COLUMBIA UNIVERSITY MEDICAL CENTER

Herbert Irving Comprehensive Cancer Center Protocol

Identifying genetic predictors of durable clinical benefit to pembrolizumab in advanced non-small cell lung cancer alone and in combination with chemotherapy

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A Cancer Center Designated by the National Cancer Institute

CUMC IRB#: AAAQ5450
Merck Study Identifier #: MISP_52575

TITLE: Identifying genetic predictors of durable clinical benefit to pembrolizumab in advanced non-small cell lung cancer alone and in combination with chemotherapy.

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Study Agent:	(Pembrolizumab) MK-3475
Other Agent:	Carboplatin, *nab*-paclitaxel (Abraxane), pemetrexed
IND Status:	IND #######

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Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (Print)

_____

Name of Institution

Protocol Synopsis

TITLE: Identifying genetic predictors of durable clinical benefit to pembrolizumab in advanced : non-small cell lung cancer alone and in combination with chemotherapy.
PROTOCOL #: AAAQ5450
Merck Study Identifier #: MISP_52575.
Phase II
METHODOLOGY: This will be a 3-arm, multi-center, open-label, non-randomized biomarker trial of pembrolizumab in patients with treatment-naïve, advanced NSCLC.
STUDY DURATION: 2 years
STUDY CENTERS: Columbia, Fox Chase Cancer Center, Perlmutter Cancer Center at NYU Langone
The primary objective is to determine if mutation load underlies sensitivity to pembrolizumab alone and in combination with chemotherapy.
OF SUBJECTS: NSCLC (n=90, 30 per cohort)
SCHEMA: Patients eligible will include EGFR and ALK wild type, chemotherapy-naïve, advanced NSCLC. Patients will receive 1 of 3 arms of treatment per investigator's choice: Cohort 1: single agent pembrolizumab 200 mg IV will be administered every 3 weeks for up to 2 years. Cohort 2: pembrolizumab 200 mg IV every 3 weeks for up to 2 years with 2 cycles of nab-paclitaxel and carboplatin administered with cycles 1 and 2 Cohort 3 (non-squamous histology): pembrolizumab 200 mg IV every 3 weeks for up to 2 years with 2 cycles of pemetrexed and carboplatin administered with cycles 1 and 2 Archived tumor material obtained by core biopsy or equivalent is required for entry; repeat baseline biopsy will be performed if sufficient archived tumor is not available. All cohorts will have tumor biopsy performed at ~C2D8. Baseline blood and serial PBMCs, serum and plasma for future research will be collected.
KEY ELIGIBILITY CRITERIA • Treatment naïve EGFR and ALK wild type advanced non-small cell lung cancer (NSCLC). • Core tumor biopsy, excisional biopsy or resection of tumor at baseline is required if sufficient archival tumor material is not available (equivalent to 2 core biopsies or greater). If insufficient archived tumor is available, new baseline tumor biopsy is required. • Mandatory biopsy at C2D8 (+/- 7 days) is also required. • Stereotactic brain radiation therapy to isolated brain metastases is allowed (without washout) • Subjects with brain metastases previously treated by whole brain radiation therapy may participate provided they are clinically stable and are not using steroids for at least 7 days prior to trial treatment. Patients with active central nervous system (CNS) metastases and/or carcinomatous meningitis are excluded.
STUDY DRUG: Pembrolizumab, nab-paclitaxel, pemetrexed, carboplatin

DURATION OF ADMINISTRATION: Up to 2 years
STATISTICAL METHODOLOGY: Per section 15

1. INTRODUCTION

Lung cancer is the most common cancer and leading cause of cancer related death worldwide, accounting for more than 1.6 million cases and 1.3 million deaths annually [1]. For patients with advanced stage non-small cell lung cancer (NSCLC), the most common form of lung cancer in the United States, cytotoxic chemotherapy improves outcomes [2, 3] but durable disease control is disappointingly rare – fewer than 5% of patients are alive 5 years later and median survival is ~10 months [4, 5]. Histology-specific chemotherapy [6], maintenance chemotherapy [7-11], the addition of bevacizumab [12], and the identification of targetable driver oncogenes [13-18] have all improved outcomes, but there remains an urgent need for better treatment strategies for the majority of patients with advanced NSCLCs.

T-cell checkpoint inhibitors, particularly those targeting programmed cell death-1 (PD-1), have recently demonstrated promising activity in NSCLC. PD-1 is an inhibitory signaling receptor expressed on the surface of T cells and negatively regulates T-cell activation [19]. Immune checkpoint inhibitors such as anti-PD-1 antibodies block the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in activation of T cell mediated immune responses against tumor cells. This T cell response can be exhausted during cancer progression; its restoration with immune checkpoint inhibitor antibodies can lead to dramatic and durable anti-tumor responses [20] [21]. The activity of immune checkpoint inhibitors has been well established in melanoma [22, 23] however the unexpected activity observed with anti-PD-1 antibodies (anti-PD-1) in non-small cell lung cancer (NSCLC) [24] has led to new hope for NSCLC. Pembrolizumab, nivolumab and atezolizumab are now FDA approved in the 2nd line setting after platinum based therapy for the treatment of NSCLC. Pembrolizumab is also now approved in the first line setting in PD-L1 positive NSCLC based on Keynote 24. Nevertheless, further understanding of response and resistance mechanisms of NSCLC is needed; the landmark progression free survival at 6 months and 12 months in this enriched subset of NSCLC from Keynote 24 was still only 62% and ~ 48%, respectively.

Further research efforts in the 1st line setting for NSCLC have explored chemotherapy combinations. In a phase 2 randomized trial, patients with chemotherapy-naïve NSCLC (unselected for PD-L1 expression) were randomized to 4 cycles of pembrolizumab plus carboplatin and pemetrexed every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy, or to 4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy [25]. The response rate was 55% vs. 29% and the PFS was 13 months vs. 9 months favoring the pembrolizumab arm. These data represent proof of concept of potential synergy between chemotherapy and immune checkpoint blockade.

However, little is known regarding the intersection of tumor genetics and response to combination chemotherapy and immunotherapy and less is known about the biologic effects of chemotherapy on the tumor microenvironment. We hypothesize the subset of NSCLC

patients that may be most apt to benefit from immune checkpoint blockade and chemotherapy are those with high mutational load. We do know that the response rate is higher in patients that are PD-L1 positive versus negative with chemotherapy and immunotherapy suggesting a relationship between the immunogenicity of a tumor and response to combination chemotherapy and immunotherapy.

In summary with the multiple therapies potentially being FDA approved in the first line setting it is challenging to determine what is the best treatment option based on simply PD-L1 expression. This biomarker trial exploring single agent pembrolizumab and 2 chemotherapy regimens will explore this relationship between genetics and response. We postulate the response to immune checkpoint blockade in highly mutated NSCLC can be induced by a short course of chemotherapy by increasing tumor antigenicity, inducing immunogenic cell death, MHC upregulation and reducing tumor-associated macrophages, regulatory T-cells and myeloid derived suppressor cells.

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

2. STUDY OBJECTIVES

Primary objectives:

- We will determine if mutation load can predict durable clinical benefit (stable disease, partial response or complete response $\geq$ 6 months) with pembrolizumab alone or in combination with 2 cycles of chemotherapy in patients with chemotherapy-naïve, advanced NSCLC.

Secondary objective

- If we identify an optimal threshold of mutation load that predicts durable clinical benefit to pembrolizumab, we will determine whether the addition of an abbreviated course of chemotherapy can improve responses at a similar or lower mutation threshold.

Exploratory Objectives

- We will characterize the genetic and immune microenvironment pre- and post-treatment after 2 cycles of pembrolizumab as single agent or in combination with chemotherapy.

- We will determine if neoantigen-specific T-cells can be detected in peripheral blood after treatment with pembrolizumab as single agent or in combination with chemotherapy

3. BACKGROUND

3.1 Mutational landscape and response to immune checkpoint blockade

Somatic mutations leading to cancer are related to endogenous or exogenous DNA damaging processes. The resultant mutations can be separated into two categories – (i) mutations that provide selective advantage for clonal expansion and (ii) mutations that do not result in growth advantage [26]. The latter have been termed passenger mutations, while the former are referred to as driver mutations. It is widely believed that the number of driver mutations in a cancer sample is limited to a handful, usually two or more but less than ten [27]. In contrast, the genome of a cancer can harbour more than a million somatic mutations [28] most of which are considered to be passengers.

Several studies have shown that these "passenger" mutations may not be oncogenic drivers but may be of importance in adaptive immune resistance of a tumor. In particular the relevant mutations are likely to be the nonsynonymous exonic mutations in tumors; these may give rise to novel proteins that differ from their wild type counterparts and are immunogenically more relevant (reviewed in [29]). These mutated proteins are proteosomally degraded into peptide sequences and presented in complex with MHC molecules on the cell surface as "neoantigens". In preclinical models these neoantigens can drive tumor-specific T-cell recognition and tumor rejection in preclinical models [30-33. However tumors can evade the host anti-tumor T-cell response through a number of escape mechanisms, including downregulation of MHC expression and antigen presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands such as PD-1. Restoration of T cell recognition and rejection with anti-PD-1 antibodies has revolutionized cancer therapy however the antigenic "drivers" of immune resistance is not well understood. Our first clue that the genetic complexity of a tumor may underlie responsive to immune checkpoint blockade came from observational data showing a greater response rate in tumors that were more highly mutated.

This was more formally evaluated in melanoma [34] and MSI high colon cancer [35] showing a correlation between mutational load and benefit to immune checkpoint blockade . In NSCLC, the first evidence that the mutation landscape correlates with DCB to pembrolizumab has also been demonstrated [36]. Tumors with higher nonsynonymous mutation load exhibited improved objective response to pembrolizumab (59% vs. 12%, p=0.01), durable clinical benefit (DCB) (79% vs. 18%, p=0.0011), and PFS (median NR vs. 3.4 months, p=0.0004). Notably, analysis within this paper suggests that mutation load was able to differentiate between responders and non-responders within a PD-L1 positive group (Table 1).

Table 1	High mutation load	Low mutation load
	PD-L1 positive (n=11)	PD-L1 positive (n=10)
Durable clinical benefit	91%	10%
No durable benefit	9%	90%

In contrast, we also observed PD-L1 negative tumors with high mutation load that did not respond to immune checkpoint blockade; one explanation we postulated was tumor heterogeneity may explain this lack of response in highly mutated NSCLC. However, a host of other mechanisms of immune escape exist including defects in antigen presentation, secretion of inhibitory molecules (TGF-β, IL-10), induction of metabolic enzymes that consume tryptophan and produce immune-inhibitory metabolites (IDO, TDO), recruitment of tolerogenic immature dendritic cells (DCs), myeloid derived-suppressor cells (MDSCs) or (inducible) regulatory $CD4^+$ T-cells. Potentially these highly mutated, PD-L1 negative tumors may respond to immune checkpoint blockade with a short course of chemotherapy to counteract these other mechanisms of immune evasion.

3.2 Chemotherapy and immunotherapy combination in NSCLC

Chemotherapy can promote immunogenic cell death (ICD) of tumor cells. ICD results in the release of tumor antigens and "danger signals," also known as damage-associated molecular patterns (DAMPS), such as calreticulin, ATP, type I IFN, and non-histone chromatin-binding protein high-mobility group box 1 (HMGB1) [37, 38]. Binding to their receptors (CD91, the purinergic receptors P2RX7 and P2RY2, IFNAR, and the toll-like receptor TLR4, respectively) on DCs, results in their activation, enhanced antigen presentation, upregulation of co-stimulatory receptors, and induction of adaptive immune responses, whereas cell death that is "immunologically silent" induces tolerance [38, 39].

In a phase 2 randomized trial, patients with chemotherapy naïve NSCLC (unselected for PD-L1 expression) were randomized to 4 cycles of pembrolizumab plus carboplatin and pemetrexed every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy, or to 4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy[25]. The response rate was 55% vs. 29% and the PFS was 13 months vs. 9 months favoring the pembrolizumab arm. Multiple phase 3 trials are now being conducted combining chemotherapy with immune checkpoint blockade in NSCLC with little understanding of the interaction between chemotherapy and immunotherapy and impact of PD-L1 expression or mutational landscape.

The combination of atezolizumab with carboplatin based chemotherapy was evaluated in 37 patients with advanced NSCLC in the phase Ib GP28328. MPDL3280A was added to carboplatin with either paclitaxel, nab-paclitaxel, or pemetrexed [40]. The ORR for the carboplatin and nab-paclitaxel arm was 62% (33-83%) with 6 PRs and 2 CRs. Responses were seen independent of PD-L1 expression.

Although the randomized phase 2 and ongoing phase 3 trial with pembrolizumab and pemetrexed and carboplatin are promising, pemetrexed is not a known inducer of immunogenic cell death and continuous chemotherapy administration may have deleterious effect on T cell responses [41]. Also not clear is the potential negative effects of steroid pre and post treatment. Taxanes on the other hand are known to have multiple favorable effects on the tumor microenvironment (TME). Paclitaxel specifically impairs cytokine production and viability in FOXP3+ Treg cells but not in FOXP−CD4+ effector cells, stimulates antigen presentation by DCs, and increases the permeability of tumour cells to granzyme B [41]. Nab-paclitaxel + carboplatin is an FDA approved chemotherapy doublet used in the first-line treatment of advanced NSCLC [42]. Importantly, this regimen can be administered without any corticosteroid administration.

In summary, chemotherapy can increase the antigenicity by inducing immunogenic cell death and MHC upregulation but can also reduce "off target" immunosuppression within the TME by reducing tumor-associated macrophages, regulatory T-cells and MSDCs. Additionally, chemotherapy is capable of enhancing cytotoxic T lymphocytes and natural killer cells. We hypothesize that a short course of chemotherapy can increase T-cell recognition of neoantigens by both increasing antigenicity as well as reducing immune suppression in the TME.

3.3 Dose Selection

Pembrolizumab administered at a flat dose of 200 mg IV every 3 weeks is a dose and schedule approved by the FDA for use in NSCLC. It is approved first line in PD-L1 positive NSCLC with a 50% threshold and in the 2nd line NSCLC setting with a 1% threshold.

Nab-paclitaxel 100 mg/m^2 administered on days 1, 8 and 15 and carboplatin AUC 5 administered on Day 1 every 3 weeks are approved in combination as first line treatment of NSCLC.

Pemetrexed 500 mg/m^2 and carboplatin AUC 5 administered on Day 1 every 3 weeks is approved in combination as first line treatment of non-squamous cell lung cancer.

Both chemotherapy regimens will be administered without corticosteroids unless deemed necessary by the treating physician.

NOTE: For patients with an abnormally low serum creatinine level, estimate GFR using a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min. If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = target AUC (mg •min/mL) × (GFR+ 25 mL/min)

The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC= 6, the maximum dose is 6 × 150 = 900 mg.
For a target AUC= 5, the maximum dose is 5 × 150 = 750 mg.
For a target AUC= 4, the maximum dose is 4 × 150 = 600 mg.

4. INVESTIGATIONAL AGENT

4.1 Pembrolizumab

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

4.2 Other agents

Nab-paclitaxel + carboplatin is an FDA approved chemotherapy doublet used in the first-line treatment of advanced NSCLC. Pemetrexed + carboplatin is an FDA approved chemotherapy doublet used in the first-line treatment of advanced non-squamous cell lung cancer. Refer to the approved product labels for further information.

5. STUDY DESIGN

This will be a 3-arm, multi-center, open-label, non-randomized biomarker trial in patients with advanced, treatment-naive NSCLC. Patients will receive 1 of 3 possible cohorts as per investigator's discretion. Patients with non-squamous histology may receive any of the 3 cohorts; patients with squamous histology may receive either cohorts 1 and 2.

Table 2: Schema

Cohort 1 (Any NSCLC histology)	Pembrolizumab 200 mg IV q 3 weeks x 2 years
Cohort 2	Pembrolizumab 200 mg IV q 3 weeks x 2 years
(Any NSCLC histology)	Nab-paclitaxel (100 mg/m2 D 1, 8 and 15) x 2 cycles
	Carboplatin (AUC 5 q 3 weeks) x 2 cycles
Cohort 3	Pembrolizumab 200 mg IV q 3 weeks x 2 years
(non-squamous histology only)	Pemetrexed 500 mg/m2 x 2 cycles
	Carboplatin (AUC 5 q 3 weeks) x 2 cycles

If sufficient archived core biopsy is available (at least 2 cores or equivalent) a pretreatment biopsy will not be required after review of the pathology report and approval by the medical monitor. If insufficient archived tumor is available a new tumor biopsy will be performed. An on treatment biopsy will be performed at approximately C2D8. New tumor biopsies will be procured as follows: a total of 5 core biopsies at each time point will be collected. Four

samples will be embedded in OCT, snap frozen and stored in liquid nitrogen or at -80°C for DNA and RNA extraction. The remaining core biopsy will be formalin-fixed and embedded in paraffin. Baseline blood will be obtained and serial PBMCs, serum and plasma will be banked for future research: pre-treatment (either screening or C1D1), C1D8, C2D1, C2D8, C3D1, every 4 cycles thereafter (every 12 weeks) and at progression.

6. SUBJECT SELECTION AND WITHDRAWAL

6.1 Inclusion Criteria

6.1.1 NSCLC patients of all histologies may enroll to Cohorts 1 and 2. Only patients of non-squamous histologies may enroll to Cohort 3. If enrollment to a cohort is completed, enrollment may continue to other open cohorts.

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

6.1.3 Chemotherapy naïve NSCLC patients.For NSCLC patients with lung adenocarcinoma, tumors must be EGFR and ALK wild-type; if a KRAS mutation is detected, EGFR and ALK testing is not required.

6.1.4 Diagnosis must be documented by histology or cytology from brushings, washings, or needle aspiration of a defined lesion but not from sputum cytology.

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

6.1.6 Have measurable disease based on RECIST 1.1.

6.1.7 Sufficient archived tumor material available (equivalent to 2 core biopsies or greater); if insufficient archived tumor material available new tumor biopsy is mandatory.

6.1.8 Have a performance status of 0 or 1 on the ECOG Performance Scale.

6.1.9 Demonstrate adequate organ function as defined in Table 3 below. All screening labs should be performed within 10 days of treatment initiation, except for Hepatitis B, Hepatitis C, and HIV, which may be done within 28 days of treatment initiation.

Table 3: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**

	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

6.1.11 Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section 8.4.4). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

6.2 Exclusion Criteria

6.2.1 Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

6.2.2 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

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

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

6.2.6 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

6.2.7 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable and are not using steroids for at least 7 days prior to trial treatment (stereotactic brain radiation therapy to isolated brain metastases does not require washout period providing no steroids are required).

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

6.2.9 Has evidence of interstitial lung disease or active, non-infectious pneumonitis. Has an active infection requiring systemic therapy.

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

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

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

6.2.13 Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
6.2.14 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
6.2.15 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
6.2.16 Has a known history of active TB (Bacillus Tuberculosis)
6.2.17 Has received a live vaccine within 30 days prior to the first dose of trial treatment.
6.2.18 History of allergy or hypersensitivity to any component of the treatment.

6.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

6.4 Subject Recruitment

Patients will be recruited from the referral population within the investigator and co-investigators' clinical practices.

6.5 Early Withdrawal of Subjects

6.5.1 When and How to Withdraw Subjects

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 12.4.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
  - *Note*: For unconfirmed radiographic disease progression, please see Section 13.
  - *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences as described in Section 10.
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

6.5.2 Data Collection and Follow-up for Withdrawn Subjects

The End of Treatment and Follow-up visit procedures are listed in Section 12 (Protocol Flow Chart) and Section 12.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 12.5.2. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

7. REGISTRATION PROCEDURES

7.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has

expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

7.2 CPDM CUMC Subject Specific Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.304.6330, with the subject line "AAAQ5450 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
- Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
- Copy of pathology and surgical reports
- Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
- Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAQ5450" Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the

review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7.2.1 Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

Affiliate Institutions will be trained during the SIV teleconference prior to activating the site. Once sites begin enrolling subjects, teleconferences will be scheduled every two weeks to discuss enrollment, safety and on-going study education

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse) via the Q5450@columbia.edu email.
2. The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at CPDMRegistration@columbia.edu (or via fax at 212.305.5292), with a request to register the patient "pending eligibility." The title of the email should read, "AAAQ5450 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b. Redacted Signed HIPAA (or institutional equivalent)
    c. MCT CPDM Velos Note to File form

3. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse) via telephone or email to communicate the following:
    - Notify of pending registration request

- Confirm method of registration request submission (email or fax)
- Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

4. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee via the Q5450@columbia.edu email:
   - A signed Affiliate Site Eligibility Checklist (signed by the investigator)
   - Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
     - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
     - Copy of pathology and surgical reports
     - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
   - **Please note**: subject line of email or fax should include the following: "AAAQ5450 Complete Subject Registration Request (PHI)".

5. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

6. Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

7. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration

Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

8. TREATMENT PLAN

8.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for Pembrolizumab described in Section 10. Appropriate dose modifications for Pembrolizumab are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Merck will send pembrolizumab directly to sub-sites, and CUMC will coordinate the first affiliate drug order. Commercial pemetrexed, nab-paclitaxel and carboplatin will be used.

The treatment to be used in this trial is outlined below in Table 4.

Table 4: Trial Treatment

All drugs will be administered as below per institutional guidelines and per the approved product labels

Cohort 1	Pembrolizumab 200 mg IV over 30 (-5, +10) minutes q 3 weeks x 2 years
Cohort 2	Pembrolizumab 200 mg IV over 30 (-5, +10) minutes q 3 weeks x 2 years
	Nab-paclitaxel[1] (100 mg/m^2) IV over 30 minutes +/- 10 minutes D 1, 8 and 15) x 2 cycles
	Carboplatin[2] (AUC 5 q 3 weeks) IV between 15-30 minutes x 2 cycles
Cohort 3	Pembrolizumab 200 mg IV over 30 (-5, +10) minutes q 3 weeks x 2 years
	Pemetrexed[3] 500 mg/m^2 IV over 30 minutes +/- 10 minutes q 3 weeks x 2 cycles
	Carboplatin[2] (AUC 5 q 3 weeks) IV between 15-30 minutes x 2 cycles

[1]Nab-paclitaxel doses should be administered at a minimum of 5 days apart. The dose should be recalculated if patient experiences ≥10% weight change from C1D1/pre-treatment labs.
[2]Carboplatin dose should be recalculated per the discretion of the investigator
[3]Pemetrexed dose should be recalculated on C2D1 if patient experiences ≥10% weight change from C1D1/pre-treatment labs.

8.2 Dose Selection

Details on preparation and administration of Pembrolizumab are provided in the Pharmacy Manual. Details on preparation and administration of nab-paclitaxel, pemetrexed and carboplatin are per the approved product label and institutional guidelines.

8.3 Biomarker Research

Table 5: Biomarker Research. Translational research is as described but not limited to as outlined below:

Tumor	
Non-synonymous mutation load	Exome and RNAseq analysis [43-53]
Mutational smoking signature	Exome and RNAseq analysis [43-53]
Neoantigen prediction	In silico neoantigen prediction [1534]
MHC, PD-L1, PD-L2, LAG3, IDO, Tim3, Ki-67	IHC/IF [54]
CD3, CD4, CD8, PD-1, FOXP3, TIA-1	IHC/IF [54]
PBMCs	
Neoantigen validation in vitro (quantitative)	Intracellular cytokine staining [55]
Neoantigen validation in vitro (qualitiative)	Multimer assays [56]
Tumor and PBMCs	
T cell receptor clonality	TCR sequencing [57]
Blood	
Germline sequencing	Exome analysis [43-53]
HLA typing	HLA sequence-based typing [58]

8.4 General Concomitant Medication and Supportive Care Guidelines

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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

8.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications

and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10.2.

8.4.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
    - Subjects are allowed to receive palliative radiotherapy for painful bone lesions after consultation with Sponsor. Targeted external beam irradiation should not be used in the primary lung field where assessment for tumor is indicated.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed..
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology (listed in Section 8.2.4 and the Investigator's Brochure). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

8.4.3 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Pembrolizumab.
Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance. Refer to Section 9 for dose modification.

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

Pneumonitis:

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration

Diarrhea/Colitis:

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.

- For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus:

If new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

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

Hyperthyroidism or Hypothyroidism:

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

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

Hepatic:

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly). Treat with IV or oral corticosteroids
- For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

- For Grade 2 events, treat with corticosteroids.
- For Grade 3-4 events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
Table 6 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

Table 6: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

	premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Supportive care guidelines for nab-paclitaxel, pemetrexed and carboplatin are per institutional guidelines and approved product labels.

8.4.4 Diet/Activity/Other Considerations

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

Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 10.2.2 - Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 10.2.

Use in Nursing Women

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

8.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 2 years or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

8.6 Duration of Follow Up

Refer to section 12.5

8.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 8.5 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

9. DOSING DELAYS/DOSE MODIFICATIONS

9.1 Pembrolizumab

Adverse events (both non-serious and serious) associated with Pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 7 below. See Section 8.4 for supportive care guidelines, including use of corticosteroids.

Table 7: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	**Hold Treatment For Grade**	**Timing for Restarting Treatment**	**Discontinue Subject**
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold Pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume Pembrolizumab when patients are clinically and metabolically stable.

Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

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

dose is given outside the +/- 3 day window, the dosing schedule will shift so subsequent cycles are initiated every 3 weeks (+/- 3 days). The reason for interruption should be documented in the patient's study record.

9.2 Carboplatin and nab-paclitaxel

Dose reductions, holds, and discontinuations for carboplatin and nab-paclitaxel may be made per approved product labels or according to physician judgment. When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the regimen, all study drugs should generally be held and resumed together to remain synchronized. However, if it is anticipated that chemotherapy will be delayed by 2 weeks or more, then Pembrolizumab should be given without the chemotherapy if there is no contraindication; this should be discussed with the Medical Monitor prior to re-initiating therapy.

ANC must be $\geq 1500/mm^3$ and platelet counts must be $\geq 100{,}000/mm^3$ on Day 1 of each cycle. Nab-paclitaxel should not be administered on Days 8 or 15 of the cycle until counts recover to an ANC $\geq 1500/mm^3$ and platelets $\geq 50{,}000$ cells/mm^3. If nab-paclitaxel cannot be administered on Day 8 or 15 of the cycle, this treatment can be skipped, and the next dose should be given per original treatment schedule as long as counts have recovered to permissible levels.

9.3 Carboplatin and pemetrexed

Dose reductions, holds, and discontinuations for carboplatin and pemetrexed may be made per approved product labels or according to physician judgment. When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the regimen, all study drugs should generally be held and resumed together to remain synchronized. However, if it is anticipated that chemotherapy will be delayed by 2 weeks or more, then Pembrolizumab should be given without the chemotherapy if there is no contraindication; this should be discussed with the Medical Monitor prior to re-initiating therapy.

9.4 Potential Overlapping Toxicities

The risk of overlapping toxicities between Pembrolizumab and chemotherapy regimens is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of Pembrolizumab.

Toxicities should initially be managed according to the recommendations above, with dose holds and modifications (if applicable) applied to the component of the study regimen judged to be the primary cause. For severe (Grade 3) or persistent Grade 1/2 diarrhea, an endoscopic

evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, Pembrolizumab is a potential inciting factor, the dose of Pembrolizumab may be held indefinitely. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Adverse events

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

10.2 Definitions

Adverse Event:
An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time. Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from

overdose (whether accidental or intentional), from abuse and from withdrawal.
Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 10.2.3.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy,

whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

10.2.3 Serious Adverse Event:

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalation, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event
- is a new cancer (that is not a condition of the study);
- is associated with an overdose

Note: Serious adverse events are only to be reported following initial treatment.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Progression of the cancer under study is not considered an serious adverse event unless it

results in hospitalization.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.
All subjects with serious adverse events must be followed up for outcome.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

10.2.4 Unanticipated Problem:

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

10.2.5 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 90 days following the last administration of study treatment, **or** 90 days **following the decision to remove the subject from study treatment, whichever is earliest.**

10.2.6 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)
Events of clinical interest for this trial include:

10.2.6.1 an overdose of Merck product, as defined in Section 10.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

10.2.7 Additional adverse events

ECIs (both non-serious and serious adverse events) from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be

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

10.2.8 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 8: Evaluating Adverse Events: An investigator who is a qualified physician, will evaluate all adverse events as to:

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

		bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
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.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without	

relationship	an associated AE.)

10.3 Sponsor Responsibility for Reporting Adverse Events

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

10.3.1 Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

10.3.2 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.3.3 Post-study Adverse Event

All unresolved adverse events (related to study drug(s))should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

10.3.4 Abnormal Laboratory Values

Abnormal Laboratory Values: All clinical laboratory abnormalities should be documented as adverse events if the severity meets grading criteria (1-5) per CTCAE version 4.0.

10.3.5 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.4 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.5 Reporting of Serious Adverse Events

10.5.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

10.5.2 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also

submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

10.5.3 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

10.5.4 Reporting to Drug Manufacturer by Sponsor-Investigator

Please refer to section 10.2.3 for further details.

10.6 **Reporting Process**

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse

Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.4.

11. PHARMACEUTICAL INFORMATION

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.

Study Drugs

Pembrolizumab, Nab-paclitaxel (Abraxane), Pemetrexed, Carboplatin

Table 9: Description

Product Name & Potency	**Dosage Form**
pembrolizumab 50 mg	Lyophilized Powder for Injection
pembrolizumab 100 mg/ 4mL	Solution for Injection
Nab-paclitaxel (Abraxane) 100 mg	Lyophilized Powder for Injection
Pemetrexed	Lyophilized Powder for Injection
Carboplatin 50 mg/5 mL	Solution for Injection
Carboplatin 150 mg	Lyophilized Powder for Injection

11.1 Treatment Regimen

For Cohort 1: Pembrolizumab 200 mg will be administered IV every 3 weeks until progression of disease.

For Cohort 2:

- Pembrolizumab 200 mg will be administered IV every 3 weeks until progression of disease
- Nab-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 every 3 weeks administered for 2 cycles concurrently with cycles 1 and 2 of pembrolizumab
- Carboplatin AUC = 5 IV on day 1 every 3 weeks administered for 2 cycles

concurrently with cycles 1 and 2 of pembrolizumab

For Cohort 3:

- Pembrolizumab 200 mg will be administered IV every 3 weeks until progression of disease
- Pemetrexed 500 mg/m2 IV administered for 2 cycles concurrently with cycles 1 and 2 of pembrolizumab
- Carboplatin AUC = 5 IV on day 1 every 3 weeks administered for 2 cycles concurrently with cycles 1 and 2 of pembrolizumab

11.2 Method for Assigning Subjects to Treatment Groups

Assignment to cohort will be per investigator choice; a maximum of 30 patients per cohort will be enrolled. For patients with squamous histology, enrollment will be allowed only to cohorts 1 or 2. For patients with non-squamous histology enrollment will be to any of the 3 cohorts. If enrollment to a cohort is completed, enrollment may continue to other open cohorts.

11.3 Preparation and Administration of Study Drug

Details on preparation of Pembrolizumab are provided in the Pharmacy Manual. Details on preparation of nab-paclitaxel, pemetrexed and carboplatin are per the approved product label and institutional guidelines.

Drug administration order:
Cohort 1: pembrolizumab only
Cohort 2: pembrolizumab followed by nab-paclitaxel followed by carboplatin
Cohort 3: pembrolizumab followed by pemetrexed followed by carboplatin

11.4 Subject Compliance Monitoring

The study team will monitor subject compliance with protocol mandated procedures. If a subject continually demonstrates non-compliance, the treating investigator (in collaboration with the CUMC Principal Investigator) will consider removing the subject from study.

11.5 Prior and Concomitant Therapy

Please refer to Section 12.2.5 for more information.

11.6 Packaging

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. This trial is open-label; therefore, the subject, the trial site personnel, the

Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

11.6.1 Clinical Supplies Disclosure

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

11.7 Blinding of Study Drug

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

11.8 Receiving, Storage, Dispensing and Return

11.8.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify agent manufacturer of any damaged or unusable study treatments that were supplied to the investigator's site.

11.8.2 Storage

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.

Storage instructions for carboplatin, pemetrexed and nab-paclitaxel are according to local practice.

11.8.3 Dispensing of Study Drug

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

11.8.4 Return or Destruction of Study Drug

Upon completion or termination of the study, all unused and/or partially used

investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

12. STUDY CALENDAR

Table 10: Study calender (Cohort 1)

Cycle (Q3W)	Screening[9]	C1D1	C1D8	C2D1	C2D8	C3+	At POD
Scheduling window (Days)	-28 to -1		+/- 3 days				
Informed consent	X						
History and Physical [1-4]	X	X	X	X	X	X	X
Pregnancy test for WOCBP[10]	X					X	
Routine bloods [5]	X			X		X	
PT/PTT[9]	X	As clinically indicated					
Thyroid function tests[6,9]	X					X	
Hepatitis B, C, HIV	X						
EKG	X	As clinically indicated					
AE assessment	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Radiographic tumor assessment	X	Every 9 weeks (±1 week)					
MRI brain[11]	X	As clinically indicated					
Research blood tests[7]	X	X	X	X	X	X	X
Tumor biopsy[8]	X				X		
Pembrolizumab		X		X		X	

[1] Medical history includes baseline symptoms as well as detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness. Smoking history should be captured at screening.
[2] Body height to be measured at screening only
[3] Vital signs include weight, temperature, pulse, blood pressure, and oxygen saturation
[4] Full physical exam for baseline and end of study visit. Other study visit physical exams may be symptom directed.
[5] Routine bloods: Hematology, Chemistry and Urinalysis as outlined in Table 13.
[6] Thyroid function tests (TSH, reflexive free T4/free T3 if TSH is abnormal) should be performed at screening, Cycle 4, and every 3 cycles thereafter.
[7] Research bloods will be drawn for T-cell subsets/PBMCs and serum and plasma for banking at pre-treatment (either screening or C1D1), C1D8, C2D1, C2D8, C3D1, every 4 cycles thereafter and at progression. Blood for germline sequencing and HLA typing will be drawn pre-treatment.

[8] Archival tissue, at minimum two core equivalents, acquired within 3 months before treatment initiation and in the absence of intervening systemic therapy may be used for the pre-treatment timepoint after review of the pathology report and approval by the medical monitor. The window for the on-treatment biopsy will be +/- 7 days from the date of C2D8.
[9] Screening labs to be performed within 10 days of Cycle 1 Day 1 except for Hepatitis B, C, and HIV, which can be done within 28 days of Cycle 1 Day 1.
[10] Pregnancy test for women of childbearing potential should be performed at screening, Cycle 4, and every 3 cycles thereafter.
[11] CT of the head can be used in place of a brain MRI

Table 11: Study calender (Cohort 2)

Cycle (Q3W)	Screening[9]	C1D1	C1D 8	C1D 15	C2D 1	C2D 8	C2D15	C3 +	At POD
Scheduling window (Days)	-28 to -1		+/- 3 days						
Informed consent	X								
History and Physical [1-4]	X	X	X	X	X	X	X	X	X
Pregnancy test for WOCBP[10]	X							X	
Routine bloods [5]	X		X	X	X	X	X	X	
PT/PTT[9]	X	As clinically indicated							
Thyroid function tests[6,9]	X							X	
Hepatitis B, C, HIV	X								
EKG	X	As clinically indicated							
AE assessment	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Radiographic tumor assessment	X	Every 9 weeks (+/- 1 week)							
MRI brain[11]	X	As clinically indicated							
Research blood tests[7]	X	X	X		X	X		X	X
Tumor biopsy[8]	X					X			
Pembrolizumab		X			X			X	
Nab-paclitaxel[12]		X	X	X	X	X	X		
Carboplatin		X			X				

[1] Medical history includes baseline symptoms as well as detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness
[2] Body height to be measured at screening only
[3] Vital signs include weight, temperature, pulse, blood pressure, and oxygen saturation
[4] Full physical exam for baseline and end of study visit. Other study visit physical exams may be symptom directed.
[5] Routine bloods: Hematology, Chemistry and Urinalysis as outlined in Table 13.
[6] Thyroid function tests (TSH, reflexive free T4/free T3 if TSH is abnormal) should be performed at screening, Cycle 4, and every 3 cycles thereafter.
[7] Research bloods will be drawn for T-cell subsets/PBMCs and serum and plasma for banking at pre-treatment (either screening or C1D1), C1D8, C2D1, C2D8, C3D1, every 4

cycles thereafter and at progression. Blood for germline sequencing and HLA typing will be drawn pre-treatment.
[8] Archival tissue, at minimum two core equivalents, acquired within 3 months before treatment initiation and in the absence of intervening systemic therapy may be used for the pre-treatment timepoint after review of the pathology report and approval by the medical monitor. The window for the on-treatment biopsy will be +/- 7 days from the date of C2D8.
[9] Screening labs to be performed within 10 days of Cycle 1 Day 1 except for Hepatitis B, C, and HIV, which can be done within 28 days of Cycle 1 Day 1.
[10] Pregnancy test for women of childbearing potential should be performed at screening, Cycle 4, and every 3 cycles thereafter.
[11] CT of the head can be used in place of a brain MRI
[12] Nab-paclitaxel doses should be administered at a minimum of 5 days apart.

Table 12: Study calender (Cohort 3)

Cycle (Q3W)	Screening[9]	C1D1	C1D8	C2D1	C2D8	C3+	At POD
Scheduling window (Days)	-28 to -1		+/- 3 days				
Informed consent	X						
History and Physical [1-4]	X	X	X	X	X	X	X
Pregnancy test for WOCBP[10]	X					X	
Routine bloods [5]	X			X		X	
PT/PTT[9]	X	As clinically indicated					
Thyroid function tests[6,9]	X					X	
Hepatitis B, C, HIV	X						
EKG	X	As clinically indicated					
AE assessment	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Radiographic tumor assessment	X	Every 9 weeks (- 1 week)					
MRI brain[11]	X	As clinically indicated					
Research blood tests[7]	X	X	X	X	X	X	X
Tumor biopsy[8]	X				X		
Pembrolizumab		X		X		X	
Pemetrexed		X		X			
Carboplatin		X		X			

[1] Medical history includes baseline symptoms as well as detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness
[2] Body height to be measured at screening only
[3] Vital signs include weight, temperature, pulse, blood pressure, and oxygen saturation
[4] Full physical exam for baseline and end of study visit. Other study visit physical exams may be symptom directed.

[5] Routine bloods: Hematology, Chemistry and Urinalysis as outlined in Table 13.
[6] Thyroid function tests (TSH, reflexive free T4/free T3 if TSH is abnormal) should be performed at screening, Cycle 4, and every 3 cycles thereafter.
[7] Research bloods will be drawn for T-cell subsets/PBMCs and serum and plasma for banking at pre-treatment (either screening or C1D1), C1D8, C2D1, C2D8, C3D1, every 4 cycles thereafter and at progression. Blood for germline sequencing and HLA typing will be drawn pre-treatment.
[8] Archival tissue, at minimum two core equivalents, acquired within 3 months before treatment initiation and in the absence of intervening systemic therapy may be used for the pre-treatment timepoint after review of the pathology report and approval by the medical monitor. The window for the on-treatment biopsy will be +/- 7 days from the date of C2D8.
[9] Screening labs to be performed within 10 days of Cycle 1 Day 1 except for Hepatitis B, C, and HIV, which can be done within 28 days of Cycle 1 Day 1
[10] Pregnancy test for women of childbearing potential should be performed at screening, Cycle 4, and every 3 cycles thereafter.
[11] CT of the head can be used in place of a brain MRI

12.1 Study Procedures

The Trial Flow Chart - Section 12 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

12.2 Administrative Procedures

12.2.1 Informed Consent

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

12.2.2 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the subject before

participation in the trial.

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

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

12.2.3 Inclusion/Exclusion Criteria

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

12.2.4 Medical History

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

12.2.5 Smoking History

Smoking history (smoker status, cigarettes per day, number of years, and start and stop dates) should be captured during the screening period. For patients enrolled prior to Protocol Version 2/8/2017, this should be done retrospectively.

12.2.6 Prior and Concomitant Medications Review

12.2.6.1 Prior Medications

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

12.2.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

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

12.3 Clinical Procedures/Assessments

12.3.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 10.2.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with Pembrolizumab all AEs of unknown etiology associated with Pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to Section 10.2.5 for detailed information regarding the assessment and recording of AEs.

12.3.2 Full Physical Exam

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

12.3.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

12.3.4 Vital Signs

The investigator or qualified designee will at study visits as specified in the Trial Flow Chart (Section 12). During dosing visits, vital signs should be assessed once prior to initiating treatment that day.Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

12.3.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 19.1) at at study visits as specified in the Trial Flow Chart. On treatment days, ECOG status should be assessed pre-dose. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

12.3.6 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 13.

Table 13: Laboratory Tests

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

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

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

12.3.7 Research Sample Evaluations

12.3.7.1 Blood Collection for T-cell subsets/PBMCs and Serum/Plasma for Banking

Sample collection, storage and shipment instructions are provided in the Laboratory Manual.

12.3.7.2 Blood Collection for Germline Sequencing

Sample collection, storage and shipment instructions are provided in the Laboratory Manual.

12.3.7.3 Blood Collection for HLA Typing

Sample collection, storage and shipment instructions are provided in the Laboratory Manual.

12.4 **Other Procedures**

12.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.2. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (Section 12.5.1) and then proceed to the Follow-Up Period of the study (Section 12.5.2).

12.5 **Visit Requirements**

Visit requirements are outlined in Section 12 - Trial Flow Chart. Specific procedure-related details are provided therein.

12.5.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs and ECIs (Events of Clinical Interest) that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

12.5.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (56 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study.

12.5.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (+/- 1 week) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

13. MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 weeks while on active treatment. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [31]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.3 Response Review

Objective response to study treatment will be assessed by RECIST 1.1 criteria [59] by a study radiologist. Partial and complete responses will be confirmed by a repeat imaging occurring at least 4 weeks after the initial identification of response; unconfirmed responses will be considered stable or progressive disease dependent on results of the second CT scan. Durable clinical benefit (DCB) will be defined as stable disease or response (complete or partial) lasting longer than 6 months. No durable benefit (NDB) will be defined as progression of disease ≤ 6 months of beginning therapy. For patients with ongoing response to study therapy, progression-free survival will be censored at the date of the most recent imaging evaluation. For alive patients, overall survival will be censored at the date of last known contact.

13.4 Unblinding Procedures

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

13.5 Stopping Rules

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

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

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

14. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 14.3.

14.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be

built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

14.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

14.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

14.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

14.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

14.6 Source Documents

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

14.7 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies).

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

14.8 Compliance with Trial Registration and Results Posting Requirements

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

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

This will be a 3-arm, multi-center, open-label, non-randomized biomarker trial of pembrolizumab in patients with treatment-naïve, advanced NSCLC. The primary endpoint will be percentage of durable clinical benefit (DCB) versus no durable benefit (NDB) within each of the treatment arms.

Secondary endpoints will include objective response rate (ORR), progression free-survival (PFS), and overall survival (OS). Other exploratory endpoints of interest include: duration of response and duration of stable disease.

Power and Sample Size

A sample size of 30 subjects in each arm achieves 80% power to identify difference as low as 40-50% in DCB rates, between low and high mutation load groups. The power was calculated assuming an overall rate of DCB to pembrolizumab in unselected patients with NSCLC of ~20%. However, to be noted that the main, hypothesis generating objective of the study is to assess if mutation load can be used as a predictor of DCB rate, and if the case, identify the optimal cutpoint with either pembrolizumab alone or pembrolizumab in combination with 2 cycles of chemotherapy.

Statistical Analysis:

The objective response and DCB rates will be reported as estimated proportions with 95% confidence intervals. The relationship between mutation load (continuous form) and clinical outcome (DCB), will first be tested in a regression model. The distribution of the continuous variable will then be explored and mutation load will be categorized (e.g., “low” versus “high” load) using different cutpoints such as median (or other quartiles) and/or other known and published cutpoints (e.g. TCGA) of the distribution of non-synonymous mutations per sample. For example, mutational landscape was significantly associated with clinical sensitivity to PD-1 blockade in NSCLC based on a cutoff of 200 mutations per sample [17]. The receiver operating characteristic (ROC) and the area under the curve (AUC) will be computed and compared for the

different cutpoints. The 'optimal' cutpoint will be chosen as the one with the highest AUC (sensitivity/specificity) of at least 0.70.
Kaplan-Meier method and log-rank test will be used to estimate and compare the PFS and OS among the three arms. Median PFS and OS will be provided with 95% CI. Additionally, Cox regressions might be employed to quantify the effect (HR) of several predictors (including dichotomized mutation load) on probabilities of progression-free and overall survival.

Candidate neoantigens: Candidate neoantigens will be broadly defined as those mutations that generate peptides that have <500nM binding affinity to patient specific MHC class I alleles. Analysis will be further refined by IEDB to identify high-affinity neoantigens predicted to elicit T-cell response. Using netMHC and IEDC, a list of candidate neoantigens will be generated, and Wilcoxon rank sum test will be used to compare the quantity of putative neoantigens between the DCB versus NCB groups. Those neoantigens significantly associated with DCB status (controlling for false-discovery rate of 5%) will be validated in further studies. Data will be compared to TCGA data to see if there are mutated sequences enriched in either the DCB or NCB group. The presence of neoantigen-specific peripheral blood and (if possible) intratumoral T-cells will be quantified in pre- and on-treatment specimens. We will present these data graphically and summarize them for the DCB and NCB groups. We are interested in whether neoantigen-specific T-cells exhibit patterns of change between the two evaluations that are different between DCB and NCB patients. The presence of neoantigen-specific lymphocytes will be quantified in samples collected at baseline and serially while on treatment. Their trajectory will be presented graphically, summarized separately for DCB and NCB groups. The mean differences between the pre-post values will be compared between the DCB and NCB groups using two-sided t-tests.

Tumor expression of co-stimulatory and co-inhibitory ligands and MHC expression will be analyzed and quantified in pre-treatment and on-treatment tissue samples. All measures, as well as percent and absolute changes between pre- and during treatment, will be summarized separately for DCB versus NCB patients. Associations between pre-treatment values and DCB status will be explored using two-sided t-tests or Wilcoxon rank sum tests (for non-normal data)

Exploratory analyses: Additional post-hoc, exploratory assessments may be performed and reported as hypothesis generating with p-values not adjusted for multiple comparisons.

15.2 Size/Accrual Rate

The study plans to accrue 90 patients study-wide at up to 5 sites. The accrual rate is expected to be 10 patients per month.

15.3 Stratification Factors

Not Applicable

15.4 Reporting and Exclusions

15.4.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

15.4.2 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

16. PROTECTION OF HUMAN SUBJECTS [MULTI CENTER STUDIES]

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB

for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

17. STUDY FINANCES

17.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

18. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

19. APPENDICES

19.1 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.	

19.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

19.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1 [31] will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

19.4 Guidelines for Affiliate Institutions in Multicenter Studies

19.4.1 Multi-site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites.
The following issues will be discussed, as appropriate:

- Enrollment information
- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

19.4.2 New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

19.5 **Regulatory Documents:**

19.5.1 Prior to Site Initiation:

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)

- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to Q5450@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

19.5.2 Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

19.6 **Protocol Deviation/Subject Waiver request for Affiliate Sites:**

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s)/correspondence should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. Please note that the HICCC DSMC will no longer be approving deviations to eligibility criteria.

19.7 Guidelines for Affiliate Site Monitoring

19.7.1 On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

19.7.2 MCT Remote Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.

- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)
- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

19.8 Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

19.9 Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Naiyer Rizvi, MD

177 Fort Washington Ave
New York NY, 10032
646-317-6344
212-305-3035
q5450@columbia.edu

The participating investigator must provide follow-up information on the serious adverse event until resolution or end of the event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

19.10 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms in real time.

19.11 Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Affiliate sites will be reporting SAEs directly to the Principal Investigator. The Multi-Center Core will report the events to the DSMC on behalf of affiliate sites.

Expected AEs must be reported at the time of continuing review of a protocol.

19.12 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

19.13 Reporting to Hospital Risk Management / Data Reporting

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

19.13.1 Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP

recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.
If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

19.13.2 Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

19.13.3 Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

19.13.4 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study. Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

19.13.5 Data Sharing

Some of data analysis are funded by the U.S. National Institutes of Health (NIH). Thus, we are required to submit the genetic and/or clinical data in coded form to one or more databases managed by the NIH. The data may be the combined or individual data of many people. Any data that is submitted **will not be labeled** with patients name or other information that could be used to easily identify them. However, it is possible that the information from individuals' genome, when combined with information from other public sources, could be used to identify them. We believe that this is unlikely to happen.

19.14 Modified CT Imaging Protocols

19.14.1 Modified Chest CT Imaging Protocol

For each CT scan, there will be the following six imaging series reconstructed.

For GE machine, the six series are (slice thickness/convolution kernel):
1) 1.25mm/Standard, 2) 1.25mm/Lung, 3) 2.5mm/Standard, 4) 2.5mm/Lung, 5) 5mm/Standard, and 6) 5mm/Lung.

For SIEMENS machine, the six series are:
1) 1mm/B30f, 2) 1mm/B70f, 3) 3mm/B30f, 4) 3mm/B70f, 5) 5mm/B30f and 6) 5mm/B70f.

All other CT scanning techniques / parameters will adopt the standard-of-care settings for the chest imaging protocol.

19.14.2 Modified Abdominal CT imaging Protocol:

For each phase CT scan (e.g., pre-contrast, arterial phase and portal venous phases), there will be the following six imaging series reconstructed.

For GE machine, the six series are:
1) 1.25mm/Standard, 2) 1.25mm/Soft, 3) 2.5mm/Standard, 4) 2.5mm/Soft, 5) 5mm/Standard, and 6) 5mm/Soft.

For SIEMENS machine, the six series are:
1) 1mm/B30f, 2) 1mm/B20f, 3) 3mm/B30f, 4) 3mm/B20f, 5) 5mm/B30f and 6) 5mm/B20f.

All other CT scanning techniques / parameters will adopt the standard-of-care settings for the abdominal imaging protocol.

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