UCSF Helen Diller Family Comprehensive Cancer Center

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A Pilot Study of Pembrolizumab-based Therapy in Previously Treated High Grade Neuroendocrine Carcinomas

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Protocol Signature Page

Protocol No.: 169524 **Version Date:** 04/14/2021

I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).

I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

I certify that I, and the study staff, have received the required training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Protocol Signature Page – Participating Sites

Protocol No.: 169524 **Version Date:** 04/14/2021

Participating Site(s)

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I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

Principal Investigator	**Site**
Printed Name	Institution Name
Signature	Date

Abstract

Title	A Pilot Study of Pembrolizumab-based Therapy in Previously Treated High Grade Neuroendocrine Carcinomas
Study Description	This is a single arm, open-label, adaptive two-stage study in biomarker "unselected" subjects with previously treated advanced extrapulmonary high-grade neuroendocrine carcinomas (excluding small cell and large cell lung neuroendocrine carcinoma, SCLC and Merkel cell carcinoma, MCC). There are two parts of the study. In Part A, subjects are treated with pembrolizumab alone and in Part B with pembrolizumab plus chemotherapy (physician's choice, paclitaxel or irinotecan). All subjects will undergo a pretreatment tumor biopsy (unless the tumor is inaccessible and/or a biopsy is not felt to be in the patient's best interest).
Phase of Study	Pilot
Investigational Products	Pembrolizumab
Study population	Adult patients of either sex with diagnosed Advanced, poorly differentiated (G3) NEC (excluding SCLC and Merkel cell carcinoma)
Primary Objective	to evaluate the best overall response rate (ORR) of pembrolizumab or pembrolizumab plus chemotherapy according to RECIST1.1 (investigator-reported).
Secondary Objectives	1) to determine the safety and tolerability of pembrolizumab-based therapy in this patient population. 2) to evaluate duration of response (DOR) in patients receiving pembrolizumab or pembrolizumab plus chemotherapy. 3) to evaluate progression free survival (PFS) in subjects treated with pembrolizumab or pembrolizumab plus chemotherapy (median PFS and 18 wk PFS). 4) to evaluate overall survival (OS) in subjects receiving pembrolizumab or pembrolizumab plus chemotherapy.
Sample Size	Approximately a total of 35 subjects (all treated by pembrolizumab) or 36-42 (first 14 treated by pembrolizumab and next 22-28 treated by pembrolizumab plus chemotherapy) will be enrolled in the study.

Duration of Study Treatment	Participants may continue study treatment until progressive disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 35 treatments (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment.
Duration of Follow up	After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAE) and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

List of Abbreviations

Abbreviation/Term	Definition
5-FU	5-fluorouracil
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASaT	All Subjects as Treated
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CNS	Central Nervous System
CPI	Checkpoint Pathway Inhibitor
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DCR	Disease Control Rate
DKA	Diabetic Ketoacidosis
DLT	dose limiting toxicity
DOR	Duration of Response
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FOLFIRI	Folinic Acid - Fluorouracil - Irinotecan
GCP	Good Clinical Practice
GI	gastrointestinal
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry

List of Abbreviations

Abbreviation/Term	Definition
IND	Investigational New Drug
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
irRECIST	Immune related RECIST (Modification of RECIST 1.1)
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
LCNEC	Large Cell Neuroendocrine Carcinoma
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mcL	Microliters
MDSC	Myeloid-derived Suppressor Cell
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
NA or N/A	Not Applicable
NCI	National Cancer Institute
NE	Neuroendocrine
NEC	Neuroendocrine carcinoma
NET	Neuroendocrine tumor
NGS	Next Generation Sequencing
NMR	Nuclear magnetic resonance
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PD-L1	Programmed Death Ligand 1
PD-NEC	Poorly-differentiated neuroendocrine carcinoma
PFS	Progression Free Survival
PK	Pharmacokinetic

List of Abbreviations

Abbreviation/Term	Definition
PR	Partial Response
PT	Prothrombin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
Q9W	Every 9 Weeks
SAE	Serious Adverse Events
SCC	small cell carcinoma
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
TB	Bacillus Tuberculosis
TCRβ	T Cell Receptor β
TGR	Tumor Growth Rate
TIL	Tumor Infiltrating Lymphocytes
TKI	Tyrosine Kinase Inhibitor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
WD-NET	Well-differentiated neuroendocrine tumor

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1 TRIAL DESIGN

1.1 Trial Design

This is a single arm, open-label, adaptive two-stage study in biomarker “unselected” subjects with previously treated advanced extrapulmonary high-grade neuroendocrine carcinomas (excluding small cell and large cell lung neuroendocrine carcinoma, SCLC and Merkel cell carcinoma, MCC). In addition to positive markers of neuroendocrine differentiation, NECs are typically defined by having small cell or large cell NEC morphology Subjects will be required to have a least one measureable lesion by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for response assessment, and have been previously treated with at least one line of systemic therapy.

There are two parts of the study. In Part A, subjects are treated with pembrolizumab alone and in Part B with pembrolizumab plus chemotherapy (physician’s choice, paclitaxel or irinotecan). All subjects will undergo a pretreatment tumor biopsy (unless the tumor is inaccessible and/or a biopsy is not felt to be in the patient’s best interest). Adaptive Simon’s two-stage design is used. The overall plan hinges on the activity of single agent pembrolizumab in the first stage of Part A. If there is sufficient activity in the first stage of Part A, the study will expand to the second stage of Part A and forgo Part B. If there is insufficient activity in the first stage of Part A, the study will proceed to the first stage of Part B (pembrolizumab plus chemotherapy). Approximately a total of 35 subjects (all treated by pembrolizumab) or 36-42 (first 14 treated by pembrolizumab and next 22-28 treated by pembrolizumab plus chemotherapy) will be enrolled in the study. Data from irinotecan and paclitaxel treated patients will be pooled.

The primary objective of this trial is to evaluate the best overall response rate (ORR) of pembrolizumab or pembrolizumab plus chemotherapy according to RECIST1.1 (investigator-reported). On study, imaging assessments will be performed every 9 weeks for 6 months (27 weeks) then every 12 weeks (Q12W) calculated from the date of allocation and independent of treatment delays. RECIST 1.1 will be used for treatment decisions until first radiologic evidence of PD. Following the first evidence of radiologic PD, treatment decisions may be made by the adaption of immune-related RECIST (irRECIST) to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g. tumor flare). For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the site investigator to continue treating the subject with pembrolizumab or pembrolizumab plus chemotherapy until PD is confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment.

Subjects will continue to be treated with pembrolizumab or pembrolizumab plus chemotherapy until PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator’s decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 treatments pembrolizumab (approximately 2 years). Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for OS until death, withdrawal of consent, or the end of the study, whichever comes first.

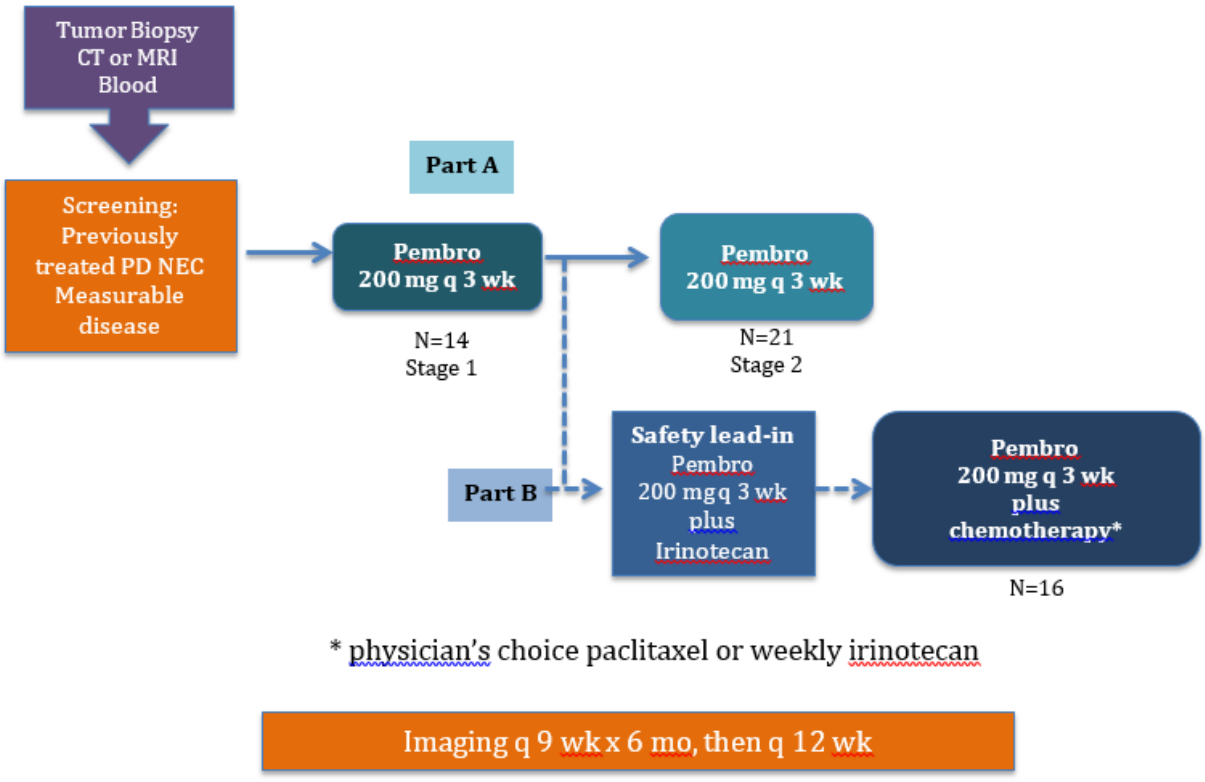
Subjects who attain confirmed CR by 2 tumor-imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix 2). After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs and ECIs will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

This study will be conducted in compliance with Good Clinical Practice.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart (Section5). Details of each procedure are provided in the Trial Procedures (Section6). Mandatory pre-treatment biopsy is required in all patients (unless the tumor is inaccessible and/or a biopsy is not felt to be in the patient's best interest).

1.2 Trial Diagram



- Single arm, open-label, adaptive two-stage study in biomarker "unselected" subjects with previously treated advanced high-grade neuroendocrine carcinomas (excluding small cell lung carcinoma, SCLC, large cell NEC of lung, and Merkel cell carcinoma, MCC).
- The overall plan hinges on the activity of single agent pembrolizumab in the first stage of Part A. If there is sufficient activity in the first stage of Part A, the study will expand to the second stage of Part A and forgo Part B (total N=35 pt).
- If there is insufficient activity in the first stage of part A, the study will proceed to Part B (pembrolizumab plus chemotherapy) after a safety lead-in (6 pt) for irinotecan plus

pembrolizumab (with an option to assess dose level -1 if there are safety concerns). The total sample size for Part B will be N=22-28.

- After all 14 patients have been enrolled to stage I of part A, and while waiting for their 18-week efficacy data, up to six patients can be accrued to the safety lead-in for Part B. This will help to avoid significant delays in accrual to the study, and streamline the transition to part B if required due to a lack of efficacy in Part A. If >2 responses occur in Part A Stage 1 before Part B safety lead-in is completed, a decision can be made whether to complete Part B safety lead-in versus discontinue and proceed with Part A Stage 2 depending on analysis of results and toxicity at that time.

2 OBJECTIVES & HYPOTHESES

2.1 Primary Objective & Hypothesis

Objective: to evaluate the best Overall Response Rate (ORR) per RECIST 1.1 assessed by investigator of pembrolizumab or pembrolizumab plus chemotherapy in subjects with previously treated poorly differentiated neuroendocrine carcinoma.

Hypothesis: Pembrolizumab or pembrolizumab plus chemotherapy have activity in previously treated high-grade extrapulmonary neuroendocrine carcinoma.

2.2 Secondary Objectives

1. **Objective**: To determine the safety and tolerability of pembrolizumab-based therapy in this patient population.
2. **Objective**: To evaluate duration of response (DOR) in patients receiving pembrolizumab or pembrolizumab plus chemotherapy.
3. **Objective**: To evaluate progression free survival (PFS) in subjects treated with pembrolizumab or pembrolizumab plus chemotherapy (median PFS and 18 wk PFS).
4. **Objective**: To evaluate overall survival (OS) in subjects receiving pembrolizumab or pembrolizumab plus chemotherapy.

2.3 Exploratory Objectives

1. **Objective:** To compare ORR, DOR, and PFS based on irRECIST with the same measures assessed by RECIST 1.1.
2. **Objective:** To characterize the molecular features of neuroendocrine carcinomas.
3. **Objective:** To correlate clinical outcomes (ORR, DOR, PFS, OS) with molecular features of neuroendocrine carcinoma.
4. **Objective:** To describe the relationship between baseline tumor growth rate (TGR) and RECIST measurements for all patients enrolled in Part A and Part B of this study.
5. **Objective**: To examine changes in TGR over time in patients treated with pembrolizumab alone (Part A) and pembrolizumab plus chemotherapy (Part B).

3 BACKGROUND & RATIONALE

3.1 Background

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

3.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. [1] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[2-6] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[7, 8] The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade.[7, 9-11] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[12, 13] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[14, 15] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[16] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[12, 17-19] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[12] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL).[20] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has been approved in the United Stated for the

treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It is also approved in head and neck squamous cell carcinoma, and PDL1 (+) non-small cell lung cancer. Nivolumab (another PD1 inhibitor) is FDA approved for the treatment of non-small cell lung cancer, metastatic melanoma, renal cell carcinoma and Hodgkin Lymphoma. Atezolizumab is a PDL-1 inhibitor approved for use in non-small cell lung cancer.

3.1.2 Preclinical and Clinical Trial Data

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

3.1.3 Preclinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, wither as a mon-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of INF-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo.[21-26] Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

3.1.4 Ongoing Clinical Trials

Clinical trials have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. Pembrolizumab is now FDA approved for use in melanoma, head and neck squamous cell carcinoma, and non-small cell lung cancer.

Ongoing clinical trials of pembrolizumab are being conducted in multiple malignancies, including advanced melanoma, non-small cell lung cancer, and a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB. Of note, studies are ongoing with pembrolizumab in combination with paclitaxel-based chemotherapy, as well as in combination with irinotecan (see https://clinicaltrials.gov).

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Population

Neuroendocrine Neoplasms: Neuroendocrine (NE) neoplasms are a diverse group of rare neoplasms distinguished by site of origin, functional status, and degree of aggressiveness.[27-29] For unknown reasons, the incidence has increased five-fold over the past 30 years.[27] In fact, taken together, gastrointestinal NE tumors (NETs) are the second most common gastrointestinal malignancies behind colorectal cancer. NETs are divided into three grades; with the low and intermediate grades (G1 and G2) being considered well-differentiated NETs (WD-NETs) and the high-grade (G3) group consisting of poorly differentiated neuroendocrine carcinomas (PD-NECs). Well-differentiated NETs are relatively indolent, with a natural history that can evolve over years or decades. They are not associated with mutations common to the exocrine cancers that arise at the same organ site and are relatively genetically stable with a low somatic mutation rate.[30]

Poorly differentiated NECS: In contrast, PD-NECs share certain microscopic features of neuroendocrine differentiation but are uniformly aggressive, demonstrate a high proliferative rate (Ki67 typically ≥60-70%) and are classified histologically as small cell carcinoma (SCC) or large cell neuroendocrine carcinoma (LCNEC).[31] There are no validated markers to discriminate between the two types.[32] Unlike WD-NETs, PD-NECs frequently (up to 40% of cases) occur in association with non-neuroendocrine precursor lesions or carcinomas ("mixed" tumors) and often share mutations with the exocrine cancers of the same organ.[28] The prototypical PD-NEC is small cell lung cancer (SCLC), which accounts for 13% of all lung cancers and 95% of all SCCs, and demonstrates a high mutation rate (1-40/Mb, average 8/Mb) and a transient, but marked, response to platinum-based chemotherapy.[31, 33]

While rare, *extrapulmonary* PD-NECs can arise nearly anywhere including the gastrointestinal tract, prostate, bladder and cervix (typically comprising <3% of malignancies in each site).[28, 31] A recent review of UCSF data revealed that *10.6% of* 262 cases of pancreatic NETs were poorly differentiated; 16% of 755 GI-NETs were poorly differentiated. Others have also reported that a sizable fraction (5-10%) of digestive NETs are high grade.[34-36] Furthermore, therapy-induced PD-NECs have been identified in the setting of resistance to androgen deprivation in prostate cancer and tyrosine kinase inhibitor (TKI) therapy in non-small cell lung cancers harboring activating mutations in *EGFR*.[37, 38] As such, high grade NECs arising outside the lungs are not as uncommon as once thought. Like SCLC they are highly aggressive and often characterized by P53 mutations and RB loss, although some genetic alterations are site specific (e.g. *TMPRSS2-ERG* gene rearrangement in 50% of PD-NECs of the prostate).[39, 40] The etiology of PD-NECs is unclear, although SCLC is associated with smoking, PD-NECs of the prostate are usually therapy-related, and Merkel cell carcinoma of the skin is associated with Merkel cell polyomavirus (MCPyV) infection. Interestingly, PD-NECs are not typically associated with inherited cancer syndromes (e.g. MEN1) and may arise though a pathway distinct from well differentiated tumors of the same tissue of origin.

There is no standard therapy for progressive *extrapulmonary* PD-NECs, which (in the absence of site-specific data) are typically treated with platinum-based chemotherapy according to SCLC guidelines.[41, 42] The optimal therapy for large cell NEC of the lung is similarly unclear. NCCN guidelines suggest that early stage disease should be treated like NSCLC (nccn.org). However, chemotherapy regimens typically used for SCLC may be most appropriate when systemic therapy is required.[43, 44] No standard therapy exists for refractory SCLC, which is typically associated with ORR 10-20% and short PFS (<4 months) regardless of chemotherapy regimen (e.g. irinotecan, paclitaxel, topotecan, temozolomide).[29, 42, 45] A recent analysis of 294 patients with extrapulmonary PD-NECs revealed a median OS 11.8 months from first line therapy (typically platinum-based, 46% ORR), 7.6 months from 2nd line, and 5.9 months from third line palliative chemotherapy.[46] Results from this and other *retrospective* studies suggest that FOLFIRI and FOLFOX also hold promise in this population.[46-48] Similarly, temozolomide-based therapy may have activity in GI-NECs (although the benefit appears greatest in "lower risk" patients with somatostatin receptor scintigraphy positive tumors and Ki67 <60%).[49] Additional treatment options are desperately needed in the face of transient responses to chemotherapy and a median OS of 12-15 months.[46]

Immunotherapy and poorly differentiated NECs: Immunotherapy with checkpoint pathway inhibitors (CPI) hold promise in high grade NECs given the relatively high mutation burden and high-programmed death ligand-1 (PD-L1) expression in SCLC, as well as the presence of shared histopathological and molecular features between SCLC and extrapulmonary NECs.[46, 50] High mutation burden has been associated with response to PD1 inhibitors (non-small cell lung cancer, melanoma, mismatch-repair deficient tumors), which has led to their approval in melanoma and squamous NSCLC.[33, 51, 52] Furthermore, mutational burden may correlate with a particular gene signature and the immunogenicity of that signature. Immunogenicity may, in

turn, correlate with neoantigen load, which may ultimately prove to be even more predictive of response to CPI than mutation rate.[52-54] Tumor-associated PD-L1 expression remains under investigation as a potential biomarker of response, but its validity has been confounded by an inconsistent predictive value across trials, use of variable cutoff points and definitions of positive expression (in tumor cells, immune cells or both), and potential dependence on tumor histology/microenvironment.[55, 56] Other data suggest that the presence of functional tumor infiltrating lymphocytes (TIL), specifically antitumor cytotoxic T-lymphocytes, is a key determinant of CPI efficacy.[57] Absent or low CTL responses (modulated by both the local and systemic immunosuppressive environment) must be induced or enhanced in order for CPI activity. An ability to quantify tumor antigen-specific T-cell recognition or expression of T-cell receptor activation markers may also be informative.[58] In the end, both host immunologic and intratumoral factors likely impact sensitivity to checkpoint blockade, making identification of valid biomarkers a challenge.[59]

Emerging data from studies of CPI in SCLC suggest promising activity and provide hope that *extrapulmonary* PD-NECs and large cell NEC of the lung will prove responsive.[60] PDL-1 and PDL-2 are expressed in a subset of poorly differentiated NECs (in tumor infiltrating macrophages) arising in and outside of the lungs. Expression correlates with the presence of tumor infiltrating lymphocytes and suggests a role for checkpoint inhibitors in at least some patients. [61] In 20 patients with PD-L1 (+) platinum-refractory SCLCs treated with pembrolizumab alone, a 35% partial response (PR) (7/20, of which 6/7 responses evident by 8 weeks; median time to response 8 weeks, range 7-16 weeks) and a 40% DCR were noted.[60] Of 147 evaluable tumors, 29% demonstrated (+) PD-L1 expression. In *unselected* .platinum-treated patients with SCLC, 40 subjects receiving nivolumab (an anti-PD-1 antibody) demonstrated an 18% PR (38% DCR); in 46 patients treated with nivolumab plus ipilimumab (an anti-cytotoxic T-lymphocyte–associated antigen 4, CTLA4, antibody), a 32% RR was noted (54% DCR).[62] The median time to response was approximately 2 months (rarely occurring after “pseudoprogression”) and responses were seen in platinum-sensitive and refractory patients. Furthermore, approximately 1/3 of tumors were PD-L1 (+), but responses were evident regardless of PD-L1 status. There was a suggestion that combination therapy was more efficacious than monotherapy. Preliminary data also suggest a very high RR with single agent pembrolizumab in previously untreated Merkel cell carcinoma, perhaps owing to MCPyV-specific immune responses (5 confirmed and 3 unconfirmed responses in the first 10 patients).[63] In gastroenteropancreatic NETs (GEP-NETs), expression of PD-L1 appears to correlate with grade (restricted to G3 in one small series) and inversely correlates with survival.[64]

3.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab: An open-label Phase I trial (Keynote 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All dose levels were well tolerated, and no dose-limiting toxicities were observed. Pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD was identified. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

The PK information from KEYNOTE-001, -002 and -006 was analyzed with the population PK approach to characterize serum concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications (see IB). Conclusions of this analysis were further verified with addition of PK data in second line (2L) NSCLC from KEYNOTE-010 and now with data including the pembrolizumab fixed dosage of 200 mg Q3W in first line (1L)

NSCLC from KEYNOTE-024 (see IB for details). Pharmacokinetic (PK) data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). The results confirm that the PK profile of pembrolizumab is consistent with other therapeutic mAbs with a low systemic clearance and a limited volume of distribution. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and supports both body weight normalized dosing or a fixed dose across all body weights. The data furthermore suggest similar efficacy and safety in melanoma at 10 mg/kg Q3W vs the regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

Support for 200 mg q3wk flat dosing. Since the anti-tumor effect of pembrolizumab is driven through reactivation of adaptive immune response by blocking PD-1 expressed on T cells, but not direct binding to cancer cells, once the PD-1 on T cells are fully saturated by pembrolizumab, the shape of the exposure-response relationship among indications is expected to be similar. The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is supported by exposure-response analysis in multiple indications and simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A flat exposure- response relationship was demonstrated between pembrolizumab exposure (or dose) and efficacy or safety within the dose range of 2 to 10 mg/kg or 200 mg to 10 mg/kg (exposure at 2 mg/kg Q3W is similar to exposure at 200 mg Q3W). The similarity in efficacy between the tested dose regimens is further supported by comparisons of overall response rate (ORR)/survival outcomes for the tested dose regimens in the melanoma and NSCLC indications. Available pharmacokinetic results in subjects with various indications (melanoma, NSCLC, HNSCC and MSI-H) support a lack of meaningful difference in PK among tumor types.

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

Chemotherapy:

Current data suggest that several chemotherapeutic agents can be used to treat PDNECs after first-line therapy. For late recurrences (>6 mo after completion of first line therapy), the initial regimen is typically reintroduced (per SCLC guidelines). In contrast, no standard therapy exists for primary refractory PD NEC, PDNEC that progresses within six months of completion of first line therapy, or late recurrence PDNEC that progresses after rechallenge with initial therapy.

Patients are typically treated according to SCLC guidelines; however, no single regimen is thought to be appreciably more active than another. In general, in the salvage setting, single agent chemotherapy is associated with <20%% ORR.[65] As such, this protocol allows investigators to choose one of two commonly used regimens: two weeks on, 1 week off administration of irinotecan and weekly paclitaxel (depending on prior therapy, co-morbidities and patient/physician preference). [66] The data from chemotherapy-treated patients will be pooled in this pilot study. Temozolomide-based therapy was not considered an option due to its very immunosuppressive effects.

Paclitaxel dose and schedule: While a variety of regimens have been tested, emerging data suggest that weekly paclitaxel (60-90 mg/m2) has an improved safety and tolerability profile (+/- improved efficacy) compared to q 3wk regimens.[66, 67] While paclitaxel can be given weekly without breaks, patients often require breaks or growth factors due to myelosuppression.[68] One commonly used regimen involves paclitaxel 80 mg/m2 IV over one hour q wk x 6, out of an 8-week cycle (23%RR in refractory SCLC). [66] However, the incidence of grade ¾ neutropenia is high (>50%, 64%) necessitating growth factor support or treatment holidays in a number of patients.[66] As such, 3 weeks on/1 week off is a commonly used regimen, still others use 2 weeks on/1 week off in practice. [69]

In addition to other common chemotherapy-associated toxicities (see package insert), paclitaxel can be associated with hypersensitivity reactions (HSR; ranging from mild pruritis and flushing to anaphylaxis). As such, patients are typically premedicated with dexamethasone, ranitidine and diphenhydramine IV 30 min before chemotherapy.[66] Given the potential complications stemming from weekly dexamethasone (including reducing the efficacy of CPI), there is interest in exploring other premedication regimens (particularly since the original schedules were designed for higher dose, q 3 wk paclitaxel regimens). While no official guidelines exist, several alternative premedication strategies appear promising including 1) dexamethasone 10 mg IV 30 min before first dose (plus H1/H2 blockade), eliminating premedications or tapering with dose #2 if no HSR 2) 20 mg dexamethasone IV before 1st dose, 10 mg IV before 2nd dose, then taper by 2 mg increments weekly if no HSR (reaching 0 mg by 9th infusion) 3) 10 mg orally 12- and 6-hour before 1st dose, tapered in subsequent weeks 4) 10 mg IV before doses 1-3, 4 mg IV before doses 4-12.[70] Taken together, studies suggest 0.3% rate of grade 3 /4 HSR with reduced dose dexamethasone, which compares favorably with 2-4% rate with higher dexamethasone (largely from higher dose paclitaxel trials).[70]

Irinotecan dose and schedule: Several small studies have suggested that irinotecan has modest activity in refractory SCLC. One study showed ORR 16% using irinotecan 125 mg/m2 per week (4 weeks on/2 off).[71] The RR was 35% in “sensitive disease”, the RR was 4% in primary resistant /refractory disease. Another study suggested DCR 17.5% (PR 7%) with irinotecan 300 mg/m3 q 3 wk.[72]

Irinotecan is moderately emetogenic and often requires dexamethasone premedication. For the same reason as above, there is an interest in exploring steroid sparing antiemetics, such as using 5HT3 receptor and NK1 receptor antagonists without steroid after cycle 1. Whether to add back dexamethasone will be driven by patient symptoms.

Chemotherapy plus pembrolizumab: While chemotherapy has the potential to be immunosuppressive, an emerging body of literature suggests that the effects are pleotropic; depending on the drugs, doses and schedules, some agents can *stimulate* an immune response. [73] For example, when delivered below the MTD, normal responses to influenza virus can be seen despite concurrent chemotherapy.

Combination studies of CPI with targeted agents or chemotherapy are also underway.[74]. Tumor cells that are killed by chemotherapy may facilitate dendritic cell activation and priming.

Furthermore, chemotherapy may sensitize tumor cells to T cell mediated killing by inhibiting T_{reg} cells and myeloid-derived suppressor cells (MDSCs) and by increasing the expression of death receptors on tumor cells.[74] In melanoma, the combination of CTLA4 blockade plus chemotherapy improves survival compared to chemotherapy alone.[75] These results suggest that CPI in combination with chemotherapy can potentially induce synergistic anti-neoplastic effect.[73]

Paclitaxel plus pembrolizumab. Microtubular inhibitors like paclitaxel interfere with mitosis leading to an increase in chromosomal content, ER stress, and exposure of calreticulin—which facilitates recognition (and elimination) of malignant cells by the immune system (e.g. dendritic cells).[73] Preclinical data suggests paclitaxel depletes MDSCs in mouse tumor models, and may boost T cell priming by dendritic cells. In addition, treatment may increase the relative abundance of circulating CTLs over T_{REG} cells.[73] The potential for a synergistic or additive effect of pembrolizumab and paclitaxel is supported by the fact that the immune modulator ipilimumab improves the efficacy of paclitaxel-based therapy in NSCLC and SCLC.[76, 77]

The safety profile of pembrolizumab is not expected to change with the addition of paclitaxel. Mature safety and efficacy data are pending, but preliminary data suggest that pembrolizumab can be combined with full-dose paclitaxel (e.g. paclitaxel 200 mg/m2 and carboplatin AUC 6 in NSCLC-KEYNOTE-21).[78] Additional combination studies are ongoing, including pembrolizumab plus weekly paclitaxel (NCT02440425) and pembrolizumab in combination with paclitaxel, carboplatin and radiation therapy (NCT02621398). In a phase II study in NSCLC, grade 3/4 events were not different between 204 patients receiving ipilimumab or placebo with carboplatin and paclitaxel. [76] NCT02440425 is an ongoing phase II study in ovarian cancer assessing standard dose weekly paclitaxel and pembrolizumab (without a dedicated phase I component or safety lead-in) (R. Wenham, PI, personal communication). A preplanned analysis of toxicity after the first 10 patients did not reveal any unanticipated toxicities and enrollment is ongoing at full doses of both agents. As such, given the relatively well-documented toxicities associated with dose-dense paclitaxel, the lack of anticipated overlapping toxicities with pembrolizumab (MK-3475), and the data available from ongoing studies with similar combinations, we believe it is reasonable to conduct a pilot trial with the combination (without a phase I component or formal safety lead in).

Irinotecan plus pembrolizumab. Topoisomerase inhibitors may also synergize with CPI. Irinotecan may stimulate MDSC accumulation in the tumor microenvironment.[73] In a murine model of melanoma, the combination of topoisomerase inhibitors and immune-based therapies leads to increased sensitivity to T cell killing.[79] Clinical studies of irinotecan plus pembrolizumab are ongoing (NCT02331251); irinotecan may need to be dose reduced when given in combination with pembrolizumab on a q 3 wk schedule in lung cancer (RPTD 250 mg/m2 q 3 wk, down from 300 mg/m2).[80] Preliminary evidence for activity has been seen in refractory SCLC.[80] A nivolumab plus irinotecan (150 mg/m2 q 2 wk) study is ongoing (NCT02423954). Given the lack of prior experience with pembrolizumab and two weeks on, one week off administration ofirinotecan (125 mg/m2), the study will include a planned analysis of toxicity after 6 patients have been treated with standard dose irinotecan plus pembrolizumab. If 2 or more patients experience dose-limiting toxicity that is clearly related to irinotecan, this agent will be de-escalated to 100 mg/m2 and 6 additional patients will be treated. Dose modification of irinotecan should be undertaken per standard practice. If further, de-escalation is required, the irinotecan will be dropped as a chemotherapy option for Part B.

Rationale for dealers' choice chemotherapy for Part B. Final recommendations for pembrolizumab/chemotherapy dose/schedule will be made if/when Part B opens, based the available data at that time. Since there is no standard therapy for refractory (non-SCLC) poorly differentiated NEC and the response to chemotherapy in this setting is uniformly low, we have proposed to pool patients getting either two weeks on, one week off administration of irinotecan

or weekly paclitaxel in Part B. This should facilitate accrual to this pilot study, allowing the treating provider to select the chemotherapy agent based on prior therapies, co-morbidities, and/or patient preference.

3.2.3 Rationale for Endpoints

3.2.3.1 Efficacy Endpoints

Primary Endpoint: The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab or pembrolizumab plus chemotherapy in subjects with previously treated PD NEC. Best overall response per RECIST 1.1 will be used as the primary endpoint (investigator-reported).

Secondary Endpoint: The secondary efficacy objectives of this study are to evaluate the DOR and PFS per RECIST 1.1 and OS in subjects with PD NEC treated with pembrolizumab or pembrolizumab plus chemotherapy.

3.2.3.2 Safety Endpoints

The safety objective of this study is to characterize the safety and tolerability of pembrolizumab or pembrolizumab plus chemotherapy in subjects with previously treated PD NEC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v4.0 (Appendix 2). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs).

3.2.3.3 Exploratory Endpoints

Molecular Characteristics of NEC

Blood and tissue samples will be analyzed to characterize baseline and/or changes in a variety of parameters- e.g. proliferation indices, metabolic profile, protein expression (candidate approach or large scale), gene expression (e.g. transcriptomics), genomic signature (mutations), immunologic profile, and other molecular features of NEC (e.g. methylome profile). We will explore associations between molecular characteristics and clinical outcomes (ORR, DOR, PFS, OS). Additional tissue- and/or blood-based biomarker research to identify factors important for pembrolizumab and/or NEC therapy may also be pursued (e.g. exosomes, microRNAs, microbiome).

For example:

Ki67 Proliferation rate in tumor

Ki67, a tumor proliferative biomarker, is determined by immunohistochemistry (IHC) of the tumor tissue. Poorly differentiated (G3) NEC arising in the GI tract and pancreas are defined by having a Ki67 >20%, and the response to chemotherapy may depend on the proliferative rate (e.g. > or <55%).[49] The relationship between baseline tumor proliferative index (as measured by Ki67) and response to immunotherapy is uncertain and will be assessed.

Baseline expression of PD-L1 in tumor

PD-L1 expression in the pre-treatment tumor biopsy will be assessed by IHC (Qualtek) and correlated with ORR, PFS, DOR, OS

Characterization and quantification of tumor-infiltrating immune cells

Baseline tumor immune profile will be assessed by quantifying the number of infiltrating T cells subsets, including cytotoxic CD8+, helper CD4+FOXP3-, and regulatory CD4+FOXP3+ T cells. The proportion of activated T cells (e.g. PD1+ and Ki67+) will also be analyzed, as will myeloid-derived suppressor cells (e.g. M2 CD68/Arg-1, M1 CD68/iNOS). Immune cell characterization will be performed by the UCSF CIL.

T cell receptor (TCR) sequencing (blood and tumor biopsy)

T cell receptor (TCR) sequencing can also be used to track immunotherapy-induced changes in T cell repertoire and T cell clonotypes in the blood and tumor tissue. T cells see antigen through their TCR, which is comprised of two subunits, α and β. Each is generated by a VDJ recombination event resulting in a broad range of T cell clones with different specificities. The β subunit has greater clonal diversity. Next-generation sequencing (NGS) of the T cell receptor β chain (TCRβ) has been used to define the diversity and frequency of T cell clones in the blood and tumor tissue of cancer patients after immunotherapy treatment and has been shown to associate with clinical response and OS.[74, 75] Fong, et al. performed TCR next-generation sequencing (NGS) on serial blood (PBMC) samples and prostatectomy samples from sipuleucel-T treated patients.[81] Changes in TCR sequence frequency and diversity showed that sipuleucel-T treatment narrows the TCR repertoire in the blood while increasing the TCR diversity in prostate tissue. The increase in common TCR sequences (clonotypes) between tumor and blood supports the notion of treatment-induced T cell migration into prostate tissue.

CTLA-4 blockade also induces global remodeling of the T cell repertoire.[82] Anti-CTLA-4 administration promotes active turnover in the T cell repertoire, which increases with sequential treatments and leads to increased repertoire diversity. These changes occurred both in naïve and non-naïve T cells, the latter of which includes the antigen-experienced, effector T cell population. Interestingly, maintenance of pre-existing, high-frequency clonotypes (greater than 1 in 1000) is associated with clinical response and improved overall survival following ipilimumab. Importantly, recent data suggest that immune repertoire diversity following immune checkpoint blockade can be detrimental as well as beneficial.[83] Patients with immune related adverse events also demonstrate a more diverse T cell repertoire with an increase in T cell clonotypes, and greater degree of change in clonal frequencies of CD8+ T cells.

Using established techniques (UCSF CIL), NGS will be used to quantify the T cell immune response induced by pembrolizumab. TCR clonotypes will be characterized at baseline (blood and pre-treatment tumor biopsy), as will changes in the T cell immune response over time (blood). The data may inform optimal use of therapies in the patient population under study and identify candidate biomarkers of response, resistance or toxicity.

Characterization of peripheral immune cell subsets (blood)

Circulating immune cells will be assessed by multiparameter flow cytometry on peripheral blood samples. T cell activation status will be characterized.

Mutation profiling (tumor)

Tumor biopsies will be assessed using a cancer gene panel for patient care (e.g. UCSF500; http://cancer.ucsf.edu/intranet/ccgl). The UCSF500 assay provides a platform for assessing the mutation status of 500 genes; selected genes are also analyzed for structural rearrangements. Molecular changes will be correlated with response to therapy.

Metabolic profiling

Tumor cells often exhibit markedly abnormal metabolism, a hallmark of cancer, which has the potential to impact efficacy of immunotherapy and response to chemotherapy.[84-89] Mass spectroscopy-based metabolomics may be used for large scale comparative metabolic profiling of baseline cell metabolism and changes over time.[90] Collaborators at UCSF have extensive experience using high resolution nuclear magnetic resonance (NMR) spectroscopy to assess for the metabolic profile.[91] The data can be linked to gene expression profiling (e.g., by RNAseq). A better understanding of aberrant cell metabolism in poorly differentiated NEC may lead to identification of alternative therapeutic strategies to counteract reprogramming of cellular metabolism.[92]

Gene and Protein expression

Gene expression and protein expression can be assessed using a candidate gene approach (e.g., PCR, immunohistochemistry) or on a larger scale using tools like RNAseq and mass spectroscopy.

Tumor Growth Rate (TGR) (imaging)

TGR has emerged as a potentially important endpoint in clinical trials in well differentiated neuroendocrine tumors (NETs). This metric derives a percentage change in tumor volume per month using the RECIST sums of target lesions, along with the time between tumor evaluations, therefore enabling dynamic and quantitative evaluation of tumor kinetics.[87] In NETs, baseline TGR and changes on study may have prognostic and/or predictive value.[88-90] As such, TGR may provide an early indicator of benefit (or lack thereof) of drugs in development for NETs.

The value of TGR in poorly differentiated NEC is unknown. However, the complexities inherent to immunotherapy confound radiologic assessment using traditional RECIST criteria. For example, studies evaluating checkpoint blockade in various cancer types, including limited cases of NEC, suggest that pseudoprogression and hyperprogression may confound interpretation of treatment efficacy using RECIST alone.[91-95] It remains unknown if TGR at baseline or if changes on treatment have prognostic and/or predictive value.

4 METHODOLOGY

4.1 Entry Criteria

4.1.1 Diagnosis/Condition for Entry into the Trial

Subjects with previously treated locally advanced or metastatic poorly differentiated neuroendocrine carcinoma, including poorly differentiated (G3) NEC of the GI tract, pancreas or other extrapulmonary sites (including small cell or large cell histology), or poorly differentiated NEC of unknown primary and/or not otherwise specified. Patients with a history of a mixed adenoneuroendocrine carcinoma (MANEC) are eligible provided the most recent biopsy shows large or small cell neuroendocrine carcinoma. (Patients with Merkel cell carcinoma or small cell or large cell NEC lung carcinoma are not eligible).

4.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.

3. Have a histologically proven locally advanced or metastatic high grade (G3) poorly differentiated neuroendocrine carcinoma (NEC)

    a. Includes small cell and large cell neuroendocrine carcinoma of unknown primary or any extrapulmonary site (and poorly differentiated NEC, not otherwise specified)

    b. Includes neuroendocrine prostate cancer (de novo or treatment-emergent) of prostate if small cell or large cell histology (histologic evidence of both adenocarcinoma and neuroendocrine carcinoma may be present in same patient)

    c. Other mixed tumors, e.g. mixed neuroendocrine neoplasms (MINENs) with NEC plus adenocarcionoma, squamous or acinar cell component are allowed if the high grade (small or large cell) NEC component comprises >50% of the original sample or subsequent biopsy

4. Have progressed during or after completion of first line systemic chemotherapy

    a. No limit to the number of prior chemotherapy regimens

    b. Early progression on/after adjuvant chemotherapy counts as first-line therapy

5. Have at least one measurable disease based on RECIST 1.1

6. Patients must agree to have a biopsy of primary tumor or metastatic tissue at baseline, and there must be a lesion that can be biopsied with acceptable clinical risk (as judged by the investigator).

    a. Patients with unsuccessful baseline biopsies may undergo an additional biopsy attempt (at the same or a different site, determined by the investigator).

    b. For patients with an intact primary and no metastatic site that can be safely biopsied, biopsy of the primary is acceptable, but must be approved by the principal investigator.

    c. Baseline tumor biopsy may be omitted if the tumor is inaccessible and/or a biopsy is not thought to post exceptionally high procedural risk due to location or other factors

    d. If fresh tumor tissue cannot be collected, the overall study (lead-site) PI may approve the use of archival tissue. The use of archival tissue in lieu of a fresh tumor biopsy will be evaluated on a case-by-case basis and must be approved by the overall study (lead-site) PI. Please see section6.6.

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

8. Have a life expectancy of greater than 3 months.

9. Demonstrate adequate organ function as defined in

10. Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 14 days 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.

12. Female subjects of childbearing potential should be willing to use two methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section4.11.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

    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.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

4.1.3 Subject Exclusion Criteria

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

1. Has Merkel cell carcinoma, small cell lung carcinoma, or large cell NEC of lung
    - Intermediate grade neuroendocrine tumors are excluded
    - Well differentiated Grade 3 neuroendocrine tumors are excluded
    - Metastatic high-grade prostate carcinoma with evidence of focal neuroendocrine differentiation on prostate biopsy (e.g., positive chromogranin staining by immunohistochemistry) without small cell or large cell NEC morphology are excluded, as are neuroendocrine prostate cancers with phenotype intermediate between adenocarcinoma and small cell
    - Atypical bronchial carcinoid and well differentiated G2 GEP-NET are excluded
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
3. Has a diagnosis of immunodeficiency
4. Is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
    - Physiologic doses of steroids (e.g. ≤10 mg prednisone/day or equivalent) are allowed. Topical, inhaled, nasal and ophthalmic steroids are allowed.
5. Has a known history of active TB (Bacillus Tuberculosis).
6. History of or high suspicion of Gilbert's disease (safety run-in, Part B only) Hypersensitivity to pembrolizumab or any of its excipients.
7. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
8. Documented progression on and/or intolerance/hypersensitivity to both paclitaxel and irinotecan (Part B only)
9. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
    - Concurrent somatostatin analog therapy is allowed (for control of hormone excess) provided patient has been on stable dose for at least two months and tumor progression has been documented

- Continuation of androgen deprivation therapy (ADT) allowed for patients with neuroendocrine prostate cancer (in the setting of castration-resistant prostate cancer, CRPC)

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

11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with asymptomatic suspected brain metastases (or small lesions of uncertain significance) <1 cm that do not require focal therapy are eligible. (Follow up imaging will be allowed on study, and focal radiation with continuation of protocol therapy allowed if there is progressive disease in the brain and systemic imaging shows stable disease/response).

    Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks and any neurologic symptoms have returned to baseline), they have no evidence of new or enlarging brain metastases (confirmed by imaging within 28 d of the first dose of trial treatment), and they are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability

12. 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

14. Has an active infection requiring systemic therapy.

15. 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.

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

17. 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.

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

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

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

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

4.2 Trial Treatments

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

Table 2 Trial Treatment

Part A

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21 day cycle	Experimental

Part B

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21 day cycle	Experimental
Irinotecan	125 mg/m2**	QW	IV infusion	Day 1, 8 of each 21 day cycle	Standard of Care
OR					
Pembrolizumab	200 mg	Q3W	IV infusion	Every 21 days	Experimental
Paclitaxel	80 mg/m2	QW	IV infusion Over 1 hr	Day 1,8, 15 of each 21d cycle*	Standard of Care

*The weekly paclitaxel regimen will allow for treatment breaks as per standard of care
** Starting dose for safety lead-in

4.3 Dose Selection/Modification

4.3.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section3– Background and Rationale. Given the ongoing clinical studies with pembrolizumab plus paclitaxel and pembrolizumab plus irinotecan, final recommendations for chemotherapy dose/schedule (and steroid premedications) will be made if/when Part B opens, based on all available data at that time.

Pembrolizumab should be prepared and administered according to institutional guidelines.

Paclitaxel: Paclitaxel will be prepared and administered per routine clinical practice using commercial drug supply. Standard premedications (typically dexamethasone and H1 and H2 blockers) will be given 30-60 minutes prior to paclitaxel (and after pembrolizumab).

- If there is no hypersensitivity reaction to paclitaxel, premedications may be omitted for future paclitaxel doses at physician's discretion.
- If a hypersensitivity reaction occurs, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to paclitaxel: dexamethasone 10 mg,

diphenhydramine 25 mg, and H_2- antagonist (e.g., ranitidine 50 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent paclitaxel doses.

- Additional antiemetics not usually required.

Irinotecan: Irinotecan will be prepared and administered per routine clinical practice using commercial drug supply. The starting dose level for irinotecan will be 125 mg/m2. Safety will be assessed after a six-patient safety lead-in. Irinotecan will be deemed "intolerable" if ≥2 of 6 patients meet DLT criteria in dose level -1.

	Irinotecan Dose Level	Pembrolizumab
Dose level 1	125 mg/m2 d 1, 8	200 mg q 21 d
Dose level -1	100 mg/m2 d 1, 8	200 mg q 21 d

4.3.2 Safety Lead-in

The first six patients enrolled in Part B will be treated with irinotecan (Dose level 1) plus pembrolizumab. Dose modifications for irinotecan should occur according to the package insert and institutional policy. Once the sixth patient in the irinotecan plus pembrolizumab safety lead-in has completed one cycle of therapy (or earlier if clinically indicated), the safety data will be reviewed. An irinotecan dose level will be considered acceptable if no more than 1 of 6 eligible patients in the safety lead-in experiences a DLT (see below). Alternatively, if a DLT is observed in two or more of the six subjects (one-third or more of the subjects), the irinotecan dose level will be considered intolerable and the maximum tolerated dose (MTD) will have been exceeded.

Dose de-escalation: If the dose for the first six patients is not tolerated, Dose Level -1 (100 mg/m2 irinotecan) will be studied in combination with pembrolizumab. If that dose level is intolerable (e.g. if ≥2 of six patients meet DLT criteria), then irinotecan will be dropped as a chemotherapy option for Part B. Of note, selection of the recommended phase II dose (RPTD) will take into consideration safety information beyond the DLT period from all cohorts.

Once the MTD for irinotecan/pembrolizumab is established, 16 additional patients will be enrolled to Part B (investigators' choice- pembrolizumab plus irinotecan or pembrolizumab plus paclitaxel).

4.3.3 Definition of DLT for irinotecan

The DLT window will be 21 days. Adverse events will be graded according to the NCI CTCAE, Version 4.0. Dose limiting toxicity (DLT) will be defined as an adverse event occurring during the first cycle (21 days) of study drug administration considered at least possibly related to irinotecan and which meets any of the following criteria:

Hematologic toxicities

- Grade 4 absolute neutropenia lasting >7 days
- Grade ≥3 febrile neutropenia (T≥38.5°C)
- Grade 4 thrombocytopenia
- Grade ≥3 thrombocytopenia with clinically significant bleeding or any requirement for platelet transfusion
- Grade 3 thrombocytopenia lasting >7 day
- Grade 4 anemia or grade 3 anemia requiring transfusion

Other toxicities

- Any treatment-related death
- Any irinotecan dose reduction required during Cycle 1 due to potential toxicity
- Any other treatment toxicity that results in a missed dose of irinotecan or a dosing delay lasting >7 consecutive days during cycle 1
- Treatment (irinotecan-related) toxicity that results in C2D1 irinotecan being delayed
- Any irinotecan-related ≥grade 3 non-hematologic toxicity except the following:
    - Grade 3 nausea, vomiting, or diarrhea lasting ≤72 hr in the absence of maximal medical therapy
    - Alopecia
    - Grade 3 hypertension that recovers to ≤2 within 5 d
    - Grade 3 fatigue, asthenia, anorexia, fever, or constipation that resolves to ≤grade 2 within 72 hr
    - Grade 3 infusion-related reaction resolving within 6 hours with medical management
    - Isolated, asymptomatic changes in laboratory values (including electrolytes abnormalities that respond to medical intervention or are clinically insignificant, asymptomatic elevation of amylase/lipase and recovery to ≤Grade 1 or baseline in ≤5 days. ≥3 grade elevation of alkaline phosphatase if asymptomatic)
- NOTE: Grade ≥3 toxicity attributed solely to pembrolizumab and not to irinotecan (e.g. grade 4 vasculitis or other irAE) will not be considered a DLT. Replacement of patients removed for an AE attributed solely to pembrolizumab during DLT window may be considered pending discussion with principal investigator.

A subject who experiences a DLT may remain in the trial and continue receiving irinotecan at a lower dose (plus pembrolizumab) if the investigator deems potential benefits outweigh the risks. Subjects who do not complete Cycle 1 for reasons other than drug toxicity may be replaced.

4.3.4 Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab and Combination Therapy

Pembrolizumab: Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in withheld for drug- Table 3 below. See Section 4.10.1 for Supportive Care Guidelines, including use of corticosteroids.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity

event to the combination, to chemotherapy, either irinotecan or paclitaxel or to pembrolizumab alone, for adverse events listed in Table 3, both interventions must be held according to the criteria in Table 3 Dose Modifications and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 3.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combinations of chemotherapy, either irinotecan or paclitaxel and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to chemotherapy, either irinotecan or paclitaxel alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab Monotherapy and IO Combination

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

*Part B: Chemotherapy should generally be held if pembrolizumab held for drug-related toxicity. However, chemotherapy may continue at the discretion of the PI in patients experiencing clinical benefit (e.g. patient with grade 2 pneumonitis who is clinically stable and responding to treatment should be allowed to continue chemotherapy while holding pembrolizumab)

Paclitaxel: Paclitaxel should be administered, held and/or dose-reduced (to as low as 50 mg/m2) as per package insert and standard of care institutional practice (including maximal supportive care and growth factors). Filgrastim is not permitted within 24 hours prior to or following any paclitaxel infusion. Pegfilgrastim (Neulasta) is not permitted in this study.

As a general rule, in order to initiate each weekly treatment (at either full or modified dose), the following criteria must be met for paclitaxel:

- ANC ≥ 1000 /mm3 on day 1 of C2 and beyond, and day 8 and day 15 of every cycle
- Platelets ≥75,000/mm3

If these criteria are not met, treatment must be delayed until counts recover to this level.

NOTE: eligibility criteria for laboratory parameters must be met for C1D1 treatment.

Irinotecan: Irinotecan should be administered, held and/or dose-reduced (to as low as 50 mg/m2) as per package insert and standard of care institutional practice (including maximal supportive care and growth factors). Filgrastim is not permitted within 24 hours prior to or following any irinotecan infusion. Pegfilgrastim (Neulasta) is not permitted in this study.

As a general rule, in order to initiate each treatment (at either full or modified dose), the following criteria must be met for irinotecan:

- ANC ≥ 1000/mm3
- Platelets ≥75,000/mm3
- Diarrhea ≤Grade 1 within the preceding 24 hr

NOTE: eligibility criteria for laboratory parameters must be met for C1D1 treatment.

If chemotherapy is held for cytopenias, pembrolizumab should be administered per protocol in otherwise stable and afebrile patients. If a chemotherapy delay of >3 weeks is required due to delayed toxicity recovery, the patient must discontinue chemotherapy permanently from the study protocol (unless approved by the Principal Investigator). Patients with stable disease or better who require discontinuation of chemotherapy due to toxicity will also be allowed to continue on study with pembrolizumab monotherapy

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 Principal Investigator. The reason for interruption should be documented in the patient's study record.

4.4 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section5). Pembrolizumab treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (C2 and beyond) when given as monotherapy, and up to 1 day before or after the scheduled Day 1 of each cycle when given in combination with chemotherapy. Chemotherapy treatment can be administered up to 1 day before or after each scheduled infusion (assuming at least 6 days between chemotherapy infusions).

Chemotherapy should generally be held if pembrolizumab held for drug-related toxicity. If day 1 pembrolizumab is held for toxicity, day 1 chemotherapy can also be held (for up to 3 weeks) shifting the start of the cycle.

However, chemotherapy may continue while holding pembrolizumab at the discretion of the Principal Investigator in patients experiencing clinical benefit (e.g. patient with grade 2 pneumonitis who is clinically stable and responding to treatment).

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks for 24 months or 35 administrations (whichever comes first). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Pembrolizumab should be prepared and administered according to institutional guidelines.

Pembrolizumab should be administered at least 30 minutes *before* premedications for chemotherapy.

Paclitaxel: Paclitaxel (80 mg/m2) should be administered IV on days 1, 8, and 15 of a 21 day cycle as per standard practice. Treatment breaks will be allowed as per standard practice. If day 8 or day 15 chemotherapy is held it will be omitted from the cycle if not given within the allotted treatment window (±1 day).

Irinotecan: Irinotecan (125 mg/m2) should be administered IV on days 1, 8 out of every 21 day cycle as per standard practice. If day 8 chemotherapy is held, it will be omitted from the cycle (not delayed to day 15) if not given within the allotted treatment window (± 1day).

Chemotherapy (irinotecan or paclitaxel) treatment breaks (for up to 3 wk) will be allowed per institutional practice.

4.5 Duration of therapy

Subjects will continue to be treated with pembrolizumab or pembrolizumab plus chemotherapy until PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 treatments pembrolizumab (or 24 months of therapy, whichever comes first).

For a clinically stable subject with first radiologic evidence of PD (e.g. unconfirmed), it is at the discretion of the site investigator to continue treating the subject with pembrolizumab or pembrolizumab plus chemotherapy until PD is confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment.

Subjects who attain confirmed CR by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR.

For Part B: Patients with stable disease or better after 9 cycles (27 weeks) of pembrolizumab-based therapy will have the option to continue with pembrolizumab alone (unless the first PR/CR is noted at 27 weeks, in which case it should be confirmed before stopping chemotherapy). Patients who elect to stop chemotherapy (either due to patient preference or chemotherapy related toxicity) will be required to go off protocol therapy at the time of radiographic disease progression.

Prior to 27 weeks, patients with stable disease or better who require discontinuation of chemotherapy due to toxicity will also be allowed to continue on study with pembrolizumab monotherapy

4.6 Trial Blinding/Masking

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

4.7 Randomization or Treatment Allocation

All enrolled subjects will be allocated to receive pembrolizumab 200 mg IV Q3W in an unblinded fashion. Whether subjects receive additional chemotherapy depends on the part and stage of the study at time of allocation. For Part B patients enrolled after the run-in with irinotecan alone, the treating investigator may choose to use either paclitaxel or irinotecan (not both) based on prior therapy, co-morbidities, and patient preference.

4.8 Stratification

No stratification based on age, sex, or other characteristics will be used in this trial.

4.9 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The 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.

4.9.1 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 7.4.2.

Concomitant use of bone modifying agents allowed at the discretion of the treating provider.

4.9.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
    - Continuation of androgen deprivation therapy is allowed in patients with neuroendocrine castrate resistant prostate cancer
    - Concurrent somatostatin analog therapy is allowed (for control of hormone excess) provided patient has been on stable dose for at least two months and tumor progression has been documented
- 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 at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids unless used as a premedication for chemotherapy or to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of

physiologic doses of corticosteroids may be approved after consultation with the principle investigator.

- Note: Inhaled steroids are allowed for the management of asthma. Topical steroids are also allowed, as are periodic local steroid injections (e.g. for pain).
- Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast dye) is permitted.

- Filgrastim is not permitted within 24 hours prior to or following any paclitaxel or irinotecan infusion. Pegfilgrastim (Neulasta) is not permitted in this study.
- 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.

4.10 Rescue Medications & Supportive Care

4.10.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. 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 Events of Clinical Interest (ECI) reporting guidance but does not need to follow the treatment guidance. Refer to Section 4.3.4 for dose modification.

- 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). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms persist, endoscopic evaluation should be considered

  - Pembrolizumab-related[93]:

        - Treat diarrhea promptly with appropriate supportive care, including loperamide. Loperamide should be implemented at the first signs of 1) poorly or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea then 2 mg after every unformed stool (daily dose should not exceed 16 mg). Avoid loperamide if there is blood or mucous in the stool or if the diarrhea is accompanied by fever.
        - 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** suspected to be due to pembrolizumab that persists greater than 3 days, administer oral corticosteroids (e.g. 0.5 mg/kg/day or prednisone or equivalent).
        - For **Grade 3 or 4 diarrhea/colitis** suspected to be due to pembrolizumab that persists > 1 week, treat with intravenous steroids (equivalent of 1-2 mg/kg/d of prednisone) 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.
    - Subjects treated with irinotecan on Part B should receive loperamide as per standard practice.
        - 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.
- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)
    - For T1DM or Grade 3-4 Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

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

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours (e.g. equivalent of prednisone 1-2 mg/kg/d).
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- Renal Failure or Nephritis:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

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

4.11 Diet/Activity/Other Considerations

4.11.1 Diet

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

4.11.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.3 -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.

4.11.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in section 7.3.

4.11.4 Use in Nursing Women

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

4.12 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section6.7– Other Procedures.

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 4.5
- Unacceptable adverse experiences as described in Section 7.5
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject

- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later
  Note: 24 months of study medication is calculated from the date of first dose.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5 (Protocol Flow Chart) and Section 6.8.3(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 6.8.3). 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.

4.12.1 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

4.13 Subject Replacement Strategy

All patients who receive any study therapy will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any study therapy may potentially be replaced after discussion with the principal investigator. Subjects who have received any dose of study therapy will not be replaced. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. However, they will not be replaced.

4.14 Stopping Rule

A stopping rule for safety will halt accrual to the study and prompt reevaluation of pembrolizumab dose if unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 4 weeks) is observed at a frequency of ≥33% in any treatment group. If we have a pembrolizumab/irinotecan cohort, then we will first recruit six patients for pembrolizumab/irinotecan at 125 mg/m2. If ≥2 patients experience dose-limiting toxicity, then 6 additional patients will be treated at 100 mg/m2 plus pembrolizumab. If ≥2 patients experience dose-limiting toxicity at this dose level, then irinotecan will be deemed intolerable and dropped as a treatment option.

4.15 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug
5. 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.

5 TRIAL FLOW CHART

5.1 Pembrolizumab alone

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 2)	1	2	3	4	5	6	7	8		Safety Follow-up [o]	Follow Up Visits	Survival Follow-Up[a]
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	EOT [n]	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration [b]		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X[k]	X
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Vital Signs, Weight and Height[c]	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X[d]	X	X	X	X	X	X	X	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum □-HCG	X[e]												
PT/INR and aPTT[f]	X[d]												
CBC with Differential[f]	X[d]	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[f]	X[d]	X	X	X	X	X	X	X	X	X	X		
LDH[f]	X[d]		X	X	X	X	X	X	X	X			
Urinalysis	X[d]												
T3, FT4 and TSH[f]	X[d]		X		X		X		X	X	X		
Efficacy Measurements													
Tumor Imaging	X[g,gg]	X[h]								X[i]		X[k]	
Brain imaging[m]	x[m]												

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 2)	1	2	3	4	5	6	7	8		Safety Follow-up [o]	Follow Up Visits	Survival Follow-Up[a]
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	EOT [n]	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Newly Obtained Tissue Collection	X[l]												
Correlative Studies Blood Collection[j]		X[p]	X	X						X[jj]			
Archival Tissue Collection	X[p]												

a) 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 +/- 14 d to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (See Section6.8.3.3)
b) The window for each visit is ±3 days unless otherwise noted.
c) Height will be measured at Visit 2 only.
d) ECOG Performance Status and Laboratory tests for screening are to be performed within 14 days prior to the first dose of trial treatment.
e) For women of reproductive potential, a serum or urine pregnancy test should be performed within 14 days prior to first dose of trial treatment. Pregnancy tests (urine or serum) should be repeated if required by local guidelines and at the discretion of the investigator.
f) Day 1 lab samples (all cycles) can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle.
g) Screening tumor imaging will be performed within 28 days prior to C1D1. Acceptable studies include multiphase CT or MRI (with or without FDG-PET). Contrast required unless contraindicated due to allergy or renal dysfunction in which case non-contrast scan allowed if radiology has confirmed pt still has measureable disease.
gg) When available, the imaging within 1- 12 months of screening scan will be retrospectively evaluated by local institution radiologists to assess baseline TGR.
h) The first on-study imaging time point will be performed at 9 weeks (63 ± 7 days) calculated from C1D1 and will continue to be performed Q9W (63 ± 7 days) for 6 months (27 weeks) then Q12W (84 ± 7 days) thereafter, or earlier if clinically indicated. Weeks are in reference to calendar week, and should not be adjusted for treatment dosing delays.
i) In subjects who discontinue study therapy without confirmed PD per RECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
j) Whole blood samples for correlative studies should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and again at treatment progression. Blood will be collected in four 10mL BD Sodium Heparin[N] (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF. With approval of the PI, blood can be processed on site (per Biospecimen Collection Manual) to accommodate Friday or holiday treatment schedule at subsites (and shipped to the UCSF Immune Monitoring Core the following week).
jj) Sample should ideally be drawn at the time of tumor progression (which may or may not be the same time as treatment discontinuation). This sample may be drawn at EOT and before progression if patient not likely to return for a study visit at progression.
k) Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed according to the "on treatment" study schedule by radiologic imaging to monitor disease status if possible (every 63 days +/- 7 days for a total of six months after enrollment, then every 12 weeks ± 14 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study.
l) Baseline tumor biopsy should be performed d-28 to d-1 and may be omitted if the tumor is inaccessible and/or a biopsy is thought to be too high risk. Cycle 1 D1 study drug should be given no sooner than 24 hours after the tumor biopsy.
m) Baseline brain MRI with contrast is preferable; however, CT scan of brain with contrast may be substituted at discretion of investigator.
n) End of treatment (EOT) is defined as date patient and/or treating physician decides to discontinue study drug. Patients who discontinue study treatment should not be considered withdrawn from the study. They should undergo EOT visit and enter the post-treatment (follow-up) period. EOT visit should occur within 30 days of last dose of study drug or the decision to discontinue study drug. If a patient discontinues study drug at a scheduled visit, the EOT visit can occur the same day. The EOT assessments (besides imaging) do not need to be repeated if done within the preceding14 days. Imaging does not need to be repeated if done in preceding 4 weeks as noted above (see "i"). The EOT visit can be combined with a safety follow-up visit.
o) Safety follow-up should occur 30 days (+/- 7 days) after last dose of study drug and should continue at monthly intervals until resolution of toxicity to < grade 2..p. Day 1 Cycle 1 Research blood sample can be drawn up to 7 days prior to Day 1 as long as no prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the lab draw; and no prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the lab draw.
p) If fresh tumor tissue cannot be collected, the lead-site PI may approve the use of archival tissue. The use of archival tissue in lieu of a fresh tumor biopsy will be evaluated on a case-by-case basis and must be approved by the overall study (lead-site) PI. Please see section 6.6

5.2 Pembrolizumab plus irinotecan

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**																								**End of Treatment**	**Post-Treatment**		
														To be repeated beyond 8 cycles															
Treatment Cycle/Title:	Screening	1			2			3			4			5			6			7			8				Safety Follow-up[o]	Follow Up Visits	Survival Follow-Up[a]
Scheduling Window (Days)[kk]:	-28 to -1				± 1			± 1			± 1			± 1			± 1			± 1			± 1			EOT[n]	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures																													
Day of cycle		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Informed Consent	X																												
Inclusion/Exclusion Criteria	X																												
Demographics and Medical History	X																												
Prior and Concomitant Medication Review	X	X			X			X			X			X			X			X			X			X	X		
Pembrolizumab Administration [b]		X			X			X			X			X			X			X			X						
Irinotecan administration[k]		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X					
Post-study anticancer therapy status																											X	X[k]	X
Survival Status																													X
Clinical Procedures/Assessments																													
Review Adverse Events	X	X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		
Full Physical Examination	X																									X			
Directed Physical Examination		X			X			X			X			X			X			X			X						
Vital Signs, Weight and Height[c]	X	X			X			X			X			X			X			X			X			X			
ECOG Performance Status	X[d]	X			X			X			X			X			X			X			X			X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																													
Pregnancy Test – Urine or Serum □-HCG	X[e]																												
PT/INR and aPTT[f]	X[d]																												
CBC with Differential[f]	X[d]	X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8		Safety Follow-up[o]	Follow Up Visits	Survival Follow-Up[a]
Scheduling Window (Days)[kk]:	-28 to -1		± 1	± 1	± 1	± 1	± 1	± 1	± 1	EOT[n]	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Comprehensive Serum Chemistry Panel[f]	X[d]	X	X	X	X	X	X	X	X	X	X		
LDH[f]	X[d]	X	X	X	X	X	X	X	X	X			
Urinalysis	X[d]												
T3, FT4 and TSH[f]	X[d]			X		X		X		X	X		
Efficacy Measurements													
Tumor Imaging	X[g,gg]	X[h]								X[i]		X[k]	
Brain imaging[m]	x[m]												
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Newly Obtained Tissue Collection	X[l]												
Correlative Studies Blood Collection[j]		X[p]	X[f]	X[f]						X[jj]			
Archival Tissue Collection	X[q]												

a) 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 +/- 14 d to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (See Section6.8.3.3)
b) The window for each visit is ±1 days C2D1 and beyond unless receiving pembrolizumab monotherapy (in which case ±3 days).
c) Height will be measured at Visit 2 only.
d) ECOG Performance Status and Laboratory tests for screening are to be performed within 14 days prior to the first dose of trial treatment.
e) For women of reproductive potential, a serum or urine pregnancy test should be performed within 14 days prior to first dose of trial treatment. Pregnancy tests (urine or serum) should be repeated if required by local guidelines and at the discretion of the investigator.
f) Day 1 lab samples (all cycles) can be collected up to 72 hours prior to the scheduled time point. Day 8 lab samples should be drawn within 24 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle.
g) Screening tumor imaging will be performed within 28 days prior to C1D1. Acceptable studies include multiphase CT or MRI (with or without FDG-PET). Contrast required unless contraindicated due to allergy or renal dysfunction in which case non-contrast scan allowed if radiology has confirmed pt still has measureable disease.
gg) When available, the imaging within 1- 12 months of screening scan will be retrospectively evaluated by local institution radiologists to assess baseline TGR.
h) The first on-study imaging time point will be performed at 9 weeks (63 ± 7 days) calculated from C1D1 and will continue to be performed Q9W (63 ± 7 days) for 6 months (27 weeks) then Q12W (84 ± 7 days) thereafter, or earlier if clinically indicated. Weeks are in reference to calendar week, and should not be adjusted for treatment dosing delays.
i) In subjects who discontinue study therapy without confirmed PD per RECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
j) Whole blood samples for correlative studies should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and again at treatment progression. Blood will be collected in four 10mL BD Sodium Heparin[N] (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF.). With approval of the PI, blood can be processed on site (per Biospecimen Collection Manual) to accommodate Friday or holiday treatment schedule at subsites (and shipped to the UCSF Immune Monitoring Core the following week).
k) Patients with stable disease or better after 8 cycles (27 weeks) of irinotecan will have the option to continue with pembrolizumab alone (unless the first PR/CR is noted at 27 weeks, in which case it should be confirmed before stopping chemotherapy). Patients who elect to stop irinotecan (either due to patient preference or chemotherapy related toxicity) will be required to go off protocol therapy at the time

of radiographic disease progression. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed according to the "on treatment" study schedule by radiologic imaging to monitor disease status if possible (every 63 days +/- 7 days for a total of six months after enrollment, and then every 12 weeks ± 14 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study.

kk) The window for each chemotherapy visit is ±1 day unless otherwise noted (C1D8 and beyond), provided no less than 6 days between chemotherapy administrations.

l) Baseline tumor biopsy should be performed d-28 to d-1 and may be omitted if the tumor is inaccessible and/or a biopsy is thought to be too high risk. Cycle 1 D1 study drug should be given no sooner than 24 hours after the tumor biopsy.

m) Baseline brain MRI with contrast is preferable; however, CT scan of brain with contrast may be substituted at discretion of investigator.

n) End of treatment (EOT) is defined as date patient and/or treating physician decides to discontinue study drug. Patients who discontinue study treatment should not be considered withdrawn from the study. They should undergo EOT visit and enter the post-treatment (follow-up) period. EOT visit should occur within 30 days of last dose of study drug or the decision to discontinue study drug. If a patient discontinues study drug at a scheduled visit, the EOT visit can occur the same day. The EOT assessments (besides imaging) do not need to be repeated if done within the preceding14 days. Imaging does not need to be repeated if done in preceding 4 weeks as noted above (see "i"). The EOT visit can be combined with a safety follow-up visit.

o) Safety follow-up should occur 30 days (+/- 7 days) after last dose of study drug and should continue at monthly intervals until resolution of toxicity to < grade 2.

p) Day 1 Cycle 1 Research blood sample can be drawn up to 7 days prior to Day 1 as long as no prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the lab draw; and no prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the lab draw.

q) If fresh tumor tissue cannot be collected, the lead-site PI may approve the use of archival tissue. The use of archival tissue in lieu of a fresh tumor biopsy will be evaluated on a case-by-case basis and must be approved by the overall study (lead-site) PI. Please see section 6.6

5.3 Pembrolizumab plus paclitaxel

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**																							**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening	1			2			3			4			To be repeated beyond 8 cycles 5			6			7			8				Safety Follow-up[o]	Follow Up Visits	Survival Follow-Up[a]
Scheduling Window (Days)[kk]:	-28 to -1				± 1			± 1			± 1			± 1			± 1			± 1			± 1			EOT[n]	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures																												
Day of cycle		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Informed Consent	X																												
Inclusion/Exclusion Criteria	X																												
Demographics and Medical History	X																												
Prior and Concomitant Medication Review	X	X			X			X			X			X			X			X			X			X	X		
Pembrolizumab Administration[b]		X			X			X			X			X			X			X			X						
Paclitaxel administration[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status																											X	X[k]	X
Survival Status																													X
Clinical Procedures/Assessments																													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X																									X			
Directed Physical Examination		X			X			X			X			X			X			X			X						
Vital Signs, Weight and Height[c]	X	X			X			X			X			X			X			X			X			X			
ECOG Performance Status	X[d]	X			X			X			X			X			X			X			X			X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																													
Pregnancy Test – Urine or Serum □-HCG	X[e]																												
PT/INR and aPTT[f]	X[d]																												
CBC with Differential[f]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8		Safety Follow-up [o]	Follow Up Visits	Survival Follow-Up[a]
Scheduling Window (Days)[kk]:	-28 to -1		± 1	± 1	± 1	± 1	± 1	± 1	± 1	EOT [n]	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Comprehensive Serum Chemistry Panel[f]	X[d]	X	X	X	X	X	X	X	X	X	X		
LDH[f]	X[d]	X	X	X	X	X	X	X	X	X			
Urinalysis	X[d]												
T3, FT4 and TSH[f]	X[d]			X		X		X		X	X		
Efficacy Measurements													
Tumor Imaging	X[g,gg]	X[h]								X[i]		X[k]	
Brain imaging[m]	x[m]												
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Newly Obtained Tissue Collection	X[l]												
Correlative Studies Blood Collection[j]		X[p]	X[f]	X[f]						X[jj]			
Archival Tissue Collection	X[q]												

a. 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 +/- 14 d to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (See Section 6.8.3.3)
b. The window for each visit is ±1 days C2D1 and beyond unless receiving pembrolizumab monotherapy (in which case ±3 days).
c. Height will be measured at Visit 2 only.
d. ECOG Performance Status and Laboratory tests for screening are to be performed within 14 days prior to the first dose of trial treatment.
e. For women of reproductive potential, a serum or urine pregnancy test should be performed within 14 days prior to first dose of trial treatment. Pregnancy tests (urine or serum) should be repeated if required by local guidelines and at the discretion of the investigator.
f. Day 1 lab samples (all cycles) can be collected up to 72 hours prior to the scheduled time point. Day 8 and Day 15 lab samples should be drawn within 24 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle.
g. Screening tumor imaging will be performed within 28 days prior to C1D1. Acceptable studies include multiphase CT or MRI (with or without FDG-PET). Contrast required unless contraindicated due to allergy or renal dysfunction in which case non-contrast scan allowed if radiology has confirmed pt still has measureable disease
gg. When available, the imaging within 1-12 months of screening scan will be retrospectively evaluated by local institution radiologists to assess baseline TGR.
h. The first on-study imaging time point will be performed at 9 weeks (63 ± 7 days) calculated from C1D1 and will continue to be performed Q9W (63 ± 7 days) for 6 months (27 weeks) then Q12W (84 ± 7 days) thereafter, or earlier if clinically indicated. Weeks are in reference to calendar week, and should not be adjusted for treatment dosing delays

i. In subjects who discontinue study therapy without confirmed PD per RECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
j. Whole blood samples for correlative studies should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and again at disease progression. Blood will be collected in four 10mL BD Sodium HeparinN (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF. With approval of the PI, blood can be processed on site (per Biospecimen Collection Manual) to accommodate Friday or holiday treatment schedule at subsites (and shipped to the UCSF Immune Monitoring Core the following week).
jj. Sample should ideally be drawn at the time of tumor progression (which may or may not be the same time as treatment discontinuation). This sample may be drawn at EOT and before progression if patient not likely to return for a study visit at progression.
k. Patients with stable disease or better after 8 cycles (27 weeks) of paclitaxel-based therapy will have the option to continue with pembrolizumab alone (unless the first PR/CR is noted at 27 weeks, in which case it should be confirmed before stopping chemotherapy). Patients who elect to stop chemotherapy (either due to patient preference or chemotherapy related toxicity) will be required to go off protocol therapy at the time of radiographic disease progression. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed according to the “on treatment” study schedule by radiologic imaging to monitor disease status if possible (every 63 days +/- 7 days for a total of six months after enrollment, and then every 12 weeks ± 14 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study.
kk. The window for each chemotherapy visit is ±1 day unless otherwise noted (C1D8 and beyond), provided no less than 6 days between chemotherapy administrations.
l. Baseline tumor biopsy should be performed d-28 to d-1 and may be omitted if the tumor is inaccessible and/or a biopsy is thought to be too high risk. Cycle 1 D1 study drug should be given no sooner than 24 hr after the tumor biopsy.
m. Baseline brain MRI with contrast is preferable, however CT scan of brain with contrast may be substituted at discretion of investigator
n. End of treatment (EOT) is defined as date patient and/or treating physician decides to discontinue study drug. Patients who discontinue study treatment should not be considered withdrawn from the study. They should undergo EOT visit and enter the post-treatment (follow-up) period. EOT visit should occur within 30 days of last dose of study drug or the decision to discontinue study drug. If a patient discontinues study drug at a scheduled visit, the EOT visit can occur the same day. The EOT assessments (besides imaging) do not need to be repeated if done within the preceding14 days. Imaging does not need to be repeated if done in preceding 4 weeks as noted above (see “i”). The EOT visit can be combined with a safety follow-up visit.
o. Safety follow-up should occur 30 days (+/- 7 days) after last dose of study drug and should continue at monthly intervals until resolution of toxicity to < grade 2
p. Day1 Cycle 1 Research blood sample can be drawn up to 7 days prior to Day 1 as long as no prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the lab draw; and no prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the lab draw.
q. If fresh tumor tissue cannot be collected, the lead-site PI may approve the use of archival tissue. The use of archival tissue in lieu of a fresh tumor biopsy will be evaluated on a case-by-case basis and must be approved by the overall study (lead-site) PI. Please see section 6.6

6 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5 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 investigator and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.2 Administrative Procedures

6.2.1 Informed Consent

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

6.2.2 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 requirements, applicable laws and regulations and Sponsor requirements.

6.2.3 Review of 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.

6.2.4 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 clinically significant by the Investigator. Details regarding the disease (high grade

NEC) for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.2.5 Prior and Concomitant Medications Review

6.2.5.1 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.

6.2.5.2 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.

6.2.6 Disease Details and Treatments

6.2.6.1 Disease Details

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

6.2.6.2 Prior Treatment Details

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

6.2.6.3 Subsequent Anti-Cancer Therapy Status

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

6.2.7 Assignment of Screening Number

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements. All patients will have a unique screening identification number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only on screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

6.2.8 Assignment of Randomization Number

All eligible subjects will be allocated to a treatment by non-random assignment (depending on whether Part A or Part B open to enrollment) and will receive an allocation number. The allocation number identifies the subject for all procedures occurring after treatment allocation. Once an allocation number is assigned to a subject, it can never be re-assigned to another

subject. The allocation number will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS).

A single subject cannot be assigned more than one allocation number.

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

Interruptions from the protocol specified treatment for greater than 12 weeks between pembrolizumab doses due for non-drug-related or administrative reasons require consultation between the investigator and Principle Investigator and written documentation of the collaborative decision on subject management.

The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered. Pembrolizumab should be prepared and administered according to institutional guidelines. Compliance with scheduled chemotherapy will also be tracked.

6.3 Clinical Procedures/Assessments

6.3.1 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 (Appendix 2). 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 **Error! Reference source not found.** for detailed information regarding the assessment and recording of AEs.

6.3.2 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,

6.3.3 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.

6.3.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the

Trial Flow Chart (Section5). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.3.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. Screening ECOG status may be completed by telephone.

6.3.6 Tumor Imaging and Assessment of Disease

Radiographic evaluations and tumor measurements will be performed at screening (within 28 days prior to the first dose of pembrolizumab), and then every 9 weeks (+/- 7 days) thereafter x 6 months (27 weeks) and every 12 weeks thereafter), including the off study evaluation. Weeks are in reference to calendar week, and should not be adjusted for treatment dosing delays. When available, imaging performed within 1-12 months of the screening scan will be collected. In order to assess baseline tumor growth rate (TGR_0), imaging within 1-6 months of the screening scan will be assessed first. Scans 6- 12 months prior to screening scan will be analyzed if additional information about baseline tumor growth rate kinetics is required to put on-study TGR data in perspective (e.g., each patient serves as his/her own control).

Imaging should include multiphase CT chest/abdomen/pelvis with contrast (or MRI abdomen/pelvis with contrast and chest CT+/- contrast-at physician discretion). If FDG-PET imaging was performed with baseline imaging, it may be included with follow-up imaging as long as cross sectional imaging is contrast-enhanced multiphase scan. When possible, the same imaging modality should be used throughout the study in given patient.

RECIST v1.1 will be used to determine radiographic response for primary endpoint. However, immune-related response criteria (irRC) will also be assessed (See Appendix 4).

6.3.7 Baseline brain imaging

A baseline brain MRI (with contrast) will be performed on all patients at screening. CT of the brain (with contrast) may be substituted at the discretion of the investigator.

6.4 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 5.

Table 5 Laboratory Tests

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

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

Laboratory tests for screening should be performed within 14 days prior to the first dose of treatment. Pre-dose laboratory procedures (Day 1, all cycles) 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.

Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of the treatment if labs are within normal range.

6.4.1 Serum/Urine β-hCG

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 14 days of receiving the first dose of study medication, and must be excluded in the event of a positive or borderline-positive test result. If a urine test is positive or borderline, a serum β-hCG test will be required. Pregnancy tests (urine or serum) should be repeated per local guidelines and at the discretion of the investigator. The results of the pregnancy testing will not be recorded.

6.5 Post-study Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer 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 the new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

6.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

All efforts should be made to collect a fresh tumor tissue biopsy at screening/ pre-treatment to determine patient eligibility. However, if fresh tumor tissue cannot be collected, the overall study (lead-site) PI may approve the use of archival tissue. The use of archival tissue in lieu of a fresh tumor biopsy will be evaluated on a case-by-case basis and must be approved by the overall study (lead-site) PI.

If archival tissue is to be used, the tissue sample must meet all following criteria;

1. Collected within 6 months prior to the start of study treatment,
2. Collected after the patient's last line of therapy (with no treatment intervention between time of collection and start of study treatment),
3. Collected from either primary tumor or metastatic site in the context of routine clinical care (samples taken for prior research study are not allowed),
4. Minimum sample requirements:
    a. Core needle biopsy (or larger sample, e.g. excisional biopsy or surgical Tru-Cut® biopsy)
    b. # of slides: 10 unstained cut 5um slides OR minimum of one x 1cm core needle biopsy
    c. Formalin-fixed paraffin-embedded (FFPE) (with fresh frozen if available)

For further details of archival sample shipment and processing requirements please reference the study lab/procedure manual.

6.6.1 Fresh Tumor Biopsy for Correlative Studies

Subjects will undergo biopsy of metastatic lesion (or primary site if safer and/or more accessible) at the time of screening (d-28 to d-1) which will be processed and banked for future correlative studies as outlined in Section 3.2.3.3.

Ideally, at least four core tumor biopsies (and a minimum of two core biopsies) will be obtained (via up to 4 passes; multiple core biopsies may be acquired with each pass):

a. Fresh frozen: Freshly harvested tissues should be flash frozen in liquid nitrogen or an ethanol/dry ice bath. Flash freezing the sample immediately helps to prevent sample degradation. Tissues should be stored at – 80°C or in liquid nitrogen until ready for shipping.

b. Formalin fixed paraffin embedded (FFPE): Fresh tissue sample will be placed into a 60 mL pre-filled polypropylene container that contains 30 mL of 10% neutral buffered formalin (NBF) WITHIN 1 MINUTE of collection. After 16-24 hours, sample will be processed and paraffin-embedded.

Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued. Samples will be sent to the Cancer Immunotherapy Lab (CIL) at UCSF (See Biospecimen Collection Manual):

Cancer Immunotherapy Lab
[redacted]
University of California, San Francisco
[redacted]

Additional details regarding tissue processing are provided in the accompanying Biospecimen Collection Manual (including shipping and handling information related to samples for analysis).

6.6.2 Blood collections for Correlative Studies

Research blood samples will be collected at four time points. Each time, four 10mL BD Sodium Heparin^{N} (NH) 158 USP Units Plus Blood Collection Tubes (green-top) will be collected and sent to the UCSF CIL (See Biospecimen Collection Manual for details).

Cancer Immunotherapy Lab
[redacted]
University of California, San Francisco
[redacted]

Correlative studies will be performed as outlined in Section 3.2.3.3.

Additional details are provided in the Biospecimen Collection Manual.

6.7 Other Procedures

6.7.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section **Error! Reference source not found.**- Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study (described in Section6.8.3).

6.7.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

6.8 Visit Requirements

Visit requirements are outlined in Section 5- Trial Flow Chart. Specific procedure-related details are provided above in Section 6- Trial Procedures.

6.8.1 Screening

Approximately 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 14 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 14 days prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened ad infinitum after failing to meet the inclusion/ exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening test if performed within the specified time frame and the inclusion/ exclusion criteria is met. Subjects who are rescreened will retain their original screening number.

6.8.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 5). Specific procedure related details are provided above in the Trial Procedures (Section 6).

6.8.3 Post-Treatment Visits

6.8.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (+/- 7d) 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 monthly (+/- 7d) until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

6.8.3.2 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 according to the "on treatment" study schedule by radiologic imaging to monitor disease status if possible (every 63 days +/- 7 days for a total of six months, and every 12 weeks ± 14 days). 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. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

6.8.3.3 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 +/- 14 d to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7 ASSESSING AND RECORDING ADVERSE EVENTS

7.1 Definition of an Adverse Event

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

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

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

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

Adverse events 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.

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

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 6.8.3.1.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. [redacted]

7.3 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. [redacted]

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

7.4.1 Serious Adverse Events

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

- Results in death;

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

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of the first screening biopsy or first dose of treatment, whichever is earlier, 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.

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. [redacted] at the time of submission to FDA.

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

7.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

For the time period beginning at the first screening biopsy or first dose of treatment, whichever is earlier, through treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at the first screening biopsy or first dose of treatment, whichever is earlier, through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1) an overdose of Merck product, as defined in Section 7.2- Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.5 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 6 Evaluating Adverse Events

An investigator, who is a qualified provider, 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 relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.6 Sponsor Responsibility for Reporting Adverse Events

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

8 STATISTICAL PLAN

8.1 Statistical Analysis Plan Summary

This study is an open-label adaptive pilot study of pembrolizumab-based therapy in previously treated PD-NECs. Given the rarity of this disease, PD-NECs of all sites (excluding SCLC and MCC) will be included (and pooled); since no standard therapy exists for refractory disease and treatment algorithms, (e.g. NCCN guidelines) typically recommend treating according to SCLC guidelines.

The study is designed in two parts. Part A is for pembrolizumab-only treated patients, Part B is for patients treated with pembrolizumab plus chemotherapy (physician's choice, irinotecan or paclitaxel). Part A is based on Simon's two-stage design, and enrollment to Part B will only occur if Part A fails after the first stage.

The analysis will include all subjects treated (ITT) and the primary efficacy endpoint will be radiographic response by RECIST1.1 (investigator reported). Count and percentage of AE will be also provided. The total sample size needed to attain 80% power will be either 35 (all treated by pembrolizumab) or 36-42 (first 14 treated by pembrolizumab and next 22-28 treated by pembrolizumab/chemotherapy) with overall type I error of 0.1.

8.1.1 Primary objective

Objectives and hypotheses of the study are stated in Section2.

The primary efficacy endpoint will be best Overall Response Rate (ORR) by RECIST 1.1 (investigator reported). ORR is defined as the proportion of the subjects in the analysis population who have a radiographic response according to RECIST 1.1 as assessed by investigator.

For subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of disease progression or death.

8.1.2 Other objectives

- Progression free Survival (PFS) – RECIST 1.1 assessed by investigator

PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

- Overall survival (OS)

OS is defined as the time from first day of study treatment to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

- Safety and Tolerability

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab-based therapy in subjects with previously treated poorly differentiated NEC. The safety analysis

will be based on subjects who experienced toxicities as defined by CTCAE, version 4.0 criteria (Appendix 2). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section7.4.2.

8.2 Statistical Analysis Plan

8.2.1 Analysis populations

Efficacy: The All Subjects as Treated (ASaT, ITT) population will be used for the analysis of ORR, PFS and OS. The ASaT population consists of all subjects who received at least one dose of the study treatment. If the final study consists of both Part A and Part B, the analysis will be done separately for each part.

The analysis population for DOR consists of responders.

Safety: The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.2 Primary Efficacy Objective: Overall response rate

The point estimate and 95% confidence interval of overall response rate will be obtained for Part A and B (if available) separately.

The sample size calculation is based on the adaptive Simon's two-stage design.[94]

Part A: We will first recruit patients for pembrolizumab only (Part A). The null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative (26% RR). In the first stage, 14 patients will be accrued.

1) If >2 responses (confirmed or unconfirmed) in the first 14 patients by 18 week scan, 21 additional patients will be accrued (stage 2) for a total of 35 patients treated with pembrolizumab alone (Part A). The null hypothesis will be rejected if 7 or more responses are observed in 35 patients. This yields a type I error rate of 0.05 and power of 80% when the true response rate is 26%.

2) If there are 2 or fewer responses in the first 14 patients by 18 weeks, the single treatment will be replaced by pembrolizumab/chemotherapy (Part B). Investigator may choose either two weeks on, one week off administration of irinotecan or weekly paclitaxel. We will now first recruit another 6 patients for pembrolizumab/irinotecan (safety lead-in, Part B) at 125 mg/m2. If more than 2 patients experiencing dose-limiting toxicity, then 6 additional patients will be treated at 100 mg/m2 plus pembrolizumab. After the safety lead-in, 16 additional patients will be accrued for a total of 22 patients treated with pembrolizumab/chemotherapy (Part B), which will provide 80% of power based on one-side binomial at a type I error rate of 0.05 to test the true response rate of 31% against of null hypothesis of 10%.

The total sample size needed to attain 80% power will be either 35 (all treated by pembrolizumab) or 36-42 (first 14 treated by pembrolizumab and next 22-28 treated by pembrolizumab/chemotherapy) with overall type I error of 0.1.

After all 14 patients have been enrolled to stage I of part A, and while waiting for their 18-week efficacy data, up to six patients can be accrued to the safety lead-in for Part B. This will help to avoid significant delays in accrual to the study, and streamline the transition to part B if required due to a lack of efficacy in Part A. If >2 responses occur in Part A Stage 1 before Part B safety lead-in is completed, a decision can be made whether to complete Part B safety lead-in versus discontinue and proceed with Part A Stage 2 depending on analysis of results and toxicity at that time.

8.2.3 Secondary Efficacy Objectives

DOR: Duration of Response is defined as the time from the date of first response (CR or PR) until the date of disease progression or death. Kaplan-Meier method will be used to summarize DOR. Median DOR and its 95% confidence interval will be obtained for Part A and B (if available) separately.

PFS: Progression free survival is defined as the time from the first day of study treatment with protocol therapy to the date of documented tumor progression or death due to any cause, whichever occurs first, as determined by irRC for irPFS and RECIST v1.1 for PFS. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Kaplan-Meier method will be used to summarize progression free survival; median irPFS and PFS will be estimated with 95% confidence interval for Part A and B (if available) separately.

OS: Overall survival is defined as the time from the first day of study treatment with protocol therapy to the date of death due to any cause. Kaplan-Meier method will be used to summarize OS. Median OS and its 95% confidence interval will be obtained for Part A and B (if available) separately.

8.2.4 Statistical Methods for Safety Analyses

All subjects will be evaluated for toxicity from the time of the first treatment with pembrolizumab. Adverse events occurring from the start of treatment until 30 days after the end of treatment will be summarized by maximum toxicity grade. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. The toxicity grade for laboratory data will be calculated using CTCAE v4.0 and the lab data will be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy. All treatment related adverse events will be graded using NCI CTCAE v4.0.

Verbatim description of treatment-related adverse events will be mapped to thesaurus terms. Adverse events assessed as related to study drug and serious adverse events will be summarized similarly. Adverse events leading to treatment discontinuation will also be summarized. Safety analysis will include a tabulation of all toxicities by grade. The frequency of toxicities will be tabulated separately for each cohort. Count and percentage of AE will be provided.

In Part B of the study, there will be a safety lead-in of six patients if needed, with de-escalation if DLT is encountered. The need for a safety lead-in will be determined at the time Part B begins based on the available clinical data at that time.

8.3 Statistical Analysis Plan Summary: Exploratory Objectives

8.3.1 Molecular Characteristics of NEC

Blood and tissue samples will be analyzed to characterize baseline and/or changes in a variety of parameters- e.g. proliferation indices, metabolic profile, protein expression (candidate approach or large scale), gene expression (e.g., transcriptomics), genomic signature (mutations), immunologic profile, and other molecular features of NEC (e.g., methylome profile). We will explore associations between molecular characteristics and clinical outcomes (ORR, DOR, PFS, OS). Additional tissue- and/or blood-based biomarker research to identify factors important for pembrolizumab and/or NEC therapy may also be pursued (e.g., exosomes, microRNAs, microbiome). Sample analysis plans are noted in the below.

8.3.1.1 Immune Infiltration

Immune cell subsets and localization will be assessed by immunohistochemistry (IHC) in baseline tissue biopsy samples. Markers will include CD3, CD8 and FoxP3. Wilcoxon rank-sum test will be used to assess whether there is a relationship between any of the immune cell subsets and objective response, and with long/short-term survivors. Furthermore, Cox-proportional hazard models will be applied to assess if there is relationship between any of the immune cell subsets and DOR, PFS and OS, respectively.

8.3.1.2 PD-L1 staining and Ki67 staining

PD-L1 IHC will be performed by Qualtek (CLIA-certified) on baseline tumor biopsies using Merck's 22C3 antibody. Descriptive statistics will be used to summarize PD-L1 scores. Wilcoxon rank-sum test will be used to assess whether there is a relationship between PD-L1 score and objective response, and with long/short-term survivors. Furthermore, Cox-proportional hazard models will be applied to assess if there is relationship between PD-L1 score and DOR, PFS and OS, respectively.

Ki67 proliferative index will be assessed using commercially available techniques. Descriptive statistics will be used to summarize KI67 proliferative index. Wilcoxon rank-sum test will be used to assess whether there is a relationship between Ki67 proliferative index and objective response, and with long/short-term survivors. Furthermore, Cox-proportional hazard models will be applied to assess if there is relationship between a Ki67 proliferative index and DOR, PFS and OS, respectively.

8.3.1.3 T Cell Receptor (TCR) Repertories

TCR clonotypes will be characterized at baseline (blood and pre-treatment tumor biopsy), as will changes in the T cell immune response over time (blood). For each subject, a baseline tumor biopsy will be obtained and blood will be collected at screening, C2D1, C3D1 and at progression. T cell repertoire before, during and after treatment will be assessed by next-generation sequencing. Besides the number of unique clonotypes and read depth, the TCR repertoire diversity will be assessed by clonality diversity index and clonality. Repertoire overlap will be measured by Baroni-Urbani and Buser index, and changes in clonotypes counts between sequencing experiments will be measured using Morisita's distance. The diversity index will be compared by paired-Wilcoxon rank-sum test between baseline and the post-treatment time point. Wilcoxon rank-sum test will also be used to assess whether the diversity index is different between responders vs. non-responders (defined by objective response), and between subjects who have progression at 18 weeks vs. those who have not progressed in each arm.

8.3.1.4 Mutational Profile and Mutation Burden

Mutation profile will be performed in baseline biopsy tissues. The mutation profile and average number of somatic mutations per tumor will be assessed by Wilcoxon rank-sum test between responders vs. non-responders (defined by objective response, complete and partial), and between subjects who have progression at 18 weeks vs. those who have not progressed.

8.3.1.5 Circulating Immune Cells

For each subject, blood will be collected at screening, C2D1, C3D1 and at progression. Flow cytometry will be performed to assess changes in circulating immune cell subsets with treatment, including effector T cells, regulatory T cells, and myeloid cells. The Wilcoxon rank-sum test will be used to assess differences in immune subsets in responders vs. non-responders (defined by objective response), and between subjects who have progression at 18 weeks vs. those who have not progressed within each group. Changes in immune cell subsets in individual subjects with treatment will be assessed using paired Wilcoxon Signed-rank test.

Objective (if proceed to Part B): To explore changes in circulating TCR profiles and circulating immune cells in patients treated with pembrolizumab alone compared to patients treated with pembrolizumab plus chemotherapy.

8.3.2 Tumor Growth Rate (TGR)

TGR studies will include assessment of clinical outcomes (ORR, DOR, PFS, OS) and correlation with TGR and RECIST classification of disease response in patients enrolled at all sites. This will involve retrospective review of at least one scan performed one to twelve months prior to baseline imaging. RECIST measurements of pre-baseline scans will be performed by local institution radiologists.

TGR will be determined from two scans as the percentage change in tumor volume per month. Specifically, tumor growth is assumed to be exponential, so TGR = 100 * (e^(TG) - 1), where TG = 3 * log (D2 / D1) / time.87 D1 and D2 represent tumor sizes (using the sum of longest diameters of target non-nodal lesions and shortest diameters of target nodal lesions, excluding non-target and new lesions) at dates 1 and 2, while time (in months) = (date 2 - date 1 + 1) / 30.44. Baseline TGR will be determined from the change between 2 pre-treatment scans, while experimental TGR(s) will be determined from changes following treatment initiation (e.g., at any on-study scans and at the time of progression or off-study for any reason). Descriptive statistics will be used to summarize these metrics in comparison to changes in RECIST (and to identify patients exhibiting hyper-progressive disease). Clinical outcomes will be compared between groups (e.g., hyper-progression patients, responding patients and the remainder of the population) by logrank test for DOR, PFS and OS; and Chi-square test (or Fisher’s exact test) for response. Chi-square test (or Fisher's exact test) and t-test will be applied to evaluate associations between categorical and continuous clinicopathologic variables, respectively.

9 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

All other supplies not indicated in Table 7 above will be provided locally by the trial site. For any commercially available product that is provided by the trial site. The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

This trial is 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.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

9.5 Returns and Reconciliation

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

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

9.6 Chemotherapy

Irinotecan: commercial drug supply will be used.

Paclitaxel: commercial drug supply will be used.

10 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR/IRB mechanism and the process of informed consent. The CHR/IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR/IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

10.2 Compliance with Financial Disclosure Requirements

For all Principal Investigators and Sub-Investigators listed on the FDA 1572, Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) will be provided as required.

10.3 Compliance with Law, Audit and Debarment

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 11.5 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

10.4 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.

10.5 Study Management

10.5.1 Pre-Study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.5.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.5.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.5.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10.5.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.5.6 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 11.5 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

10.5.7 Multicenter Communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

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

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.

10.5.8 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

10.5.9 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

10.6 Data Management

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

11 References

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APPENDIX 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
*As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 2: 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)

APPENDIX 3: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:

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

In addition, volumetric analysis will be explored by review for response assessment.

APPENDIX 4: Immune-Related Response Criteria (irRC) for Evaluation of Immune Therapy Activity in Solid Tumors

Immune-related response criteria (irRC)* will also be used in this study for assessment for tumor response.

* As published in Clinical Cancer Research:

J.D. Wolchok, A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G Nichol, R Humphrey, S.F. Hodi . Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009 Dec;15(23): 7412-7420.

APPENDIX 5: Data and Safety Monitoring Plan: Multicenter Phase 2 or 3 Trial with Safety Lead-In

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of all participant data in safety lead-in phase.
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair.
- Semiannual auditing after safety lead-in phase (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

2. Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

All institutional Phase II or III therapeutic studies with a lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial.

After the completion of enrollment in the safety lead-in phase, the Study Chair will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the study. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited by a DSMC Monitor/Auditor on a semiannual basis with a random selection of twenty percent of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. Additionally, a regulatory audit will occur on a biennial basis to review all regulatory documents for the trial.

The participating site's source documents are audited remotely via either review of redacted

source documents downloaded by the site into the PC console of OnCore or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

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

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.

- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All grade 3-5 adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution assignment from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business days of becoming aware of the event. The SAEs are reviewed and audited by the UCSF Data and Safety Monitoring Committee on an ongoing basis

and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, then the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair (or Vice Chair) and the DSMC Director within 1 business day of this notification.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC Chair (or Vice Chair) and the DSMC Director at the time the increased rate is identified via a report. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

Data and Safety Monitoring Committee Contacts:

[redacted] (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

[redacted] (DSMC Director)
[redacted]
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