VANDERBILT UNIVERSITY
MEDICAL CENTER

A single arm trial of adjuvant pembrolizumab in patients with limited stage small cell lung cancer

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1.0 TRIAL SUMMARY

Abbreviated Title	Adjuvant pembro LS-SCLC
Trial Phase	II
Clinical Indication	Patients with limited stage (stage I-III) small cell lung cancer (LS-SCLC) without progression after definitive intent surgical resection or concurrent chemoradiation
Trial Type	Single arm
Type of control	Historical
Route of administration	Intravenous pembrolizumab every three weeks for one year
Treatment Groups	One – receipt of adjuvant pembrolizumab for one year
Number of trial participants	20
Estimated enrollment period	Two years
Estimated duration of trial	Four years
Duration of Participation	Four years
Estimated average length of treatment per patient	One year

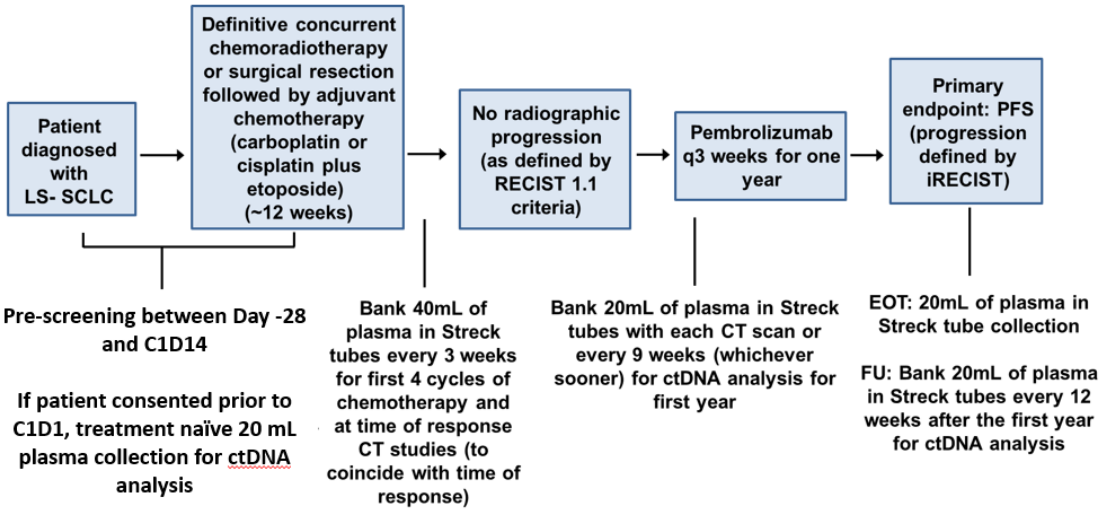
2.0 TRIAL DESIGN

2.1 Trial Design

This is a single arm, phase II trial evaluating adjuvant pembrolizumab for one year following definitive intent concurrent chemoradiation or surgery and adjuvant chemotherapy among patients with limited stage small cell lung cancer (LS-SCLC). The target accrual is 20 patients at a single center. Imaging will be performed per standard of care, with staging PET and brain MRI at diagnosis, followed by brain MRI and chest CT upon definitive therapy completion, and surveillance chest CT every 3 months during pembrolizumab therapy. Tumor samples (if available) and plasma will be banked and analyzed retrospectively in conjunction with Natera. The primary endpoint is progression free survival (PFS), and secondary endpoints include safety and overall survival (OS).

The translational research study design is integrated into the full study schema as below regarding timepoints and amounts of specimen collection.

2.2 Trial Schema



2.3 Schedule of Assessments

Protocol Activities *1 Cycle = 3 weeks (21 days)*	Screening (Day -28 to Day 14)	CYCLE 1		CYCLES 2-4		CYCLES 5-21	Post-Treatment	
		Day 1	Days 2 & 3	Day 1 (± 7d)	Days 2 & 3	Day 1 (± 7d)	EOT (≤14d after decision to end treatment) [f]	Long Term Follow-Up (28d +7d after last study dose) [g]
Clinical Assessments								
Consent, Baseline Characteristics & Eligibility	X							
Physical and Dermatologic Exam	X	X		X		X	X	X
ECOG Performance Status	X							
Height & Weight	X							
Vital Signs	X	X		X		X	X	X
Review of Con Meds & Adverse Events	X	X		X		X	X	X
Laboratory Assessments								
CBC with Differential	X			X		X	X	X
Serum Chemistry (including LFTs, bilirubin) [a]	X			X		X	X	X
INR or PT; aPTT	X							
TSH, T3, free T4	X					X [c]	X	
Pregnancy Test [b]	X	X [b]		X		X		
Urinalysis (with microscopy)	X			X		X	X	X
Troponin and BNP	X							
Viral Testing: HBV, HCV, HIV	X							
12-lead ECG	X							
Disease Assessments								
CT Chest						X [d]		
PET Scan	X							
MRI Brain	X					X [e]		
Survival Follow-up[h]								X [h]
Biospecimen Collection								
Blood Collection[i]	X	X		X		X	X	X
Archival Tumor Tissue	X							
Treatment								
Cisplatin or Carboplatin		X		X				
Etoposide		X	X	X	X			
Pembrolizumab						X		

Study Calendar Notes:

(a) Direct bilirubin required if total bilirubin is elevated above the ULN.
(b) For WOCBP- if a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy test on c1d1 required only if pregnancy test during screening done >72 hours prior to initiation of first dose of study-indicated treatment. Pregnancy testing monthly or as clinically indicated.
(c) TSH, T3, free T4 every 2 cycles during Cycles 5-21 (i.e. Day 1 of Cycles 5, 7, 9, etc).
(d) CT Chest every 12 weeks. The first on-study imaging assessment should be performed ≤ 14 days prior to the start of the first dose of study-indicated pembrolizumab. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) after the first dose of study-indicated pembrolizumab or more frequently if clinically indicated.
(e) MRI Brain during Cycles 5-21 per standard of care – specifically, upon definitive therapy completion and if symptoms suggestive of possible central nervous system metastasis.
(f) EOT Visit: Participants required to return to clinic approximately 14 days after the last dose of study intervention for poststudy visit. If poststudy visit occurs <14d after last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.
(g) Mandatory Safety Follow-Up Visit should be conducted approximately 30 days (acceptable window 28 to 35 days) after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first. See additional detail in Section 6.1.6, including information about efficacy follow-up for participants who complete protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression.
(h) Participant survival follow-up status assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, end of the study, or for up to a maximum of 2 years after patient's final dose of pembrolizumab received in the study, whichever occurs first.
(i) Biospecimen blood collection occurs prior to therapy initiation, every 3 weeks while on concurrent chemoradiation, every 9 weeks during the first year of surveillance (Pembrolizumab), and every 12 weeks thereafter during Follow Up after first year of adjuvant Pembrolizumab for a maximum of 2 years.

3.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

3.1 Primary Objective(s), Hypothesis(es), and Endpoint(s)

Primary Objective: Our primary clinical objective is to investigate progression free survival per RECIST 1.1 as assessed by the investigator in patients with limited stage small cell lung cancer treated with adjuvant pembrolizumab.

Hypothesis: We hypothesize that adjuvant pembrolizumab will prolong progression free survival in patients with limited stage SCLC compared to standard of care observation.

Primary Endpoint: Progression free survival

Secondary Objectives:

A) Assess median overall survival compared to the historical control dataset (CONVERT trial[1]) median OS of 30 months.

B) Assess the safety and tolerability of adjuvant pembrolizumab in patients with limited stage SCLC.

Hypothesis: We hypothesize that adjuvant pembrolizumab will prolong overall survival in patients with limited stage SCLC compared to standard of care observation, and that it will be safe and tolerable.

Secondary Endpoints:

A) Overall survival

B) Adverse events, dose interruptions, drug discontinuations, adverse events of special interest

3.2 Exploratory/Translational Objective(s)

Objective: Our primary translational objective is to determine whether patients with detectable ctDNA after curative intent therapy ("MRD positive") experience shorter median PFS compared to patients without detectable ctDNA after curative intent therapy ("MRD negative."). We hypothesize that patients with LS-SCLC with detectable ctDNA after induction chemoradiation or surgical resection followed by adjuvant chemotherapy represent the cohort of patients most likely to benefit from adjuvant ICI[2]. We hypothesize that clearance of ctDNA with pembrolizumab represents tumor response, and non-clearance of ctDNA represents tumor resistance to pembrolizumab. Our secondary translational objective includes determination of whether patients with ctDNA clearance at any point during curative intent therapy have superior median PFS compared to patients who do not experience ctDNA clearance during curative intent therapy.

4.0 BACKGROUND & RATIONALE

4.1 Background

Limited stage small cell lung cancer (LS-SCLC) is treated with concurrent chemoradiation followed by observation, with recurrence rates of 70%, median progression free survival (PFS) of 10-15 months, and median OS of 25-30 months[1].

Patients with stage III non-small cell lung cancer had similar outcomes to patients with LS-SCLC until the introduction of adjuvant checkpoint inhibitors instead of observation alone following concurrent chemoradiation (PMID 28885881).

Reduction of recurrence after concurrent chemoradiation in patients with LS-SCLC is a large, unmet clinical need. Pembrolizumab has been demonstrated to be safe when administered concurrently with chemoradiation to patients with LS-SCLC[5].

We propose a single arm, prospective trial evaluating adjuvant pembrolizumab use in patients with LS-SCLC after completion of concurrent chemoradiation or definitive surgical resection followed by adjuvant chemotherapy with a primary endpoint of progression free survival.

We initially propose q3 week dosing of pembrolizumab, though the study concept is amenable to a q6 week dosing regimen.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure (IB).

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in limited stage small cell lung cancer.

4.1.2 **Preclinical and Clinical Trial Data**

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Limited stage small cell lung cancer (LS-SCLC) is treated with concurrent chemoradiation or surgical resection followed by adjuvant platinum and etoposide for four cycles followed by observation, with recurrence rates of 70% and median OS of 25-30 months[1].

Reduction of recurrence after concurrent chemoradiation in patients with LS-SCLC is a large, unmet clinical need Pembrolizumab has been demonstrated to be safe when administered concurrently with chemoradiation to patients with LS-SCLC[5].

We propose a single arm, prospective trial evaluating adjuvant pembrolizumab use in patients with LS-SCLC after completion of concurrent chemoradiation or definitive surgical resection followed by adjuvant chemotherapy with a primary endpoint of progression free survival.

4.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose

of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

We have selected median PFS as our primary endpoint as this is the first measurable and reliable demonstration of failure of curative intent therapy and has significant clinical implications. From historical controls, we know that the median PFS in this patient population has been approximately 15 months. As secondary endpoints, we will also collect information on OS and adverse events.

5.0 STUDY POPULATION

5.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Has LS-SCLC (Stage I-III, by AJCC 8th Edition Cancer Staging) and no evidence of extensive stage disease. Participants may enroll at any time between diagnosis and surgery (if undergoing operative management) or day -28 and C1D14 of definitive chemotherapy and radiation . Correlative analyses collected during standard of care definitive concurrent chemoradiation or surgery followed by adjuvant chemotherapy are mandatory (C1D1 blood collection is optional if enrollment occurs after C1D1 of chemotherapy).

2. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of small cell lung cancer or high grade neuroendocrine carcinoma will be enrolled in this study.
    - *Contraception requirements should conform with CTFG guidelines. The pembrolizumab standard for use of highly effective contraceptive methods for POCBP is 120 days (5*

half-lives) after the last dose. Please either list the contraception requirement for each compound in the study OR use the longest timeframe that covers requirements for ALL compounds in the study. Please reference Appendix 3.

- *Similarly, Company standard for abstaining from breastfeeding after study intervention is at least 5 half-lives. For pembrolizumab, this is 120 days.*

3. No definitive radiological imaging evidence of disease progression after completion of definitive concurrent chemoradiation or surgery followed by adjuvant chemotherapy.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

6. Participants who are HBsAg positive are eligible if they have received HBV anti-viral therapy for at least 4 weeks, and have undetectable HBV viral load prior to randomization.

   Note: Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

   Hepatitis B screening tests are not required unless:
   - Known history of HBV infection
   - As mandated by local health authority

7. Participants with a history of HCV infection are eligible if HCV viral load is undetectable at screening.

   Hepatitis C screening tests are not required unless:
   - Known history of HCV infection
   - As mandated by local health authority

   Note: Participants must have completed curative anti-viral therapy at least 4 weeks prior to randomization.

8. HIV-infected participants must have well-controlled HIV on ART, defined as:
   a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening
   b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening

c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months.
d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

9. Have adequate organ function as defined in the following (Table 1). Specimens must be collected within 10 days prior to the start of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

5.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

2. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to allocation.

3. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities requiring corticosteroids, and not have had radiation pneumonitis. The last radiotherapy treatment must have been performed at least 7 days before the first dose of study drug.

4. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

5. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of pembrolizumab.

7. Has a known additional malignancy that is progressing or requires active treatment. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, localized prostate adenocarcinoma, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) untreated in active surveillance with stable disease are not excluded.

8. Has known active CNS metastases and/or carcinomatous meningitis.

9. Has severe hypersensitivity (≥Grade 3) to pembrolizumab.

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 and is allowed.

11. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

12. Has an active infection requiring systemic therapy.

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

14. Has had an allogenic tissue/solid organ transplant.

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

17. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Coordinating Center and Merck as described in Section 5.3 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 Coordinating Center (which will subsequently inform Merck). If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Coordinating Center (which will subsequently inform Merck) and followed as described in Section 9.7.

6.0 ENROLLMENT PROCEDURES

The Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center will coordinate enrollment in the study. Eligible participants will be entered on study centrally at the VICC Coordinating Center. Clinic staff should email the Coordinating Center at Coordinating.Center@vumc.org to obtain subject ID number.

All patients MUST be registered with the VICC Coordinating Center prior to the start of study procedures such as tissue acquisition. Registration can only be conducted during the business hours of 8AM – 5PM Central Time, Monday through Friday.

1) Email the VICC CTSR Coordinating Center at Coordinating.Center@vumc.org to notify of upcoming registration and ensure slot availability. The following information should be included in this email:
    1. Patient initials
    2. Anticipated consent date
    3. Anticipated start date
2) If a subject ID number is required prior to patient enrollment (i.e. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Coordinating Center:
    - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
    - VICC Patient Enrollment Form.

    The Coordinating Center will then provide a subject ID number via email.
3) Upon completion of all screening procedures, email the following documents to the Eligibility Office (viccctsrregistrar@vumc.org) for eligibility review and the Coordinating Center (Coordinating.Center@vumc.org) for patient enrollment:
    - Patient's signed and dated main consent, including documentation of the consent process.
    - VICC Patient Enrollment Form
    - Signed and completed Eligibility Checklist. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.

Note: The Eligibility office requires 2 business days to review all documents and confirm eligibility. Registrations will only be accepted with prior notice and discussion with the Lead Institution. Please

email the CTO Eligibility Office if enrollment is needed sooner at viccctsrregistraroffice@vumc.org and coordinating.center@vumc.org.

Upon satisfactory review of eligibility documents submitted, the Eligibility Office will approve enrollment and the Coordinating Center will issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from the Eligibility and Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin the study consistent with the protocol no later than 28 days after registration/enrollment by the VICC Coordinating Center. If a participant does not begin the study following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact will be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Coordinating Center will require a new, signed Informed Consent document.

Issues that would cause treatment delays should be discussed with the sponsor-investigator.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

7.0 TRIAL INTERVENTION(S)

The intervention(s) to be used in this trial is outlined below in **Table 2**

Table 2 Trial Intervention(s)

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle for 1 yr	Investigational

Trial intervention(s) should begin as close as possible to the date on which study eligibility is confirmed by the Coordinating Center.

7.1 Timing of Dose Administration

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Activities, Section 2.3. Trial interventions may be

administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial interventions will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks over the course of one year. 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 and/or product label contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

7.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs deemed by the investigator as possibly, probably or definitely related to pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	· Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper · Add prophylactic antibiotics for opportunistic infections	· Monitor participants for signs and symptoms of pneumonitis · Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	· Administer corticosteroids (initial dose of 1 to 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	· Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	· Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence	Withhold [d]	· Initiate insulin replacement therapy for participants with T1DM · Administer antihyperglycem	· Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	of beta-cell failure		ic in participants with hyperglycemia	
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 [d]		
Hyperthyroidism	Grade 2	Continue	· Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	· Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2,	Continue	· Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care · Monitor for signs and symptoms of thyroid disorders	
	Grade 3 or 4	Withhold until clinically stable or permanently discontinue[d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	· Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	· Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	or Grade 4			

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids	No subsequent dosing

medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, pembrolizumab is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

7.3 Randomization or Treatment Allocation

This is a single arm study, no randomization will occur.

7.4 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 or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

7.4.1 Acceptable Concomitant Medications

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

concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered within 28 days after the last dose of trial intervention are to be recorded as defined in Section 5.3.

7.4.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy to a symptomatic solitary lesion or to the brain may be permitted based upon principal investigator review.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - For the prevention of emesis
    - To premedicate for IV contrast allergies
    - To treat asthmas or COPD exacerbations
    - For chronic systemic replacement not to exceed 10mg/day prednisone equivalent.

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

7.4.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, Table

3. Where appropriate, these guidelines include the use of oral or IV 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 in Table 3 are intended to be applied when the Investigator determines the events to be possibly, probably or definitely related to pembrolizumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

7.5 Participant Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 2.3 unless the participant has withdrawn from the study (Section 5.7).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor
- Radiographic disease progression outlined in Section 6.1.4.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.2.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test

Completion of pembrolizumab Q3W monotherapy consists of 17 treatments (approximately 1 year).

The number of treatments is calculated starting with the first dose of pembrolizumab.

Participant Withdrawal From Study

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.1.6.1.

7.5.1 Participant withdrawal From Study

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.1.6.1.

7.5.2 Clinical Criteria for Early Trial Termination

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

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

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

7.5.3 Duration of Follow-up

Participant survival follow-up status assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, end of the study, or for up to a maximum of 2 years after patient's final dose of pembrolizumab received in the study, whichever occurs first.

In general, it is intended that patients will be treated until disease progression or intolerable toxicity for a maximum of 2 years. Criteria for patient discontinuation include those listed in Section 7.5. Patients should at least be assessed within 30 days after patient's final protocol-indicated treatment.

Contact can be made via clinic visit, chart review, obituary or similar observation (e.g., Social Security death index), or by telephone.

8.0 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Trial Procedures

- Study procedures and their timing are summarized in The Schedule of Activities, Section 2.3.
- Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria
- Additional evaluations/testing may be deemed necessary by the investigator, the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.2 Administrative and General Procedures

- Informed Consent

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial. If there are changes to a participant's status during the study (e.g. health requirements) the investigator must ensure appropriate consent is in place.

- General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may reasonably be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

- Inclusion/Exclusion Criteria

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

- 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 at least the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study may be recorded separately and not listed as medical history.

- Prior and Concomitant Medications Review

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 participant within 28 days before participant's first dose of treatment in the trial. Treatment for the disease for which the participant has enrolled in this study may be recorded separately and not listed as a prior medication.

Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 5.3.

- Disease Details and Treatments

Disease Details

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

Prior Treatment Details

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

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 participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

- Clinical Procedures/Assessments

Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Schedule of Activities 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 5.0 (see Appendix 5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 5.3 for detailed information regarding the assessment and recording of AEs.

- Physical Exam

The investigator or qualified designee will perform a physical exam during the screening period and additional time points as indicated in the Schedule of Activities Section 2.3. Clinically significant abnormal findings should be recorded as medical history. After the first dose of pembrolizumab, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Vital Signs

The investigator or qualified designee will take vital signs at time points as indicated in Section 2.3 specified in the Schedule of Activities (Section 2.3). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

- Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at Screening as specified in the Schedule of Activities (Section 2.3).

- Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at screening using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals.

- Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Assessment for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Assessment.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF.

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 21 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

- Laboratory Safety Evaluations (Hematology and Chemistry)

Laboratory tests for hematology and chemistry are specified in Appendix 2.

- Pregnancy Testing

It is recommended to for pregnancy testing prior to each cycle (max 72 hour window; 24-hour window preferred).

The length of time required to continue pregnancy testing for each study intervention is:

- Carboplatin 180 days
- Cisplatin 180 days
- Etoposide 180 days
- Pembrolizumab 120 days
- Optional Tumor Tissue Collection and Correlative Studies Blood Sampling

When available, archival or fresh tumor tissue will be banked for further analysis. We will collect correlative blood samples prior to therapy initiation, every 3 weeks while on concurrent chemoradiation, every 9 weeks during the first year of surveillance, and every 12 weeks thereafter. We will collaborate with Natera, Inc to analyze tumor and correlative blood samples to better define minimal residual disease (MRD) in this patient population.

8.3 Tumor Imaging

8.3.1 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Brain imaging is required for all participants at screening. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

8.3.1.1 **Initial Tumor Imaging**

Initial tumor imaging at Screening (i.e. PET scan and MRI brain) must be performed within 28 days prior to the date of first dose of systemic chemotherapy (i.e. cisplatin, carboplatin or etoposide).

8.3.1.2 **Tumor Imaging During the Study**

The first on-study imaging assessment should be performed ≤ 14 days prior to the start of the first dose of study-indicated pembrolizumab. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) after the first dose of study-indicated pembrolizumab or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 12 (84 days ±7 days) weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

8.3.1.3 **End of Treatment and Follow-up Tumor Imaging**

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the investigator elects not to implement iRECIST, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by standard of care tumor imaging using the same imaging schedule used while on treatment (every 12 weeks for up to 1 year after last dose of pembrolizumab) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.3.2 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2

per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Table 5 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm disease progression	May continue study treatment at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
First radiologic evidence of disease progression by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm disease progression.	May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment

8.4 Discontinuation and withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 5.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 5.3.

8.5 Blinding/Unblinding

No blinding is involved in this open-label study.

8.6 Visit Requirements

Visit requirements are outlined in Section 2.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

8.6.1 Post-Treatment Visits

8.6.1.1 **Safety Follow-Up Visit**

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (acceptable window 28 to 35 days) after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first.

8.6.1.2 **Efficacy Follow-up Visits**

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by standard of care radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study, or 2 years after final dose of pembrolizumab received in the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

8.6.1.3 **Survival Follow-up Contacts**

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, end of the study, or for up to a maximum of 2 years after patient's final dose of pembrolizumab received in the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase (see immediately above section), the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.6.1.4 **End of Treatment (EOT) Visit**

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

9.0 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES), AND OTHER REPORTABLE SAFETY EVENTS

9.1 Adverse Event definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

NOTE: For purposes of AE definition, study intervention (also referred to as Merck product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by Merck for human use in this study.

9.1.1 Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

9.1.2 Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

9.2 Definition of Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect; or
- Jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

9.3 Expectedness

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

9.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.

- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

9.5 Additional Events Reported in the Same Manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Coordinating Center and Merck in the same time frame as SAEs to meet certain local requirements. Therefore, these events are also considered serious for collection and reporting purposes in this study (see also Section 5.3):

- New cancer (that is not a condition of the study), or
- Associated with an overdose of pembrolizumab.
- 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.

9.6 Recording AE and SAE

9.6.1 AE and SAE recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

There may be instances when copies of medical records for certain cases are requested by the Coordinating Center and/or Merck. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Coordinating Center and Merck.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

9.6.2 Assessment of intensity/toxicity

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following: <https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf>.

Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

9.6.3 Assessment of causality

1. Did pembrolizumab cause the AE?

2. The determination of the likelihood that pembrolizumab caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

3. The following components are to be used to assess the relationship between pembrolizumab and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab caused the AE:

   Exposure: Is there evidence that the participant was actually exposed to pembrolizumab 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 pembrolizumab? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies 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.

Dechallenge: Was pembrolizumab 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 pembrolizumab; (3) the study is a single-dose drug study; or (4) pembrolizumab is only used 1 time.)

Rechallenge: Was the participant re-exposed to pembrolizumab 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 study is a single-dose drug study; or (3) pembrolizumab is used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF RE-EXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

4. Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding pembrolizumab or drug class pharmacology or toxicology?

5. The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of pembrolizumab relationship).

Yes, there is a reasonable possibility of pembrolizumab relationship:

There is evidence of exposure to pembrolizumab. The temporal sequence of the AE onset relative to the administration of pembrolizumab is reasonable. The AE is more likely explained by pembrolizumab than by another cause.

No, there is not a reasonable possibility of pembrolizumab relationship:

Participant did not receive pembrolizumab OR temporal sequence of the AE onset relative to administration of pembrolizumab is not reasonable OR the AE is more likely explained by another cause than pembrolizumab. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Coordinating Center. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Coordinating Center.

9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

9.6.4 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the CRF.

The investigator will submit any updated SAE data to the Coordinating Center (which will subsequently report to Merck) within 2 business days but no longer than 3 calendar days of receipt of the information.

9.7 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Coordinating Center and Merck

General Considerations

All adverse events will be captured on a centralized electronic case report form. Specified members at each participating site will submit all regulatory documents to the sponsor.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF and not reported as an SAE.

A pre-existing medical condition is one that is present prior to initiation of protocol specified treatment. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

9.7.1 Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed or scanned to:

ATTN: VICC CTSR Personnel

EMAIL: Coordinating.Center@vumc.org

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study device/medication. The Coordinating Center will be responsible for reporting of events to supporters, as appropriate (outlined below).

9.7.2 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

9.7.3 Food and Drug Administration (FDA)

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to study treatment (as determined by the sponsor-investigator) will be reported to the FDA via MedWatch 3500A, currently available at: < https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf >. Submissions by the sponsor can be submitted via fax or electronically (e.g. email) and must be addressed to the Regulatory Project Manager in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

9.7.4 Reporting to Supporters

SAE reports and any other relevant safety information are to be forwarded by the Coordinating Center to Merck. Vanderbilt University Medical Center acting as the Coordinating Center will

notify Merck of any serious adverse event (SAE) that occurs during the reporting period as defined above in Section 5.3. Within 2 business days but no longer than 3 calendar days after the Coordinating Center initially receives the safety information from the site, the Coordinating Center will report the SAE on the Vanderbilt SAE form to a point of contact specified by Merck: **SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229.**

Follow-up SAE reports received by the Coordinating Center should be sent within 2 business days but no longer than 3 calendar days to the funder using the same procedure used for transmitting the initial report.

Additionally, at the time of submission to the FDA within 2 business days but no longer than 3 calendar days after FDA submission, a copy of all IND safety reports (7-Day Reports, 15-Day Reports and Follow-up IND safety reports) and Annual Progress Reports submitted to the FDA by the Coordinating Center regarding this study will be submitted to a point of contact specified by Merck: **SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229.**

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** **Consent to Pembrolizumab initiation**	**Reporting Time Period:** **Pembrolizumab initiation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of receipt of information
Pregnancy/Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of receipt of information

Type of Event	**Reporting Time Period:** **Consent to Pembrolizumab initiation**	**Reporting Time Period:** **Pembrolizumab initiation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
	initial screening is not a reportable event.			
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of receipt of information

9.7.5 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.7.6 Sponsor Responsibility for Reporting Adverse Events

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

9.7.7 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Coordinating Center and Merck.

All reported pregnancies 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.

9.7.8 Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events are also known as Events of Clinical Interest (ECIs) and must be reported to the Coordinating Center and Merck in expedited fashion via the same process as an SAE (see Appendix 5).

Events of clinical interest for this study include:

12. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, 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. In the event of overdose, the participant 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.

13. 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.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 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.

Pembrolizumab will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

10.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements. Please reference investigator brochure and package insert for Pembrolizumab (Keytruda).

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text.

10.4 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. Please reference investigator brochure and package insert for Pembrolizumab (Keytruda).

10.5 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 participants and the amount remaining at the conclusion of the trial.

After receiving written authorization in advance from the sponsor-investigator or designee upon completion or termination of the study or earlier, 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.

11.0 DATA SAFETY AND MONITORING

11.1 Data Management and Reporting

Data will be collected using a centralized electronic case report form called Online Clinical Oncology Research Environment (Oncore). Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. The system is capable of storing basic protocol information (e.g., IRB approval dates, dates for annual renewals) and clinical trial research data. Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. Oncore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. Oncore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as

SPSS). This system will be used to manage VICC clinical trials data. Oncore is maintained and supported in the VICC Clinical and Research Informatics Resource.

11.2 Meetings

The Vanderbilt Thoracic team includes medical oncologists, research nurses, data managers, and regulatory specialists. The team meets on a regular basis to discuss AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, etc. pertaining to cancer studies conducted by the team. In addition, teleconferences between the VICC Multi-Institutional Coordinating Center. and the participating institutions will occur in order to discuss relevant issues related to the trial (e.g., AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, and reviews).

11.3 Auditing and Monitoring

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and/or remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

11.4 Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, the site investigator agrees to keep records including: the identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

Queries resulting from review of the eCRFs will be generated for the site and corrections will be made by the study site personnel. This will be done on an ongoing basis.

12.0 REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the sponsor-investigator and the local IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the sponsor-investigator (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the sponsor-investigator (or designee), who will communicate as appropriate with the FDA.

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments and will disseminate this information to the participating centers.

12.2 Informed Consent

The investigator (or designee) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution.

The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The participant should read and consider the statement before signing and dating it and will be given a copy of the document. No patient will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

12.3 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly assisting with the trial.

12.4 Study Termination

The sponsor-investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements;
- Insufficient enrollment;
- Safety concerns;
- Decision by suppliers to modify or discontinue the availability, development or manufacture of protocol-indicated treatment; and
- A request to discontinue the study by the IRB or FDA.

13.0 STUDY COORDINATION

13.1 Trial Compliance

This is an investigator-initiated trial (IIT). The Principal Investigator, Evan Osmundson, MD, PhD. (who may also be referred to as the Sponsor-Investigator), is conducting the study and acting as the sponsor. Therefore, the legal and ethical obligations of the Principal Investigator include both those of a sponsor and those of a principal investigator.

Vanderbilt is the Coordinating Center for this study. All aspects of the study will be carefully monitored by the VICC Multi-Institutional Coordinating Center for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

13.2 Changes to Protocol and Informed Consent Documents

Any change to the protocol or informed consent document must be reviewed and approved by the Coordinating Center before being submitted to the Institutional Review Board/Independent Ethics Committee at participating institutions. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard to study subjects.

13.3 Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

13.4 Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be brought to the attention of the investigator and/or the investigator's staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or the investigator's staff.

13.5 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information inclusive of:

- Source documents (patient registration list, CRF info, toxicity assessments, tumor measurements/responses, etc.) are required to be provided within 30 days of visit or 10 days in advance of a monitoring visit or audit.

- Essential Documents (IRB approval documents, financial disclosure forms, 1572 forms, delegation of authority log, protocol training, etc.) are required to be provided within one week of receiving the updated documents.

Personnel from the VICC Clinical Trials Office will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

13.6 Study Closure

The Coordinating Center reserves the right to discontinue a site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

13.7 Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at such time that the records may be destroyed.

14.0 STATISTICAL CONSIDERSATION

14.1 Statistical Analysis Plan

Among patients with LS-SCLC, the rate of recurrence is 70%, with the most recent data indicating a median time to recurrence of 10 months among patients treated with standard dose radiation (45 Gy) compared to a median time to recurrence of 18 months among patients treated with high dose (60 Gy) thoracic radiation[6]. Therefore, a majority of patients treated with curative intent with LS-SCLC will

experience lethal disease recurrence within 1-1.5 years, and standard clinical practice remains predominant use of the 45 Gy regimen due to poor tolerance of the high dose regimen.

Based on an estimated historical median PFS of 10 months in this patient population, and estimating a median PFS of 22 months in this single arm trial, we have 80% power to detect a statistically significant difference at a two-sided α of 0.05 with a patient population of 20.

14.2 Analysis Plan

Based on a previous publication evaluating ctDNA detection (using a 14 gene, custom NGS panel from Resolution Bioscience) at the completion of concurrent chemoradiation among 21 patients with LS-SCLC, we anticipate approximately 25% of patients will have detectable ctDNA at therapy completion, with an additional 25% of patients demonstrating ctDNA detection prior to radiographic recurrence (Iams et al, *JTO CRR* 2020). Estimating a 50% ctDNA detection rate (based on the increased sensitivity of the Natera Signatera assay compared to the preliminary data assay) at the end of concurrent chemoradiation and using an alpha of 0.05, we will have 80% power to detect a statistically significant difference in ctDNA clearance with 12 patients enrolled (our target enrollment is 20 patients). Furthermore, we have completed a power calculation regarding differences in median PFS between the ctDNA+ and ctDNA- groups:

Power was calculated from a two-sided log-rank test with an overall sample size of 20 subjects (10 in the ctDNA+ group and 10 in the ctDNA- group) and type I error of 0.05. The study lasts for 48 months of which subject accrual (entry) occurs in the first 24 month period.

Median PFS (months) for ctDNA+	Median PFS(months) for ctDNA-	Power(%)
6	18	60
6	24	76
6	30	85
6	36	90

In order to evaluate whether the presence of ctDNA (at a variant allele frequency of 0.1% or greater) is prognostic before, during concurrent chemoradiation, or at first sample collection after completion of definitive chemoradiation (within 12 weeks of treatment completion), we will use the Kaplan-Meier method with a Log-rank test to compare median progression free survival (PFS; defined as the time from the first treatment start date to the date of radiographic relapse, last follow-up without progression, or death) and median OS between patients with no ctDNA detected in the treatment-naïve setting, during the any cycle of concurrent chemoradiation, immediately upon completion of concurrent chemoradiation, at initiation of pembrolizumab, and at all time points, including therapy completion, with pembrolizumab, and patients with any ctDNA detected in the treatment-naïve setting, during the any cycle of concurrent chemoradiation, immediately upon completion of concurrent chemoradiation, at initiation of pembrolizumab, and at all time points, including therapy completion, with pembrolizumab. Estimated hazard ratios and 95% confidence intervals will be used to measure the effect of the association between ctDNA clearance with PFS and OS. All statistical inferences will be assessed

at a two-sided 5% significance level, and all summary statistics, graphics, and survival models will be generated using R version 3.6 statistical software.

We plan to use the Natera Signatera assay, which follows patient specific genomic variants throughout their treatment course**.** This breadth of analysis will provide hypothesis generating information regarding mechanisms of chemoresistance and immunotherapy resistance among patients with LS-SCLC who demonstrate treatment refractory disease or experience disease recurrence.

14.3 Efficacy Endpoints and Planned Analyses

The efficacy endpoints will include progression-free (PFS) and overall survival (OS).

- Progression-free survival (PFS) is defined as the time from the date of first treatment to PD or death due to any cause, whichever occurs first. Patients not experiencing PD or not dying at the time of the data cut or the database lock will have their event times censored at the date of last adequate disease assessment. For patients who receive new anticancer therapies, the PFS will be measured from the date of first treatment to the date of last disease assessment prior to the start of new anticancer therapies.
- Overall survival (OS) is defined as the time from the date of first treatment to the date of death due to any cause. Patients who do not die by the time of data cut or the database lock will have their event times censored on the last date of their known survival status.

PFS and OS will be estimated using the method of Kaplan and Meier (product limit estimator). Logistic and Cox (proportional hazards) regression will be used to assess the association between important prognostic variables (e.g, gender, age) with PFS and OS, respectively. The odds ratio (OR) for response and hazard ratio (HR) for PFS and OS will be presented with 95% confidence intervals as measure of effect size.

14.4 Data Collection Responsibilities

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator as well as the VUMC Clinical Research Office.

<u>Protocol Chair</u>

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites.

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submission of AEs and SAEs to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

15.0 REFERENCES

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16.0 APPENDICES

Appendix 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.	

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
%Reticulocytes</td><td>WBC count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Chemistry</td><td>BUN</td><td>Potassium</td><td>AST/SGOT</td><td rowspan="2">Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)</td></tr>
<tr><td>Albumin</td><td>Bicarbonate</td><td>Chloride</td></tr>
<tr><td>Creatinine
Glucose</td><td>Sodium
Calcium</td><td>ALT/SGPT
Alkaline phosphatase</td><td>Total Protein</td></tr>
<tr><td>Pregnancy Testing</td><td colspan="4">• Serum or urine hCG pregnancy test (as needed for WOCBP)</td></tr>
<tr><td>Other Screening and On-Study Tests</td><td colspan="4">• Urinalysis (with microscopy)
• FSH (as needed in WONCBP only)
• INR or PT
• aPTT
• TSH
• T3
• Free T4
• Troponin
• BNP
• Viral testing: HBV, HCV, HIV</td></tr>
<tr><td colspan="5">ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential; INR=international normalized ratio; PT= prothrombin time; aPTT=activated partial thromboplastin time; TSH= thyroid stimulating hormone; T3= triiodothyronine; T4=thyroxine; BNP=B-type natriuretic peptide.</td></tr>
</table>

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile–vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 9 during the protocol-defined time frame in Section 5.1. Contraception requirements should conform with CTFG guidelines. The pembrolizumab standard for use of highly effective contraceptive methods for POCBP is 120 days (5 half-lives) after the last dose.

Table 9 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [a, b] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Additional References

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