/Treg). Patterns of change in other immunologic endpoints assessed in the tissue and blood will be estimated along with 90% confidence intervals. The purpose is not to make definitive comparisons between arms but to obtain preliminary estimates of change in $CD8^+$ T-cells and regulatory T cells over time for the different treatment schedules.

Arm 1: pembrolizumab after completion of CRT
Arm 2: pembrolizumab concurrent to CRT

7.1 Evaluation Criteria

7.1.1 Safety Endpoints

All patients receiving any protocol treatment will be evaluated for safety. Safety assessments will include:

i. Incidence and severity of adverse events.
ii. Incidence of dose limiting toxicities (DLT) defined in section 7.4.

7.1.2 Immunologic Endpoints

All eligible patients for which the required follow-up tissue and blood samples are obtained will be evaluated for the difference in pre and post-CRT samples; difference in pre and during CRT samples; and difference in during CRT and post-CRT samples:

i. ratio of CD8+ T cells to Tregs
ii. HPV E2
iii. E7 specific CD8+ T cells
iv. regulatory FoxP3+ T cells (Tregs)

7.1.3 Efficacy Endpoints

All eligible patients for which a PET/CT imaging is obtained 12 weeks after CRT will be evaluated for complete metabolic response.

All eligible patients with follow-up information on disease status will be evaluated for the occurrence of distant metastasis as the first site of recurrence, progression-free survival and overall survival.

7.1.4 Exploratory Endpoints

Levels of specific markers involved in regulation of T cell activation and lymphocyte infiltration as assessed in the tumor immune microenvironment and the systemic immune response.

7.2 Sample size and accrual

Results in Jordanova ES, et al 2008, report estimates of CD8+/Treg for normal cervix and cervical cancers tissue for cervical cancer patients who underwent radical hysterectomy with lymphadenectomy.[4] These data provide the assumed "natural baseline" of cancer patients' in this study with CD8+/Tregs being lower in cancer tissue, and results in a Cohen's d_{av} effect size (ES) of 0.45. Estimated sample size is based upon being able to detect a similar effect size between CD8+/Tregs at baseline and end of CRT, and baseline to the 12 weeks post CRT assessment without correction for multiple comparisons. Data from Nilges, K et al, 2003, indicates a mean (standard deviation) of 23.32 (15.39) in CD8+/Tregs measured in the tumor infiltrating lymphocytes (TIL) from patients with cervical cancer. Given these data, 44 eligible patients are required (per arm) to assess change in pre/post CD8+/Tregs with an ES of 0.45 with type I and II errors of 10%. Each within arm comparison supports the following hypothesis. Cisplatin can kill T cells, therefore the CRT may eliminate both CD8+ HPV CTL and Tregs, and the ensuing or concurrent pembrolizumab treatment may increase the CD8+/Treg ratio (test that pembrolizumab will increase CD8+/Tregs to an ES of 0.45).

Adjusting for an overall 10% ineligibility/drop-out rate, maximum accrual to the study is estimated at 98 patients. Accrual is estimated at 4 patients a month, thus accrual to the study should be completed by 2.0 years with primary analysis at 3 years.

7.3 Randomization

Patients will be randomized in a 1:1 ratio to arms 1 and 2, respectively. Block randomization within site with random block sizes of 2, 4 or 6 will be employed.

7.4 Safety and Futility Monitoring

7.4.1 Safety monitoring

Dose Limiting Toxicity (DLT) is defined as an adverse event which: i) is determined to be at least possibly related to treatment with pembrolizumab; ii) occurs within the first 30 days after the first pembrolizumab infusion; and iii) meets one of the below criteria:

- Pneumonitis Grade ≥ 3
- Any non-hematological toxicity Grade ≥ 3, **except for the following:**
    - Grade 3 toxicity that is expected from standard of care cisplatin and radiation
    - Grade 3 Colitis, hypophisitis, or hyperthyroidism lasting less than 7 days
    - Grade 3 electrolyte toxicities that are corrected to grade 1 or less within 24 hours
    - Grade 3 hypertension that can be controlled with oral medications and does not require treatment delay for > 7 days
    - Grade 3 diarrhea that is not refractory to anti diarrhea medications and is corrected to Grade 1 or less within 48 hours
    - Grade 3 nausea and vomiting that is not refractory to anti-emetic therapy and is corrected to Grade 1 or less within 48 hours
    - Grade 3 rise in creatinine, if corrected to Grade 2 or less after up to 2 liters of intravenous fluids within 24 hours
    - Grade 3 elevation in AST/ALT if < 1.5 times the baseline level
    - Grade 3 elevation of ALP (alkaline phosphatase)
    - Grade 3 hypoalbuminemia
    - Grade 3 lymphopenia

  - Grade 3 rash if it returns to ≤ grade 2 after 1 week of symptomatic treatment
- Any Grade ≥ 4 toxicity
- Other AEs if they are clearly related to pembrolizumab and are causing substantial morbidity for subjects, as determined by the study chair.

Within each arm, safety will be assessed by monitoring the number of patients who experience a DLT. Results reported in ASCO 2015 abstracts [22, 23] for pembrolizumab in combination with other treatments resulted in an overall DLT rate of 1/59=2% with a 90%CI(1%, 8%). For this study the upper boundary of a sequential probability ratio test (SPRT) based upon a binomial test of proportions for DLT will be used for monitoring to protect against excessive failure rates. The stopping boundary is for a SPRT contrasting a 5% versus 25% DLT rate, with nominal type I and II errors of 10% and 10%, respectively. The slope of the parallel line for monitoring is 1.190 and the intercept is 0.128.

Safety stopping guidelines for the occurrence of DLTs are detailed in the following table. If a stopping bound is crossed in either arm then accrual to the study will be suspended until the study PI, co-investigators and the DSMC can review the data, and determine if the study should continue, be amended or be closed to further accrual.

Incidence of treatment related DLTs	
Number of patients in an Arm	Stopping boundary
2-6	≥ 2
7-14	≥ 3
15-21	≥ 4
22-29	≥ 5
30-37	≥ 6
38-44	≥ 7

7.4.2 Futility monitoring

In general, for futility assessment, destroying all the CD8s in the tumor and all the HPV-specific response in the blood would argue that we are likely preventing an immune response with the current CRT treatment, thus making the addition of pembrolizumab ineffective. Clinical response to pembrolizumab is most commonly associated with CD8+ T cell infiltration into tumors, and response rates for other solid malignancies are approximately 20% with pembrolizumab as a monotherapy. Thus, if CRT causes a reduction in the number of patients with T cell infiltration we could anticipate that CRT reduces the likelihood of patients responding to treatment. Assuming the current study population has a similar potential to respond to pembrolizumab, we would deem the study futile if early evidence indicates a potential to respond in a much lower percentage of subjects. We have set this lower target to be 5%. Futility will be monitored separately for each arm.

For each subject, the potential to respond will be determined at the end of the 12 week treatment window. We will assess the subject's tumor and blood for the presence of immune infiltrate and HPV specific T cell responses. Futility will be assessed by monitoring the number of patients with the absence of both CD8+ T cells and NK cells in the tumor, and a concomitant loss of HPV T cell reactivity in the blood. For the assessment of futility, each subject will be deemed to have the potential to respond if there are CD8+ T cells or NK cells in the tumor, or no loss of HPV T cell

reactivity in the blood. A 3-stage design structure will be used to monitor for a null potential to respond of 5% versus and alternative rate of 20%.

Within an arm, the futility assessments will occur after accrual of 14, 29 and 44 subjects have been accrued and followed for 12 weeks. The study specific arm will be deemed futile if 0/14, <4/29 or <6/44 subjects have the potential to respond for assessment at stages 1, 2 or 3, respectively. The decision guideline has type I and II error rates of 0.015 and 0.185, respectively.

7.5 Analyses

The study is designed with sufficient power to assess pre/post change in immune measures with an ES of .45 within each arm and not to detect a predetermined difference in the changes overtime between the two arms. However, data from the study will be used to estimate; the magnitude of the difference in pre/post change for all parameters of interest between the two arms; as well as progression–free and overall survival. With 44 eligible patients per arm we have 67%, 75% and 87% power to detect an ES of 0.45, 0.5 and 0.6, respectively, for continuous immune parameters (normality assumed) with a 10% level t-test. With 44 patients the width of a 90% CI (exact Clopper-Pearson) around the complete metabolic response at 3 months of 70% and the distant metastases rate at 3 years of 20% are (57%, 81%) and (10%, 33%), respectively. Thus, any estimated rate outside of these bounds would be considered promising. For each arm, progression free survival (PFS) and overall survival will be estimated by the product-limit method of Kaplan and Meier along with 90% confidence bands. In patients with complete metabolic response at 3 months, 3-year PFS is 78% (Schwartz et al, 2007). This result will be used to guide interpretation of results on PFS from this study.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 10.

Table 10. Product Descriptions

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

8.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

8.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-Investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.4 Storage and Handling Requirements

Clinical supplies 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.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's 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.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to all ICH E6 principles and Good Clinical Practice (GCP), to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

9.2 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. The Institutional Review Board will approve all aspects of this study, including the clinical trial protocol, informed consent documents, and patient materials. Modifications to the protocol or consent form will be reviewed and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the study participants. The study will undergo continuing IRB review based on the level of risk as assessed by the IRB. This review will take place no less than annually. Participating sites will be responsible for ensuring their consent forms are written in accord with 21 CFR 50.

9.2.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval/favorable opinion.

For any such emergency modification implemented, a UVA IRB modification form must be completed by study Personnel within five (5) business days of making the change.

9.2.2 Other Protocol Deviations/Violations

Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants

- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

Study personnel will record the deviation, and report to any Sponsor-Investigator or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Violations should be reported by study personnel to the IRB within one (1) week of the investigator becoming aware of the event.

9.3 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.4 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations, all applicable local regulatory laws and regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. It is the responsibility of the Principal Investigator to ensure that all study site personnel are aware that the study protocol and all data generated is confidential and should not be disclosed to third parties (with the exception of local and national regulatory bodies which require access for oversight purposes).

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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11.0 APPENDICES

11.1 ECOG Performance Status

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

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

11.2 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 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)