SPONSOR: The University of Chicago

TITLE: A randomized, double-blind Phase II study of pembrolizumab versus placebo in patients with head and neck cancers at high risk for recurrence or low-volume residual disease – the PATHWay Study.

Short Title: **PATHWay** – **P**embrolizum**A**b in the **T**reatment of **H**ead and neck cancer **W**ith high risk (tre**a**tment for 1 **y**ear)

IND NUMBER: 130496

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This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab for HNC at high-risk for recurrence
Trial Phase	*II*
Clinical Indication	Head and Neck Cancer (HNC)
Trial Type	Randomized, placebo controlled
Type of control	placebo
Route of administration	intravenously
Trial Blinding	blinded
Treatment Groups	Pembrolizumab, Placebo
Number of trial subjects	100
Estimated enrollment period	*2 years*
Estimated duration of trial	*4-5 years*
Duration of Treatment	1 year

2.0 TRIAL DESIGN

2.1 Trial Design

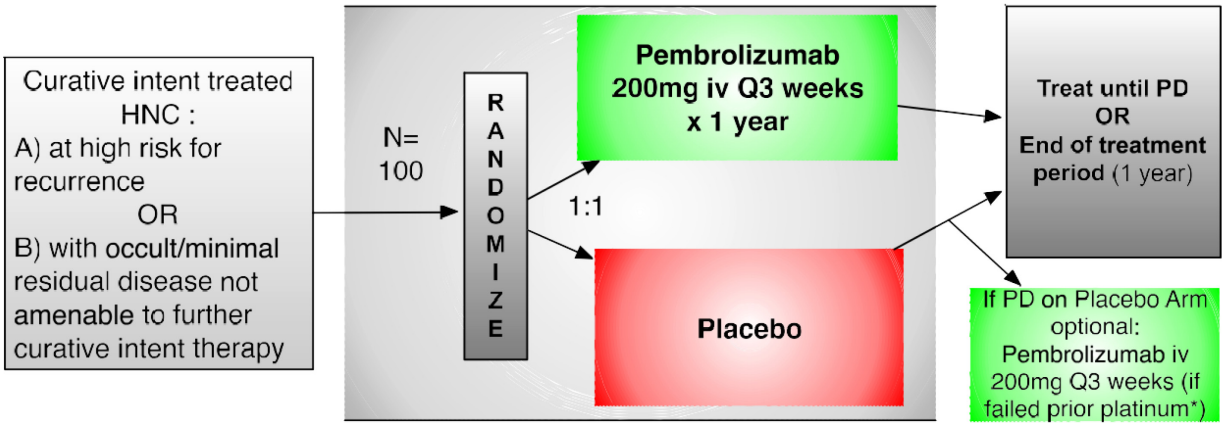
Randomized Placebo Controlled trial

1. Pembrolizumab 200mg, every three weeks, iv, x 1 year

2. Placebo iv, every 3 weeks, x 1 year

→ OPTIONAL: in patients treated with placebo who recur, pembrolizumab treatment may be offered as a salvage therapy upon disease recurrence as part of this trial.

2.2 Trial Diagram



*See section 5.8.2 for further details about prior platinum failure. Platinum failure does not apply to the chemoprevention setting or other situations where platinum is not appropriate/standard of care (see 5.8.2).

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** PFS

Hypothesis: PD-1 blockade with pembrolizumab in HNSCC at high risk for recurrence/potential small amount of residual disease s/p curative intent therapy will improve progression free survival.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: PFS, in gene expression Profile (GEP) positive patients

Hypothesis: PD-1 blockade with pembrolizumab in HNSCC at high risk for recurrence/potential small amount of residual disease positive for gene expression profile (GEP) s/p curative intent therapy will improve progression free survival.

(2) **Objective**: PFS, in PD-L1 >10% positive patients

Hypothesis: PD-1 blockade with pembrolizumab in HNSCC at high risk for recurrence/potential small amount of residual disease positive for PD-L1 expression in ≥10% of cells or stroma s/p curative intent therapy will improve progression free survival.

(3) **Objective**: OS in the overall patient population, and in gene expression signature (GES) positive or PD-L1 positive (≥10%) patients

Hypothesis: PD-1 blockade with pembrolizumab in HNSCC at high risk for recurrence/potential small amount of residual disease will improve overall survival, both overall and within GES and PD-L1 positive subgroups.

3.3 Exploratory Objective

(1) **Objective:** Gene Expression Profile (*Seiwert ASCO 2015*), HNC intrinsic subtype (*Keck et al CCR 2015*) determination, and broader RNAseq analysis: correlation with recurrence

(2) **Objective:** Gene Expression Profile evaluation in blood at baseline and 3-4 week after Pembrolizumab treatment (*Seiwert ASCO 2015*) and correlation with recurrence.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475/pembrolizumab.

4.1.1 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 States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

PD-1 blockade was shown to be effective in HNSCC with a response rate of **24.8%** as reported at ASCO 2015 (Keynote 12 study) (*Seiwert ASCO 2015*) or 18% by central review (*Seiwert Lancet Oncology 2016*), with an estimated median overall survival of ~12 months (*Chow ESMO 2014*) despite a heavily pretreated population (~60% of patients had 2 or more prior lines of therapy) compared to a median overall survival of 10.1 months using the EXTREME regimen (platinum/5-FU/cetuximab) in first line recurrent/metastatic HNSCC (*Vermorken NEJM 2008*). Furthermore evidence of long-term survival is seen in ~40% of patients (*Chow et al ESMO 2014*).

Please refer to the Investigator's Brochure for Preclinical and additional clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Squamous Cell Carcinoma of the Head and Neck

Squamous cell carcinoma of the head and neck (HNSCC) is the fifth most common malignancy worldwide and consists of HPV-negative and HPV-positive HNSCC. Both entities are currently treated using the same approaches, with the majority of patients presenting with locoregionally-advanced disease and undergoing curative intent therapy using chemo- or bio-radiotherapy either as a definitive or post-surgery treatment.

Study Rationale

While the majority of such patients with HNC can be treated with curative intent using multimodality approaches, a significant fraction of patients will fail therapy (typically within 12-18 months), especially those patients with high risk features such as advanced/bulky nodal stage, non-response to induction chemotherapy, residual disease on salvage surgery, and HPV-negative status.

Since pembrolizumab has shown significant single agent activity in HNC with a response rate of 21.6%-24.8% (*Seiwert ASCO 2014, ASCO 2015*), excellent tolerability, and potentially affords long-term survival in a fraction of patients (*Chow ESMO 2014*), pembrolizumab may be an ideal agent for therapy of HNC at high risk for recurrence/potential small amount of residual disease following curative intent therapy. Hence we propose a placebo-controlled, randomized study using pembrolizumab treatment for one year in order to potentially improve progression free survival in a HNSCC cohort at high-risk for recurrence/potential small amount of residual disease.

While drug development of pembrolizumab is ongoing in Phase III studies in the 2nd and 1st line recurrent/metastatic disease setting, ultimately the biggest impact based on patient volume and survival will likely be in the curative intent setting, if pembrolizumab proves active in this setting.

This randomized study of pembrolizumab is intended to explore early integration after curative intent setting and is intended to look at subgroups of PD-L1 positive, inflamed tumor (as measured by a gene expression profile) patients in order to identify a robust signal in a smaller study that we will be able to fully enroll in less than two years using an established network of HNC centers with a track record enrolling in this treatment setting.

HNSCC as a target disease for immunotherapy.

HNSCC shows some of the highest levels of a CD3+/8+ lymphocyte infiltration (TILs), and T-cell inflammation, and multiple immune escape mechanisms are present (*Saloura/Seiwert, ASCO 2014, Lyford-Pike 2013*). PD-L1 expression is prominent in up to 70% of tumors, and similarly to other cancer types (*Powderly 2013*) correlated with response in the Keynote 12 study (*Seiwert, ASCO 2014/2015*) as well as a smaller cohort using the anti-PD-L1 antibody Durvalumab/MEDI4636 (*Gibson ASCO 2015*).

PD-1 and PD-L1 Antibodies

PD-1 is a major pathway that was recently found to mediate immune evasion in a wide spectrum of tumors including malignant melanoma, squamous cell carcinoma of the lung, adenocarcinoma of the lung, and renal cell carcinoma. While the normal function of PD-1 is to counteract excessive immune responses directed against normal tissues, various types of cancer have manipulated this function by up-regulating the natural ligand of PD-1, PD-L1 to evade immune recognition.

The critical role of this pathway in HNC was recently demonstrated for HNC in the Keynote 12 study (*Seiwert et al ASCO 2014*) with a response rate of 20% in both HPV-negative and HPV-positive cohorts, and evidence of long-term survival in ~40% of patients, and estimated median survival of 12-13 months (*Chow et al ESMO 2014*).

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in 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. across a 5-fold difference in 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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Progression free survival is a surrogate marker of overall survival or rate of cure in the curative intent treatment setting for head and neck cancer (*Cohen JCO 2014*).

4.2.3.2 Biomarker Research

In an effort to identify those patients who may be more likely to respond to pembrolizumab, baseline tumor samples will be evaluated for PD-L1 expression using an established IHC assay in a CLIA setting and analyzed for GEP scoring retrospectively. Based on data from hundreds of patients in numerous pembrolizumab studies in multiple cancer types, these biomarkers may potentially prove to be predictive of patient benefiting from pembrolizumab and are hence included as part of the secondary objectives. The purpose of this trial is to assess whether potential benefit from therapy is also related to PD-L1 and/or GEP biomarkers.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must fulfill the following entry criteria:

1. Patients must have histologically confirmed head and neck cancer (Squamous cell histology), and may be poorly differentiated, Stages IVA, IVB, and select cases of Stage III (see additional criteria below) or any stage that meets criterion 3, A-F (see below).

    a. HPV status is required prior to randomization for oropharyngeal primary tumors, other anatomic sites will be classified as HPV- unless requested per the treating physician

    b. EBV status is required prior to randomization for nasopharyngeal primary tumors, other anatomic sites will be classified as HPV- unless requested per the treating physician

2. Completed curative intent therapy, without additional standard of care curative intent therapy feasible (see below for additional details) within 20 weeks prior to study enrollment.

3. **After prior curative intent treatment for HNC have estimated risk of recurrence ≥40-50% and fall into <u>one</u> of the below categories (A, *<u>OR</u>* B, *<u>OR</u>* C, *<u>OR</u>* D, *<u>OR</u>* E, OR F).** While exact estimation of the risk of recurrence can be difficult the following categories will be included reflecting patients at substantial risk for tumor recurrence or already with early evidence of recurrence**:**

    -A- Any of the below HNC patients are eligible for treatment on this protocol AFTER completion of curative intent therapy:

- HPV(-) HNC: N2C, N3, **bulky** N2B disease (≥5cm LN/tumor conglomerate).
- HPV(+) HNC: N2C, N3, AND ≥10 pack years of tobacco use
- HPV(+) HNC with multilevel nodal involvement, AND bulky N2B disease (≥5cm LN/tumor conglomerate), AND ≥ 10 pack years of tobacco use
- EBV(+) NPC may be eligible if other criteria under A, or alternative criteria B, or C, or D, or E are met.
- HNC with supraclavicular or mediastinal nodal involvement (either HPV+/- or EBV+/-) at the time of curative intent treatment and were treated as part of curative intent therapy (e.g. inclusion in the radiation field)
- Residual mass in area of prior tumor that on biopsy does not show residual tumor, is equivocal/not highly-suspicious on imaging (e.g. TET/CT/MRI) but remains of concern, requires close follow-up AND is not resected/amenable to resection OR immediate palliative treatment.
- Non-responders to induction chemotherapy (PD on induction, or lack of tumor shrinkage (<15% per RECIST)
- Interrupted treatment course or lower than intended radiation dose – i.e. interruption of radiation by ≥3 weeks (cumulative), or delivery of ≤50 Gy as part of a radiation based treatment (that was NOT a de-escalation approach).

- B- Patient treated with salvage treatment (i.e. salvage surgery or re-irradiation) for residual or recurrent tumor after prior radiation based therapy (either HPV+ or HPV- or EBV+) AND not a candidate for additional curative intent therapy (for various reasons including poor performance status, comorbidities, refusal of patient, prior radiation or re-irradiation, etc). Positive margins or residual tumor may still be acceptable (see D). Patients should also not be appropriate for systemic palliative therapy (e.g. in the case of overt disease)

- C- Mx or indeterminate distant lesions that are not appropriate for either local radiation/SBRT treatment and also not appropriate for initiation of palliative system therapy (e.g. in the setting of overt metastatic disease). Such lesions should be negative/equivocal by PET imaging and if amenable negative by biopsy, but remain of concern and require close follow-up.

-D- Oligometastatic disease treated with SBRT or other **curative-intent** therapy (e.g. surgery or RFA, etc) for oligometastatic disease.

- E- Microscopic or very low volume residual tumor after surgery or radiation based treatment (including salvage treatment or SBRT for oligometastatic disease), AND not a candidate for either additional curative intent therapy (for various reasons including feasibility, poor performance status, comorbidities, refusal of patient, prior radiation or re-irradiation, etc) AND also not a candidate for systemic

palliative therapy (for various reasons including microscopic/non-(RECIST) measurable low volume disease). Very low volume disease is defined as non-RECIST measurable).

- F- Patients with multiple recurrences or multiple primaries: specifically patients who had malignant or pre-malignant tumors/changes (with severe dysplasia present), who have undergone surgery ≥2 times, and currently do not have an indication for additional (adjuvant) treatment such as radiation, or surgery, or other treatment. This may include multiple recurrences/incidences of early stage tumors or premalignant lesions, however at least one lesion needs to show squamous cell carcinoma on pathology.

→ There may be additional scenarios for patients that are considered very high risk for disease recurrence and not appropriate for either curative or standard of care palliative therapy. Such patients can be considered for enrollment after discussion and approval by the Lead PI and/or co-PI.

4. Availability of tumor tissue (≥10 slides) for PD-L1, gene expression profiling (GEP), and additional testing.

5. Be willing and able to provide written informed consent/assent for the trial.

6. Be ≥ 18 years of age on day of signing informed consent.

7. Have a performance status of 0 or 1 on the ECOG Performance Scale. An ECOG performance status of 2 is acceptable if the patient was ECOG 0/1 prior to curative intent therapy and is in the midst of recovery from curative intent therapy

8. Demonstrate reasonable organ function as defined in Table 1, all screening labs should be performed within 10 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
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤2.0 X upper limit of normal (ULN) **OR** ≥40 mL/min for subject with creatinine levels > 2.0 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 2 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 2 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
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.	

9. Female subject of childbearing potential should have a negative urine or serum pregnancy test 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.

10. Female 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 (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

1. Measurable disease that is amenable to curative intent therapy, or amenable to standard of care systemic/palliative therapy (e.g. platinum containing chemotherapy, cetuximab, pembrolizumab or other approved options).

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (>10mg of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 2 weeks of the first dose of treatment.

4. Has a known history of active TB (Bacillus Tuberculosis)

5. Has hypersensitivity to pembrolizumab or any of its excipients.

6. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy or typical side effects from radiotherapy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer or any tumors that are not likely to influence life expectancy in the subsequent 3 years without active treatment (e.g. low grade prostate cancer in absence of therapy).

9. Has known active (=growing) central nervous system (CNS) metastases and/or carcinomatous meningitis. Radiation or resected brain metastasis are acceptable if clinically stable.

10. 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.

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

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the 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.

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

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

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: 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 within 30 days prior to initiation of treatment.

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	**200 mg flat dose**	**Q3W**	**IV infusion**	**Day 1 of each 3 week cycle**	**Experimental**
Placebo	**--**	**Q3W**	**IV infusion**	**Day 1 of each 3 week cycle**	**Experimental**

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Dose Selection/Modification

5.2.1.1 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.

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

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

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. 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.

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). • 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
	Grade 4	Permanently discontinue		

				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	Grade 2	Withhold	• Administer corticosteroids	• Monitor changes of renal function

dysfunction	Grade 3 or 4	Permanently discontinue	(prednisone 1-2 mg/kg or equivalent) followed by taper.	
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).

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

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all 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 Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.3 Trial Blinding/Masking

This is a double-blind placebo controlled trial; therefore, neither the investigator nor the subject will know the treatment administered.

Unblinding will occur at the conclusion of the study (approximately 2 years after completion of accrual) OR if in the setting of tumor recurrence/progression – i.e. in order to allow a potential cross-over to pembrolizumab or eligibility for another trial including immunotherapy agents. Specific safety concerns may also trigger unblinding upon review by the lead Statistician and PI.

Please also see section defining radiologic progression (treatment until confirmed progression is acceptable/advised if clinically appropriate with a 2nd scan 4-8 weeks from first scan).

5.3 Randomization or Treatment Allocation

Patients should be enrolled within 20 weeks of completion of curative intent therapy and the last element/last day of curative intent therapy is used as a cutoff date.

Ideally the start of therapy should be within 4-6 weeks post completion of treatment to achieve the highest chance of treatment success, but later initiation is acceptable up to 20 weeks post treatment.

Patients will be randomized to receive pembrolizumab 200 mg or placebo.

Expected treatment duration is one year from day 1 of pembrolizumab or placebo administration.

A secure online registration interface has been developed to register patients (eVelos). Randomization will be performed by the site pharmacists using the web-based randomization module in REDCap.

Stratified randomization sequences will be generated using the method of permuted blocks. At the time of patient registration an electronic notification will be sent to the study pharmacist. To randomize this patient, the pharmacist will login into the REDCap system, which will provide the randomized treatment assignment. Only the pharmacist will have access to the treatment assignment to maintain the blinding.

5.4 Stratification

Randomization will be stratified for:

1. **Tumor Etiology: HPV+/EBV- versus HPV-/EBV- versus EBV+/HPV-** (please note that there are no EBV/HPV double positive tumors described)

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy for vaccination may be required. The investigator should discuss any questions regarding this with the Lead PI. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 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.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.3.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) 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
    - Note: Radiation therapy to a symptomatic/clinically threatening lesion/s or to the brain may be allowed at the investigator's discretion and after Lead PI approval. Pembrolizumab treatment should be held during the time of radiation and for 7 days after radiation.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- 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 Lead PI.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 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 intended to be applied 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 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. 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.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **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).

    - 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 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - 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 for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients 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.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients 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** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - 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** events, treat with corticosteroids.
  - For **Grade 3-4** 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.

- **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 4 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)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

- **Management of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis:**

To date, approximately 11,000 patients in clinical trials and 27,000 patients in the post-marketing setting have been treated with KEYTRUDA®. One fatal case of SJS in a clinical trial and one fatal case of TEN in the post-marketing setting have been reported in patients treated with KEYTRUDA®. Including these cases, there have been 8 cases of SJS (6 in clinical trials, and 2 post-marketing) and 2 cases of TEN (both post-marketing) all of which were serious.

- For signs or symptoms of SJS or TEN, withhold KEYTRUDA® and refer the patient for specialized care for assessment and treatment.
- If SJS or TEN is confirmed, permanently discontinue KEYTRUDA®.

- **Management of Immune-mediated myocarditis:**

A total of 6 cases of myocarditis have been reported in patients treated with KEYTRUDA® in clinical trials or in an expanded access program. There were was 1 fatal case reported in a clinical trial.

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 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) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not

heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. 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.

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 defined in section 7.3.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. 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.

5.7.3 Use in Pregnancy

If a subject inadvertently 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 and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.3.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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 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 Section 7.2.7.1.

A subject must be discontinued from treatment for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression (=2nd scan within 4-8 weeks) if on treatment arm

  Note: Confirmed disease progression will lead to unblinding and those patients on the placebo arm will have the opportunity to cross over to the pembrolizumab arm if patients have failed prior platinum (see Section 5.8.2).

  Note: For unconfirmed radiographic disease progression, please see Section 6.2

  Note: A subject may be granted an exception to continue on treatment if certain criteria are met (see section 6.2).
- Unacceptable adverse experiences as described in Section 7.3.3.1
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab or 18 administrations of study medication, whichever is later.

  Note: 12 months of study medication is calculated from the date of first dose. Subjects who recur/progress on the control arm during study period may be eligible for up to one year of treatment with pembrolizumab open label (optional cross-over, see 5.8.2)
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1 (Trial Procedures). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.8.4). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing

consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, the end of the study, or two years after the last patient randomized received their last dose of study drug, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

For subjects who meet ALL of the following criteria: A) **overt disease** at any point during treatment (either on the pembrolizumab treatment arm with radiologically visible disease, OR on the placebo arm receiving treatment with optional pembrolizumab treatment after PD), B) attain a **confirmed** CR upon pembrolizumab treatment, and C) have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared - discontinuation of treatment may be considered. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via a Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation and treatment can be continued for up to 12 months.

5.8.2 Pembrolizumab treatment for patient on the Placebo Arm upon disease recurrence/progression

For subjects, who show evidence of disease recurrence/progression, treatment will be unblinded and those on the placebo arm will have the opportunity to receive pembrolizumab treatment (if they have been exposed and failed prior platinum therapy (e.g. cisplatin/carboplatin in a prior line of therapy, and if clinically indicated/appropriate {e.g. platinum requirement does not apply in the prevention setting}). Treatment for up to 1 year is planned. However additional therapy can be considered as part of standard-of-care outside of this trial using FDA approved PD-1 inhibitors and patients will be followed for survival progression, and response for up to an additional year.

5.9 Subject Replacement Strategy

Patients who receive 0, or only 1 dose will be considered non-evaluable, although they will continue to be followed for outcomes. An intention to treat analysis will be performed as a secondary analysis, but for the primary analysis only patients with adequate treatment exposure of ≥2 doses of pembrolizumab will be included. Randomization of new patients will continue until enrollment of 100 evaluable patients is achieved.

5.10 Clinical Criteria for Early Trial Termination

Early trial termination at a participating site 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 Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles** (cycle length is 21 days)								**End of Treatment** [1]	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discontinuation	Safety Follow-up		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon.	30 days post Discon.		Every ~12-16 weeks x2 years
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X												
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status										X	X		X
Survival Status and Assessment of Disease Status (Disease free versus evidence of PD)[2]	X	X	X	X	X	X	X	X	X	X	X		X[2]
Clinical Procedures/Assessments													
Review Adverse Events			X	X	X	every 6-9 weeks				X	X		
Full Physical Examination	X	X		X		every 6-9 weeks				X	X		
Vital Signs and Weight	X	X	X	X	X	Prior to every treatment				X	X		
ECOG Performance Status	X	X		X		every 6-9 weeks				X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG	X												

Trial Period:	**Screening Phase**	**Treatment Cycles** (cycle length is 21 days)								**End of Treatment** [1]	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discontinuation	Safety Follow-up		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon.	30 days post Discon.		Every ~12-16 weeks x2 years
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X												
T3, FT4 and TSH	X			X		Every 2-4 months or as clinically indicated				X	X		
Efficacy Measurements													
Tumor Imaging[3]	X				X	Every 12 weeks for the initial 12 months while on treatment unless tumor is present then imaging should be done every 9 weeks. If clinically indicated additional scans should be obtained. During year 2 in absence of tumor, imaging should be performed every 4 months. If clinically indicated additional scans should be obtained.				X			Every 3 months during first year, every 6 months during second year or as indicated for clinical reasons

Trial Period:	**Screening Phase**	**Treatment Cycles** (cycle length is 21 days)								**End of Treatment** [1]	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discontinuation	Safety Follow-up		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon.	30 days post Discon.		Every ~12-16 weeks x2 years
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection (≥10 slides)	X												
Correlative Studies Blood Collection	X		X	Additional draws upon suspected or proven progression are encouraged									

1 End of Treatment = end of 1 year of treatment OR disease recurrence. However in the setting of disease recurrence and treatment on the placebo arm (unblinding), patients may continue for 1 additional year of pembrolizumab treatment, using every 2 month tumor imaging or as clinically indicated. Also research blood draws before pembrolizumab treatment and at cycle 2 should be done (similar to initial blood draw schedule).

2 Survival follow-up can be done via phone if patient is not coming in for additional care

3 Radiographic assessments (CT, PET-CT, PET and/or MRI as appropriate) must be performed within 56 days of starting study treatment (or within 28 days if tumor is present). CT, PET-CT, PET and/or MRI as appropriate should be performed every 12 weeks for the initial 12 months while on treatment – unless tumor is present then imaging should be every 9 weeks. If clinically indicated additional scans should be obtained. During year 2 in absence of tumor imaging should be performed every 4 months. If clinically indicated additional scans should be obtained.

4 Patients, who recur/progress on the Placebo arm are allowed to cross over to active therapy and receive treatment x1 year with pembrolizumab if patients have failed prior platinum (see 5.8.2), unless not clinically appropriate (e.g. patient in the chemoprevention setting typically do not have an indication for platinum, e.g. after resection). The same schedule as above will be followed, although assessment of tumor burden every 8 weeks is recommended and discontinuation of therapy upon clinically confirmed progression on pembrolizumab is recommended.

Please note that new tissue from the recurrent tumor needs to be obtained.

Clinical practice is pathologic confirmation of recurrence/progression for almost all patients after curative intent therapy that show lesions suggestive of recurrence. If however a biopsy is not feasible/safe, this requirement can be waived after Lead PI approval.

6.2 Treatment After Initial Evidence of Radiologic Evidence of Disease Progression

If radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging (confirmatory scan) shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar if PD is no longer present per RECIST 1.1 measurement (=PD is not confirmed). If repeat imaging confirms PD per RECIST 1.1, subjects will be discontinued from study therapy. In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions (e.g. if present at baseline) as well as non-target lesions (refer to RECIST 1.1 guidelines)).

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the subject as described in the below Table.

Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Table: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A

Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 9 weeks	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments every 9 weeks	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

7.0 TRIAL PROCEDURES

7.1 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 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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

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's approval/favorable opinion 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 that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB requirements and applicable laws and regulations.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the 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.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Randomization Number

A unique identifier will be assigned for each patient per the central site (University of Chicago). Please also see Sections 7.1.5.2 and 10).

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Patients are expected to follow the outlined treatment schedule, and violation of trial procedures may lead to trial discontinuation (see Section 5.8) if compliance is felt to impact treatment in a meaningful way or interpretability of data (consultation with the Lead PI recommended).

7.1.2 Clinical Procedures/Assessments

7.1.2.1 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 and recorded throughout the study and during the follow-up period 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.

Please refer to section 7.3 for detailed information regarding the assessment and recording of AEs.

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ±7 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and

tolerability will be assessed according to the NIH/NCI CTC http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to treatment must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of > 12 weeks from the intended day of the next scheduled dose, then the patient must be discontinued from treatment.

7.1.2.2 Full 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. A full physical exam should be performed during screening,

7.1.2.3 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.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of dose of trial treatment every 6 weeks and discontinuation of trial treatment as specified in the Trial Flow Chart, except for stable patients where the interval can be increased to every 9 weeks as indicated in the trial schema.

7.1.2.5 Tumor Imaging and Assessment of Disease

Tumor imaging will be performed as outline in the flowchart under Section 6, typically every 8-16 weeks or as clinically indicated.

Radiologic recurrence/progression of disease should be confirmed 4-8 weeks after the initial scan and patients can continue treatment until confirmation if clinically stable and no other immediate reason for discontinuation is present.

Whenever possible clinical progression should be confirmed radiologically.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

A minimum of 10 slides (from the original tumor prior to initiation of curative intent therapy) will be collected.

Blood will be obtained at baseline and at the time of the second treatment. Please see tissue/blood collection SOP provided separately.

7.2 Research Tests

Tissue obtained (PRIOR to curative intent therapy) from the diagnostic biopsy/panendoscopy and/or during surgical resection, and blood samples (in PAXGene tubes/ctDNA tubes).

The correlative work will be performed/coordinated at the University of Chicago.

7.2.1 Sample Shipping and Storage

All the tissue, whole blood and serum samples will be packaged and transported by carrier service in batched samples following the government regulation 42 CFR Part 72 – "Interstate Shipment of Etiologic Agents", which describes the requirements for the proper packaging and shipping of infectious substances and other biomedical material. All the samples will be packaged and delivered in such a way that the contents will not leak and will arrive in good condition.

Further specifics are described in the Tissue and Blood Collection SOP which are provided separately.

All institutional requirements for safety and confidentiality will be met during specimen transmittance.

All samples must be accompanied by a Sample Shipping Form (see separate Tissue and Blood Sample Collection Form that is contained in the Tissue and Blood Collection SOP).

All of the specimens collected for this study will be stored at the following address:

Human Tissue Resource Center (HTRC)
The University of Chicago Medicine
5835 S. Cottage Grove/Room P-524
Chicago, IL 60637

7.2.2 IHC staining

→ Multicolor immunohistochemistry will be performed and results will be descriptive and presented in tabular with a focus on highlighting changes from pre- treatment samples.

Multicolor IHC markers will include PD-L1, and CD8.

PD-L1 testing will be performed in addition in a dedicated IHC assay using the available 22C3 PD-L1 antibody assay originally developed by Merck (or a comparable assay).

Additional staining for FOXP3, CD163, IDO, CD206, CD11a, CD163, and related markers if appropriate based on assay availability may be added.

7.2.3 Nanostring Analysis/Inflammatory Gene Expression Profiling (GEP)

GEP for an inflammatory phenotype will be performed using an assay developed by Merck on the Nanostring platform.

Briefly – RNA will be extracted from 3-5 FFPE slides using a Qiagen RNA from FFPE tissue kit (and respective protocol).

A Nanostring nCounter will be use to immune gene expression and a composite score calculated (*Ribas ASCO 2015, Seiwert ASCO 2015*).

7.2.4 Tumor DNA Analysis

Exome sequencing from tumor and normal blood white cells will be performed on the tumor samples for an exploratory analysis of correlation of genetic aberrations, immune phenotype and tumor response. In addition tumor RNAseq analysis will be performed from tumor tissue. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

7.2.5 Germline DNA analysis

Blood will be obtained from all patients for exome sequencing of normal DNA (see above). Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

7.2.6 RNA/ctDNA analysis from blood

Blood samples will be obtained at baseline and after 3-4 weeks (administration of cycle 2 dose was done). Samples will be processed for RNA/DNA expraction (e.g. using thje PAXgene RNA kit/tubes/ctDNA tubes (see lab manual)). RNA will be analyses by Nanostring (see above) or RNAseq) in an exploratory fashion comparing baseline with on-treatment inflammatory markers as well as NGS for detection of ctDNA levels. Specific processing information will be made available in a continually updated SOP for tissue collection and processing. Additional blood samples upon concern for PD may be drawn.

7.2.7 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below under Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	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.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.2.6.1 Pharmacodynamic Evaluations

7.2.6.1.1 Blood Collection for RNA

Blood will be collected at baseline at the time of 2nd administration of pembrolizumab. Details are provided in a separate Tissue and Blood SOP.

No Pharmacokinetic evaluations will be done.

7.2.7 Other Procedures

7.2.7.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 12 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.2.8.4.1) and then proceed to the Follow-Up Period of the study (described in Section 7.2.8.5).

7.2.7.2 Blinding/Unblinding

Unblinding will occur at the conclusion of the study (approximately 2 years after completion of accrual) OR if in the setting of tumor recurrence/progression (typically confirmed with a 2nd scan 4-8 weeks post initial scan) – i.e. in order to allow a potential cross-over to pembrolizumab (see 5.8.2) or eligibility for another trial including immunotherapy agents (also see Section 5.2.3). Specific safety concerns may also trigger unblinding upon review by the lead Statistician and PI.

7.2.8 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.

7.2.8.1 Screening period

Screening period is 30 days prior to initiation of study drug. See flow chart under Section 6 for specific items.

x All patients must have completed curative intent therapy for locally advanced HNSCC within 24 weeks prior to enrollment.

x Tissue must have been collected **PRIOR** to starting curative intent therapy on all patients (see eligibility criteria)

7.2.8.2 Treatment Assignment and Online Registration

x Patients must be enrolled within 6 months of completion of curative intent therapy, but can be consented anytime during or before curative intent therapy

x Patients will be randomized to receive pembrolizumab or placebo

x Treatment assignment will be double-blinded. Unblinding will occur at the conclusion of the study (approximately 2 years after completion of accrual) or if required for patient safety, or in the setting of disease progression to allow cross-over or participation in another study – e.g. with immunotherapy. Unblinding (except for the conclusion of the study) will be performed by the site pharmacist, who will communicate the assigned treatment to the physician investigator.

x Expected treatment duration is 1 year from day 1 of pembrolizumab or placebo administration

x Randomization will be stratified for (also see 5.4)
1) Tumor Etiology: HPV+/EBV- versus HPV-/EBV- versus EBV+/HPV-

x **A secure online registration interface has been developed to register patients (eVelos), and is integrated with the data collection and storage system.** Randomization will be performed by the site pharmacists using the web-based randomization module in REDCap. Once a patient has been deemed eligible, the CRA will notify the pharmacist via email that the patient should be randomized, and will provide the pharmacist the patient ID number, initials, and stratum information.

x Stratified randomization sequences will be generated using the method of permuted blocks. At the time of patient registration an electronic notification will be sent to the study pharmacist. To randomize this patient, the pharmacist will login into REDCap, which will provide the randomized treatment assignment. Only the pharmacist will have access to the treatment assignment to maintain the blinding.

7.2.8.3 Treatment Period

Treatment period is 1 year or until progression. Upon progression however patient treatment arm will be unblinded and patients on the control are eligible to receive up to 1-year of pembrolizumab treatment analogous to the pembrolizumab arm (optional cross-over, see 5.8.2).

7.2.8.4 Post-Treatment Visits

7.2.8.4.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.2.8.5 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 3 months by radiologic imaging during the first year, and every 6 months during the second year or as indicated for clinical reasons, to monitor disease status for up to 2 years (Section 6). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria specified will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.2.8.5.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone approximately every 12 to 16 weeks to assess for survival status until death, withdrawal of consent, the end of the study, or two years after the last patient received their last dose of pembrolizumab, whichever occurs first.

7.3 Assessing and Recording Adverse Events

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 the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product 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.

Adverse events will be recorded only for patients on treatment or who have received treatment in the past.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time of first treatment on study through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.3.3.1.

Immune-mediated adverse events that occur within 90 days of the end of treatment will be followed and recorded.

7.3.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, 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 Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product 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 and within 2 working days hours to Merck Global Safety as described in section 10.7 below.

7.3.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male 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 and within 2 working days to Merck Global Safety as described in section 10.7 below.

7.3.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.3.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product 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

Refer to Table 6 for additional details regarding each of the above criteria.

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 the first dose of study drug is received through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety as described in section 10.7 below.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by a qualified investigator to be related to Merck product 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 and to Merck.

This study will be conducted under an investigator-held IND at the University of Chicago. Annual Progress Reports will be submitted as required by FDA. Additionally the IND holder will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

The investigator must assess and record the relationship of each SAE to the specific study drug, and follow the procedures described in section 10.7 below. The original copy of the SAE Report and the fax confirmation sheet must be kept at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

7.3.3.2 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 and within 2 working days to Merck Global Safety as described in section 10.7 below. Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined – above in the Section entitled "Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor", 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.

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 and within 2 working days to Merck Global Safety as described in section 10.7 below, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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.

7.3.4 Evaluating Adverse Events

A qualified investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

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Table 6 Evaluating Adverse Events

A qualified investigator will evaluate all adverse events as to:

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?	
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 a qualified investigator. 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 LEAD PI 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?
The assessment of relationship will be reported on the case report forms /worksheets by a qualified investigator according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.3.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable laws and regulations.

7.4 Efficacy assessment

The primary study endpoint is progression-free survival, defined as the time from randomization until disease progression or death from any cause. Patients alive and progressionfreewillbecensored as of the data of the last negative exam. Disease progression (PD) will be evaluated by clinical and radiographic methods and date of progression will be recorded. Radiographic progression should be confirmed with a second scan 4-8 weeks after initial scan and treatment can continue until then.

If in question, disease progression should be confirmed pathologically. Site of disease progression will be classified as local (progression at primary tumor site), regional (progression in cervical lymph nodes), and/or distant (metastatic disease).

A diagnosis of second primary tumor must be confirmed pathologically. Deaths on study should be classified as disease (HNSCC), non-disease, or study treatment related.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan

This is a multicenter, randomized, placebo-controlled, double blind Phase II clinical trial of pembrolizumab vs. placebo. Patients will be randomized after the completion of curative intent therapy.

The primary endpoint is progression-free survival (PFS). Progression-free survival will be estimated using the method of Kaplan- Meier, and compared between the two treatment arms using a stratified logrank test, i.e., stratified by the randomization factors. Multivariate Cox regression models will be fit to compare treatment effect between treatment groups adjusting for other important prognostic factors. The proportional hazards assumption will be checked using numerical and graphical techniques. Overall survival (OS) will be analyzed in a similar manner. Adverse event rates will be summarized and compared between treatment groups using chi-squared or Fisher's exact test. Continuous variables will be compared between groups using t-test or Wilcoxon rank sum test as appropriate, and categorical outcome variables will be compared using chisquare tests.

8.2 Sample Size

Assuming uniform 2-year accrual and 2.5-year follow-up, a **one-sided logrank** test with a

sample size of 90 (45 patients per treatment arm (assuming 10% loss of follow up in N=100 patient trial) will achieve 93% power at alpha=0.10 (one-sided) to detect a difference between 50% and 72.5% progression free survival at 2 years, which corresponds to a hazard ratio (HR) of 2.2 (Lakatos, 1988).
Approximately 51 events are required to detect such a difference.

An interim look for safety will be conducted after 20 patients have been randomized to the treatment arm. If >3 (>15% toxicity rate) Grade 3/4 immune-related side effects occur, the Lead PI will consider terminating or amending the trial

- Analysis of secondary objectives

The stratified logrank test will also be used for the analysis of secondary endpoints, specifically comparing PFS in patients with a PD-L1 positive tumor. Whereas progression-free survival is expected to be roughly similar between PD-L1+ and PD-L1- patients in the placebo arm, PD-L1+ patients on pembrolizumab are expected to do better than PD-L1- patients; alternatively the treatment effect should be greater in the PD-L1+ subgroup. Based on data in HNSCC (*Seiwert ASCO 2015*) 60-71% PD-L1+ as well as 60-70% GEP prevalence in each arm is expected (n=20 biomarker (-) (PD-L1 or GEG) and n=25 biomarker+ among n=45 randomized to each arm). PD-L1 and GEP analysis will independent of each other. Due to the low expected number of events in each subgroup, this analysis will have limited power and be exploratory in nature.

NOTE: PD-L1 testing will be performed using the 22C3 antibody based assay (or a comparable assay).

The stratified logrank test will also be used for the analysis comparing PFS in patients with a GEP profile. Whereas progression-free survival is expected to be similar between GEP+ and GEP- patients in the placebo arm, GEP+ patients on pembrolizumab are expected to do better than GEP- patients; alternatively the treatment effect should be greater in the GEP+ subgroup. Based on data in HNSCC (Seiwert ASCO 2015) 60% GEP+ prevalence in each arm is expected (n=20 GEP- and n=25 GEP+ among n=45 randomized to each arm). Due to the low expected number of events in each subgroup, this analysis will also be exploratory.

NOTE: The GEP assay is implemented as a clinical grade assay (via Merck) and will be used as previously established. Should this assay not be accessible for an investigator-initiated protocol a similar assay would be performed at the University of Chicago using the available Nanostring platform, however the results would be considered exploratory rather than be used as a secondary outcome.

While the detectable differences are quite large, they are comparable to those observed in other studies – for example, patients with FOE+ and FOE- in the retrospective study (Nathan et al, 1999) had median PFS of 82 and 31.5, which corresponds to HR=2.6. Also a strong trend may ultimately inform a larger Phase III study.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 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 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Placebo (no product/active ingredient will be added to the injection solution)	Identical or comparable solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

This trial is blinded and placebeo controlled;. Drug identity (name, strength) will not be included in the label text.

9.4 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.

9.5 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Food and Drug Administration (FDA) Approval

This study will be conducted under an investigator-held IND at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

10.2 New Protocol Distribution and IRB Submission

Once final Merck and University of Chicago (U of C) IRB approval is received, the protocol and consent form will be distributed to the participating affiliate institutions electronically. Upon receipt of the email, the affiliate institution is expected to do the following:

- The affiliate institution is expected to submit the protocol to their IRB as soon as possible after receipt.
- **The U of C version date must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on every page of the protocol and consent form.

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official local IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

10.3 Amendment Distribution and IRB Submission

All modifications to the protocol, consent form, will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

10.4 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the affiliates' IRBs at least once a year for the duration of the study. The annual IRB renewals for the affiliate institution should be emailed promptly to the Regulatory Affairs Administrator. If the institution's IRB requires a new version of the consent form with the annual renewal the consent form should be included with the renewal letter.

10.5 Departure from the Protocol

An investigator cannot modify the protocol without satisfying procedures in this protocol as outlined in the study calendar. Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the study subject, must be reviewed and approved by the local IRB. When a variation from the protocol is deemed necessary for an individual subject, the Lead Principal Investigator must be contacted. Such contact must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study.

The Lead Principal Investigator must be informed of all intentional or unintentional departures from the protocol and will decide whether or not the subject is to continue in the study. All departures from the protocol, intentional and unintentional, along with the decision of the principal investigator will be submitted to the local and University of Chicago IRB per institutional guidelines.

10.6 Registration

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed above. Eligible patients will be entered on study centrally by the University of Chicago study coordinator. All sites should call the study coordinator at (773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

When a potential patient has been identified, notify the CRA via phone or email to ensure a reservation on the study ((773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu). Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.

- Once a patient has been deemed eligible, the CRA will notify the pharmacist via email that the patient should be randomized, and will provide the pharmacist the patient ID number, initials, and stratum information.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.

The date the patient is randomized will be considered the patient's "OnStudy Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

10.7 Reporting of Adverse Events to the Coordinating Center

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined above) and all adverse events that have been specified as Events of Special Interest occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, the University of Chicago CRA and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form or MedWatch 3500A Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-1746
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

Any serious adverse event, or follow up to a serious adverse event, whether or not related to Merck product, must be reported within 2 working days of coordinating site awareness to Merck Global Safety. The coordinating site, the University of Chicago, will take responsibility for reporting the SAE to Merck. Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

An unexpected adverse event is are those not listed at the observed specificity or severity in the protocol, informed consent or IB. An unexpected adverse event is considered to be an unexpected adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report

using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

10.8 Reporting of Adverse Events by the Coordinating Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

10.9 Data Management

Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago CRA will provide you with the applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, you may be required to provide supporting source documentation. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject

enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

10.10 Data and Safety Monitoring

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of

the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures

10.11 Auditing

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan. For institutions who are formal members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

10.12 Record Retention

Study documentation includes all CRFs, 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 patient 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.

10.13 Obligations of Study Site Investigators

The Study Site 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 and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she 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.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

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

11.3 RECIST 1.1 reference

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

* As published in the European Journal of Cancer:

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

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Journal for ImmunoTherapy of Cancer 2015, 3(Suppl 2):O7

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