Full Study Protocol and Statistical Analysis Plan

Study Title: Pembrolizumab for the Treatment of Recurrent High Grade Neuroendocrine Carcinoma (PembroNEC)

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Pembrolizumab for the Treatment of Recurrent High Grade Neuroendocrine Carcinoma (PembroNEC)

Merck Protocol Number: MK-3475: PN713

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Drug Manufacturer	Merck

Investigational Agent	Pembrolizumab
IND Number	Exempt

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Version 3: 10DEC2018

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation or Term[1]	Definition/Explanation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival

Abbreviation or Term[1]	Definition/Explanation
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Frederichia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office (compliance@hci.utah.edu). Retain a copy in the regulatory binder.

Signature of Principal Investigator **Date**

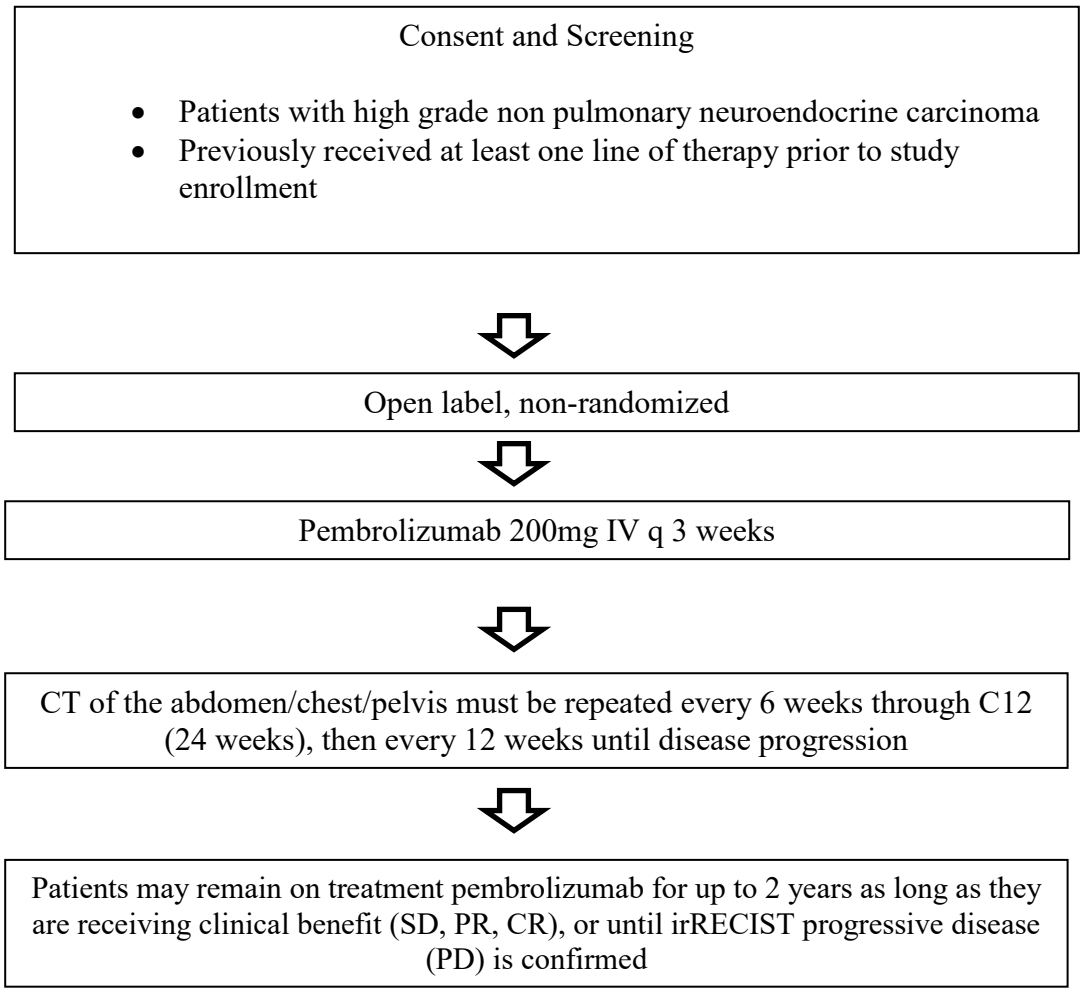
Principal Investigator Name (Print)

Name of Institution

STUDY SUMMARY

Title	Pembrolizumab for the treatment of recurrent high grade neuroendocrine carcinoma
Short Title	Pembro NEC
Protocol Number	IRB#102310
IND	IND Exempt
Phase	Phase 2
Design	Open label, non-randomized with subjects receiving 200mg Pembrolizumab to assess response rate in patients with NEC.
Study Duration	Accrual anticipated over 30 months, time to complete 42 months
Study Center(s)	This trial will open as a multi-site study conducted at the Huntsman Cancer Institute-University of Utah (including various other satellite sites and Intermountain Healthcare).
Objectives	To assess overall response rate, clinical benefit rate, progression free survival and overall survival in patients that receive Pembrolizumab using irRECIST
Number of Subjects	30 – 40 total
Diagnosis and Main Eligibility Criteria	High grade (Grade 3 defined by Ki-67 >20% or >20 mitoses/10 hpf) non-pulmonary neuroendocrine carcinoma. Patients must have failed at least one line of therapy but no maximum number of therapies is exclusionary (i.e. second-line therapy and beyond)
Study Product, Dose, Route, Regimen	Pembrolizumab 200 mg IV q3weeks
Duration of administration	24 months
Reference therapy	none
Statistical Methodology	Simon two-stage design based on expected RR of 25%.

SCHEMA


Consent and Screening
• Patients with high grade non pulmonary neuroendocrine carcinoma
• Previously received at least one line of therapy prior to study enrollment
Open label, non-randomized
Pembrolizumab 200mg IV q 3 weeks
CT of the abdomen/chest/pelvis must be repeated every 6 weeks through C12 (24 weeks), then every 12 weeks until disease progression
Patients may remain on treatment pembrolizumab for up to 2 years as long as they are receiving clinical benefit (SD, PR, CR), or until irRECIST progressive disease (PD) is confirmed

1 OBJECTIVES

1.1 Primary Objectives and Endpoint

To evaluate overall response rate of pembrolizumab (irPR + irCR) using immune related (ir)RECIST in patients with non-pulmonary, high grade neuroendocrine carcinoma.

1.2 Secondary Objectives and Endpoint

1.2.1 To evaluate clinical benefit rate of pembrolizumab (irPR + irCR + irSD) using irRECIST in this setting.

1.2.2 To evaluate progression free survival of patients treated with pembrolizumab in this setting.

1.2.3 To evaluate the median overall survival (OS) of patients treated with pembrolizumab in this setting

1.2.4 To evaluate safety and tolerability of the pembrolizumab in this setting.

1.3 Exploratory Objectives and Endpoint

1.3.1 To evaluate the correlation of response to tumor mutational burden.

1.3.2 To evaluate the correlation of response to PD-L1 expression in primary tumor.

1.3.3 To evaluate the correlation of response to proliferative rate in Grade 3 NECs (Ki-67 20-55% vs. Ki-67 >55%).

2 BACKGROUND

2.1 Hypothesis

Pembrolizumab will be clinically active in patients with high grade NECs as demonstrated by clinical response

2.2 Neuroendocrine carcinoma (NECs) / Neuroendocrine Tumors (NETs)

Neuroendocrine tumors (NETs) make up a relatively rare but heterogeneous family of neoplasms. Historically considered rare, the incidence of NETs has been steadily increasing since the 1970s, with SEER registry data suggesting an increase in incidence of almost 500% over this period of time in the United States (**1**). These tumors arise from neuroendocrine cells that are found primarily in the gut and make up the largest group of hormone-producing cells in the body. The hallmark of NETs is evidence of predominant neuroendocrine differentiation; namely, they have distinctive morphologic characteristics and expression of specific tissue markers including chromogranin A, synaptophysin, and neoron-specific enolase. These tumors commonly arise in the lung, intestine and pancreas but can arise in various anatomic locations including the larynx, thymus, kidneys, cervix, prostate, ovaries, and other sites. No primary site is identified in approximately 10 – 15% of metastatic NET cases (**1**).

2.3 NET / NEC Classification and Grading

The pathologic classification of non-pulmonary neuroendocrine malignancies is complex and continually evolving. Low grade, well-differentiated neuroendocrine neoplasms are commonly referred to as "neuroendocrine tumors" (NETs) whereas high grade, poorly differentiated neuroendocrine neoplasms are commonly referred to as "neuroendocrine carcinoma" (NECs). Pathologic specimens are distinguished based on morphologic evidence of differentiation. Well-differentiated NETs show a solid, trabecular, gyriform, or glandular pattern with uniform nuclei, salt-and-pepper chromatin, and finely granular cytoplasm. Poorly differentiated NECs resemble small cell or large cell neuroendocrine carcinoma of the lung. Small cell NECs are comprised of small round cells with small amounts of cytoplasm with hyperchromatic nuclei; large cell NEC cells are arranged in organoid, trabecular, or palisading patterns with prominent necrosis.

The 2010 WHO classifications of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) adopted a classification system previously endorsed by the European Neuroendocrine Tumour Society (ENETS). Namely, well-differentiated tumors are separated into low-grade and intermediate-grade with poorly-differentiated tumors generally classified as high grade depending on mitotic count and/or Ki-67 proliferation indices (Table 1). The WHO Grade 3 (G3) of NECs is somewhat heterogenous. Namely, the majority of NECs exhibit a poorly differentiated morphology and will fall in the range of G3 tumors based on mitotic or proliferative indices; however, a subset of patients will exhibit a well- or moderately-differentiated histology but higher grade based on mitotic and proliferative indices. These tumors are considered "grade discordant." Their clinical behavior generally falls somewhere between lower grade NETs and poorly differentiated, G3 NECs.

Table 1: 2010 WHO tumor grading for gastrointestinal neuroendocrine tumors

Grading of GEP-NETs	Mitotic Index	Ki-67 labelling index
Grade 1 (G1)	<2 mitoses/10 hpf	≤2%
Grade 2 (G2)	2-10 mitoses/10 hpf	3-20%
Grade 3 (G3)	>20 mitoses / 10 hpf	>20%

Well-differentiated NETs are frequently associated with clinical syndromes depending on hormone secretion. Namely, NETs arising in the small bowel are often associated with "carcinoid syndrome," manifest by diarrhea, flushing, palpitations, wheezing and other symptoms predominantly due to excess serotonin secretion. Similarly, pancreatic NETs may secrete insulin, glucagon, gastrin, vasoactive intestinal peptide (VIP), somatostatin, or other hormones with clinical syndromes directly related to this hormone secretion. On the other hand, poorly differentiated NECs do not closely resemble non-neoplastic neuroendocrine cells and are not generally associated with specific clinical syndromes due to excessive hormone secretion. Like SCLC, however, poorly differentiated are relatively frequently associated with other paraneoplastic syndromes (e.g. hypercalcemia, hyponatremia, venous thromboembolism, etc.).

2.4 Prognosis and Treatment

While most NETs are relatively slow-growing (G1 or G2) with a median survival of many years, the prognosis of patients with poorly differentiated G3 NECs is dismal with a median

survival of approximately 12 months (**2**). Common sites of metastases include liver, lung, bones, and brain. Histologically, poorly differentiated NECs can be classified as either "small cell" or "large cell" NEC. Clinically these entities behave very similarly and standard treatment for both large and small cell NEC is usually identical, although some practitioners favor temozolomide-based chemotherapy regimens over platinum-based regimens in patients with poorly differentiated NEC with Ki-67 <55% (**2**).

As this is a relatively rare patient population, large-scale, randomized phase III trials have been very difficult to perform. Standard accepted therapies have been extrapolated from experience in the treatment of SCLC or are based on smaller phase II trials in this specific population. First-line treatment generally involves chemotherapy, either platinum-based (e.g. carboplatin or cisplatin in combination with etoposide) or temozolomide-based (e.g. single-agent temozolomide, capecitabine + temozolomide). Response rates range from 10 – 70% but are generally not durable with no standard second-line treatment (**2-4**). Extrapolating from treatment algorithms used in small cell lung cancer (SCLC), chemotherapy is often administered in the second-line setting with disappointingly low response rates and early clinical progression (**5-7**).

3 DRUG INFORMATION

3.1 Pembrolizumab

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

3.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar

to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

3.1.2 Preclinical and Clinical Trial Data

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

3.2 Rationale for the Trial and Selected Subject Population

3.2.1 Rationale for anti-PD-1 therapy in high grade (G3) NET/NECs

Immunotherapy, in particular therapy with immune checkpoint inhibitors such as anti-PD-1 antibody therapy, has recently shown significant efficacy in a wide variety of tumors with FDA approved indications for anti-PD-1 antibody therapy includes melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, renal cell cancer, and Hodgkin lymphoma. Additionally, phase II trials have demonstrated activity in other cancer types including small cell lung (SCLC), merkel cell, bladder, gastric, hepatobiliary, breast and prostate cancers. Included in this list of cancers where activity has been demonstrated are two aggressive neuroendocrine cancers: Merkel cell carcinoma and small cell lung cancer.

The multicenter, phase 2 clinical trial leading to wide acceptance of pembrolizumab therapy in patients with advanced Merkel cell carcinoma demonstrated an objective response rate of 56% with a response duration ranging from 2.2 months to at least 9.7 months and a 6-month progression-free survival rate of 67% (**9**). Similarly, trials demonstrating activity of anti-PD-1 antibody therapy in SCLC include the KEYNOTE-028 trial and the CHECKMATE-032 trial. In the KEYNOTE-028 trial, patients with metastatic SCLC with evidence of PD-L1

expression by immunohistochemistry who were previously treated with platinum-based chemotherapy were treated with pembrolizumab. Early data suggest a 25% response rate with response duration lasting > 4 months (**10**). The CHECKMATE-032 trial enrolled a similar patient population. Patients were treated with nivolumab either alone or in combination with ipilumumab with response rates of 13% and 31% respectively and duration of responses lasting > 6 months (**11**). With this encouraging data, multiple ongoing trials are evaluating the role of anti-PD-1 therapy and other immune checkpoint inhibitors in the treatment of patients with Merkel cell carcinoma and SCLC. These trials all support the rationale for treatment with immune checkpoint blockade in patients with high grade NET/NECs.

Among biologic correlates evaluated with anti-PD-1 therapies, none have defined a clear subset to definitively predict clinical efficacy. However, some correlates have emerged as strong predictors for clinical benefit. Three leading correlative markers predictive of benefit include: 1) mutation burden (namely, cancers with higher mutation burden tend to be more likely to respond to anti-PD-1 therapy, likely due to an increase in neoantigen expression) (**12**); 2) PD-L1 expression (**13-14**); and, 3) tumor T cell infiltration, associated with PD-L1 expression by infiltrating immune cells (**15-16**). High grade NECs have been shown to have a high mutation burden (**17-18**). Similarly, NECs have been found to express PD-L1, which is more commonly expressed in G3 NECs (**19**). Lastly, the majority of extra-pulmonary higher grade NETs have also been shown to exhibit intratumoral T cell infiltration on histopathologic review (**20**). Together, these features suggests a higher likelihood of clinical benefit in this patient population.

3.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a

fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

4 STUDY DESIGN

4.1 Description

This is an open label, non-randomized phase 2 study to assess overall response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and progression free survival (PFS) in patients with high grade neuroendocrine tumors treated with pembrolizumab 200mg Q 3 Weeks.

Simon Optimum Two-Stage designs will be used. A Type I error rate alpha equal to 0.10 and a Type II error rate beta equal to 0.20 will be used. Null and alternative hypotheses are associated with treatments. See Section 12 for additional details

4.2 Number of Patients

A total of 34-40 subjects will be recruited to one treatment arm in this study with the goal of enrolling 34 evaluable patients (defined in sections 11.1 and 11.3).

4.3 Number of Study Centers

This trial will open as a multi-site study conducted at the Huntsman Cancer Institute including various other satellite sites and Intermountain Healthcare.

4.4 Study Duration

We would anticipate that on average, patients will remain on treatment approximately 24 weeks (range of 2 to 52 weeks comparatively). However, patients may remain on treatment pembrolizumab for up to 2 years as long as they are receiving clinical benefit (SD, PR, CR), or until irRECIST progressive disease (PD) is confirmed. Confirmation of progression will occur 4-6 weeks after first detection prior to subject coming off study.

Accrual is anticipated to take 24-30 months. Estimated duration of accrual and patient participation is approximately three and half years.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Histologically confirmed, metastatic or unresectable neuroendocrine carcinoma of non-pulmonary origin, high grade as indicated by Ki-67 >20% and/or > 20 mitoses/10 hpf. Patients must have existing Ki-67 results from archival tissue or available tissue for Ki-67 testing. If no archival tissue is available the subject must agree to a fresh biopsy for testing to qualify for the study.

5.1.2 _____ Patients must have progressed during or after first-line treatment for metastatic or unresectable disease with either a platinum-based regimen (e.g. carboplatin + VP16, cisplatin + VP-16, FOLFOX) OR temozolomide-based regimen. Patients must have failed at least one line of therapy but no maximum number of therapies is exclusionary (i.e. second-line therapy and beyond).

5.1.3 _____ Have measurable disease based on irRECIST.

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

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

5.1.6 _____ Demonstrate adequate organ function as defined in Table 2, all screening labs should be performed within 14 days of treatment initiation.

Table 2: **Adequate Organ Function Laboratory Values:**

	System	**Laboratory Value**
☐	**Hematological:**	
	Absolute Neutrophil Count ANC	≥ 1,500/uL
	Platelets	≥ 100,000/uL
	Hemoglobin	≥ 9 g/dL
☐	**Renal**	
	Serum Creatinine OR measured calculated creatinine clearance (GFR may also be used in place of creatinine or CrCl)	≤ 1.5 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 ≥ 1.5 ULN
	AST or ALT	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
☐	**Coagulation**	
	International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN If on active anticoagulants prior to study treatment, levels must be within standard therapeutic ranges per investigator.

5.1.7 _____ Subjects with a history of known central nervous system (CNS) metastases must have documentation of stable or improved brain imaging for at least 2 weeks after completion of definitive treatment. Definitive treatment may include surgical resection, whole brain irradiation, and/or stereotactic radiation therapy.

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

5.1.9 _____ Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year (according to Section 8.4.2).

5.1.10 _____ 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 (according to Section 8.4.2).

5.1.11 _____ Must have recovered from adverse effects of any prior surgery, radiotherapy or other antineoplastic therapy.

5.1.12 _____ Last dose of any antineoplastic therapy ≥ 2 weeks (including chemotherapy, small molecule inhibitors, radiation, and/or other investigational anticancer agents). Patients receiving hormone manipulation (e.g. SERMs, aromatase inhibitors, LHRH agonist, etc.) for reasons other than treatment of metastatic breast cancer may continue this treatment at the discretion of the investigator.

5.1.13 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

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

5.2.2 _____ Has a diagnosis of immunodeficiency or receiving steroid therapy of any other form of immunosuppressive therapy within 7 days prior to first dose of trial treatment. Subjects who receive daily steroid replacement therapy serve as an exception to this rule. Daily prednisone at doses of 5 to 7.5 mg (or hydrocortisone equivalent doses) is an example of replacement therapy.

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

5.2.4 _____ Hypersensitivity to pembrolizumab or any of its excipients.

5.2.5 _____ 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.

5.2.6 _____ 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. Patients receiving hormone manipulation (e.g. tamoxifen, aromatase inhibitors, LHRH agonist, etc.) for reasons other than treatment of metastatic breast cancer may continue this treatment at the discretion of the investigator.

5.2.7 _____ 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. Patients on long-term adjuvant therapy with no evidence of disease are not excluded if felt appropriate by investigator.

5.2.8 _____ Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 2 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

5.2.9 _____ Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, 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.

5.2.10 _____ Has known history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

5.2.11 _____ Has an active infection requiring systemic therapy.

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

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

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

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

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

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

5.2.18 _____ Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

6 STRATIFICATION FACTORS

Not applicable – all patients will be enrolled on one arm

7 TREATMENT PLAN

Treatment should be administered on Day 1 of each cycle after all procedures and assessments have been completed as detailed on the Study Calendar (Section 9). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

7.1 Administration Schedule

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

7.2 Pembrolizumab (MK-3475) Treatment

7.2.1 How Supplied, Stored, Packaged and Labeled

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 the table below.

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

7.2.2 Packaging and Labeling Information

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

7.2.3 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.

7.2.4 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.

7.2.5 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.

7.2.6 Preparation and Administration

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial: pembrolizumab (MK-3475) Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C) and protected from light.

Note: vials should be stored in the original box to ensure the drug product is protected from light.

Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry. When the diluent is provided by Merck, the drug accountability log should be used for collection of diluent information.

Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS.

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion

In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the drug product between the pharmacy and the clinic

DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION IS OBSERVED.

DO NOT SHAKE OR FREEZE THE VIAL(S).

DO NOT ADMINISTER THE PRODUCT AS AN (INTRAVENOUS (IV) PUSH OR BOLUS).

DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.

Any departure from the guidance listed in this protocol, must be discussed with sponsor

7.3 Dose Calculation

<u>200 mg Fixed Dose</u>

- 2 vials (100 mg/4 mL)
- 8 mL total

7.4 Preparation of Infusion Solution

Aseptic technique must be strictly observed throughout the preparation procedure preferably in a biologic safety cabinet or hood since no anti-microbial preservative is present in the solutions.

Equilibrate required number of pembrolizumab MK-3475 vials to room temperature

The preferred method of dose preparation is the volumetric method, gravimetric method is not permitted.

Choose a suitable infusion bag size so that the following conditions are met:

- Concentration of pembrolizumab MK-3475 is between 1 mg/mL and 10 mg/mL
- The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.

Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline. The following infusion bag materials are compatible with pembrolizumab (MK-3475):

- PVC plasticized with DEHP
- Non-PVC (polyolefin)
- EVA
- PE lined polyolefin

Contact Sponsor for materials not listed above

Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above

If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle.

Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

Note: If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

Add the required pembrolizumab (MK-3475) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion.

In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

DO NOT FREEZE THE PEMBROLIZUMAB (MK-3475) INFUSION SOLUTION.

Discard any unused portion left in the vial as the product contains no preservative

7.5 Administration

Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

The following infusion set materials are compatible with (pembrolizumab) MK-3475:

- PVC Infusion set that is plasticized using DEHP
- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
- Polyethylene lined PVC infusion set
- PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
- Polyurethane set

Contact Sponsor for materials not listed above

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to

use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered according to institutional guidelines for saline flushing.

Document volume administered according to data entry guidelines.

In case of infusion reactions, infusion rate may differ; refer to protocol section 8.2 for specific instructions.

Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes.

Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.

DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.

UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.

7.6 Accountability and Compliance

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

7.7 Concomitant Medications

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 study sponsor (principal investigator). The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

7.7.1 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 7.2.

7.7.2 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. Hormonal therapies or other long-term adjuvant therapies may be approved after discussion with the principal investigator.
- 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 for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study sponsor (principal investigator).

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.

7.8 Duration of Therapy

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.
- Radiographic disease progression by irRECIST (progression must be confirmed with follow up scan no less than 4 weeks and no more than 8 weeks after the first scan shows disease progression)
- Unacceptable adverse experiences as described in Section 8.1
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 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 9 (Protocol Calendar). 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 or until a new cancer treatment is started, if sooner). 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 for overall survival, withdrawal of consent, or the end of the study, whichever occurs first.

8 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting.

8.1 Dose modification and toxicity management guidelines for pembrolizumab

8.1.1 Dose modification and toxicity management for immune-related AEs associated with Pembrolizumab

AEs associated with pembrolizumab exposure 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 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 trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification

and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3: Dose modification and toxicity management guidelines for immune-related AEs associated with Pembrolizumab.

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Grade** CTCAE v4	**Action taken with pembro**	**irAE managements**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable

	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of	Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis	AE administer corticosteroids	
	Grade 4 or recurrent Grade 3	Permanently discontinue		
Notes: 1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. 2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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

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

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

	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 study drug treatment**	
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: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids 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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

8.3 Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the study sponsor (principal investigator). The reason for interruption should be documented in the patient's study record.

8.4 Diet/Activity/Other Considerations:

8.4.1 Diet

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

8.4.2 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.

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

Female subjects will be considered of non-reproductive potential if they are either:

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) Practice abstinence[†] from heterosexual activity;

OR

(2) Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

8.4.3 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, IRB/DSMC and Merck without delay and within 24 hours to the Sponsor and DSMC 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, IRB/ DSMC and Merck and followed as described above and in Section 16.8.

8.4.4 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.

9 STUDY CALENDAR

CYCLE Calendar: 1 cycle = 21 days (± 3 days)

Examination	Screening[1]	C1[13]	C2	C3	C4	C5	C6	C7 and beyond	End of Treatment	Follow-up[12]
Informed consent	X									
Medical history/baseline AE	X									
Eligibility criteria	X									
Vital signs	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	
Hematology[2]	X	X	X	X	X	X	X	X	X	
Chemistry[3]	X	X	X	X	X	X	X	X	X	
Urinalysis	X								X	
T3, free T4, TSH[4]	X				X			X[4]		
PT, PTT, INR	X									
Pregnancy test[5]	X									
Review Adverse events and events of clinical interest		X	X	X	X	X	X	X	X	
Review of concomitant medications	X	X	X	X	X	X	X	X		
Archival tissue for PD-L1 analysis[6]	X									
Archival tissue for TMB analysis[7]	X									
Archival tissue for Ki-67 analysis[8]	X									
ECG[9]	X									
CT scans (c/a/p)[10]	X			X		X		X[10]	X	X[10]
Disease Assessment (irRECIST)[10]	X			X		X		X	X	X
MRI[14]										
Study drug[11]		X	X	X	X	X	X	X		

1 ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 14 days prior to study enrollment.

2 Hematology includes CBC with differential and platelets

3 Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen

4 T3, free T4, TSH to be performed at screening and every 9 weeks (every third cycle) while on treatment

5 Pregnancy test must be done at screening and within 72 hours of starting study treatment for all women of childbearing potential and repeated as clinically indicated. Serum or urine tests may be used. If urine pregnancy is positive, confirm with serum.

6 If the patient consented to the optional testing and tissue is available (either from archival tissue or fresh biopsy tissue), PD-L1 analysis will be performed at central lab. If fresh tissue is being used, it should be obtained during screening window prior to study treatment. See section 15.

7 If clinically indicated, and not previously performed, tumor mutation burden analysis will be performed at central lab. If performed, results should be collected for the study. See section 15.

8 Patients must have existing Ki-67 results from archival tissue or available tissue for Ki-67 testing. If no archival tissue is available the subject must agree to a fresh biopsy for testing to qualify for the study. Ki-67 analysis will be performed at local lab if not previously performed. See section 15.

9 ECG will be done if medically indicated

10 CT of the abdomen/chest/pelvis must be repeated every 6 weeks through C12 (36 weeks), then every 12 weeks until disease progression. Progression must be confirmed no earlier than 4 weeks and no later than 8 weeks. Scans must be completed within 7 days prior to the next dosing cycle.

11 Pembrolizumab 200 mg IV q3weeks

12 Follow-up should occur no less than every 6 months for 4 years following study enrollment

13 Baseline procedures do not need to be repeated if screening procedures have been done within 7 days of start of treatment

14 MRI may be required at baseline for subjects with previously treated brain metastases

10 STUDY PROCEDURES

10.1 Screening Evaluations

- Informed Consent
- Physical examination with vital signs and ECOG Performance Status
- Review of medical history/baseline symptoms
- Review baseline concomitant medications
- Laboratory assessments:
  - CBC with differential
  - CMP to include sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, AST, ALT, alkaline phosphatase, total bilirubin
  - Coagulation to include PT/INR and aPTT
  - Thyroid function tests to include TSH, total T3, and free T4
  - Serum or urine pregnancy test (for women of childbearing potential) within 72 hours of starting study treatment
  - Urinalysis
- 12-lead ECG if clinically indicated
- CT scans and disease assessments for baseline irRECIST
- MRI only for subjects with previously treated brain metastases
- Archival tissue or fresh tissue biopsy (if archival tissue is not available) for Ki-67 testing (see footnote #8 in calendar)
- Archival tissue or fresh biopsy for central PD-L1 analysis if patients consent to optional testing.

10.2 On-Treatment Evaluations (every three weeks unless otherwise noted)

- Physical examination with vital signs and ECOG Performance Status
- Laboratory assessments (do not need to be repeated if screening labs were performed within 7 days of C1D1):
  - CBC with differential
  - CMP to include sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, AST, ALT, alkaline phosphatase, total bilirubin
  - Coagulation to include PT/INR and aPTT
  - Thyroid function tests to include TSH, total T3, and free T4 *at the beginning of every third cycle (C4D1, C7D1, C10D1, etc.)*
  - Serum or urine pregnancy test (for women of childbearing potential) *only on C1D1 if not performed during screening and within 72 hours of C1D1. Testing during treatment is required as clinically indicated*
- Safety assessment: monitoring and recording of all adverse events and serious adverse events.
- Review of concomitant medications

- CT scans and review of response every 6 weeks through C12 (36 weeks), then every 12 weeks until disease progression.
- Treatment with pembrolizumab 200 mg

10.3 End of Treatment Assessments:

- Physical examination with vital signs and ECOG Performance Status
- Laboratory assessments:
  - CBC with differential
  - CMP to include sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, AST, ALT, alkaline phosphatase, total bilirubin
  - Thyroid function tests to include TSH, total T3, and free T4 *at the beginning of every third cycle (C4D1, C7D1, C10D1, etc.)*
  - Urinalysis
- Safety assessment: monitoring and recording of all adverse events and serious adverse events.

10.4 Follow-up Assessments

After coming off treatment patients will be followed per standard of care practice for progression free survival. For patients who come off trial prior to disease progression, disease assessments should continue every 12 weeks. Follow-up should occur no less than every 6 months for 4 years following study enrollment.

11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Efficacy

Disease assessments will be measured by CT or MRI scan and assessed according to Immune related RECIST (irRECIST) based on Nishino et. al. (21)

Response rate is the primary response objective. Generally, evaluable patients should have baseline scans and one 6 week follow-up scan to be evaluable for response assessment. Patients should also have received at least 2 cycles of Pembrolizumab to be considered evaluable for response.

11.1.1 irRECIST

Measurable disease/non-measurable and target/non-target criteria- using one-dimensional measurements (simulating RECIST 1.1):

The following definitions and criteria (irRECIST) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor measurements according to Nishino, an adaptation of Wolchok (22).

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥20 mm with x-

ray. Lymph nodes which are defined as measurable at baseline must meet the criterion of a short axis > 15mm by CT scan.

Non-measurable lesions - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or <20 mm with x-ray).

Target Lesions - all measurable lesions, up to a maximum of **five lesions,** should be identified as *target* lesions to be measured and recorded on the medical record at Screening. The *target* lesions should be representative of all involved organs. In addition, *target* lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the patient's tumor burden. At screening, a sum of the products of diameters (SPD) for all *target* lesions will be calculated and considered the baseline sum of the products of diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the *target* lesions at tumor assessment (TA).

Non-Target Lesions - measurable lesions, other than *target* lesions, and all sites of non-measurable disease, will be identified as *non-target* lesions. *Non-target* lesions will be recorded on the medical record and should be evaluated at the same assessment time points as the *target* lesions. In subsequent assessments, *non-target* lesions will be recorded as "stable or decreased disease," "absent," or "progression."

New Lesions and non-target lesions - In irRECIST a new lesion does not automatically indicate progressive disease

New measurable lesions are added to the sum of the longest diameters of the previously existing target lesions, and the sum of the longest diameters is followed at each subsequent tumor assessment

New measurable lesions are defined using the same criteria as for baseline target lesions in RECIST 1.1. New measurable lesions shall be prioritized according to size and the largest lesions shall be selected as new measured lesion up to 2 lesions per organ and 5 new lesions total.

Non-target lesions (baseline and new non measurable) are used for determination of Complete Response. The RECIST 1.1 definitions for the assessment of non-target lesions apply.

Response Categories:

- Complete Response (irCR): disappearance of all not-nodal target lesions and non-target lesions in two consecutive observations not less than 4 weeks apart. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to <10mm (sum of diameters may be greater than zero at the time of CR, if nodal lesion are including as target lesions).
- Partial Response (irPR): at least a 30% decrease in the sum of diameters of all target lesions including new target lesion in two consecutive observations not less than 4 weeks apart, taking as reference the baseline sum of diameters.

- Progressive Disease (irPD): at least a 20% increase in the sum of diameters of all measured target lesions including new measurable lesions. The reference for irPD will be the smallest sum of diameter of all target lesions recorded at original baseline or subsequent. Progression must be confirmed with a follow up scan no less than 4 weeks and no more than 8 weeks after the first scan that shows disease progression.
- Stable Disease (irSD): neither a sufficient shrinkage to qualify of irPR or irCR, or an increase in the sum of target lesions which would qualify for irPD.

11.1.2 Evaluation of Best Overall Response

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

Target Lesions	Non-Target Lesions	Evaluation of New Lesions	Best Overall Response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

11.1.3 Progression Free Survival

Time to progression (TTP), progression-free (PFS) survival, and overall survival (OS) will be determined, but are not primary study endpoints. Patients will be followed for progression free survival beginning with C1D1 of pembrolizumab on this trial through the date of progression, or death, whichever comes earlier. Progression will be assessed by irRECIST. Patients will be followed for survival endpoints every 6 months for 4 years following study enrollment.

11.2 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination:

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs:

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained.

Safety Laboratory Determinations:

Laboratory evaluations will be performed as noted in the flow chart.

11.3 Stopping Rules

Up to a total of 34 response evaluable patients are required. Generally, evaluable patients should have baseline scans and one 6 week follow-up scan to be evaluable for response assessment. Patients should also have received at least 2 cycles of Pembrolizumab to be considered evaluable for response. Enrollment and evaluation of response based on irRECIST.

An initial analysis will be done on the first 13 response evaluable patients enrolled to the Pembrolizumab treatment regimen. Recruitment will be terminated (stopped) if there are only 0 – 1 responses (irCR/irPR). If there are 2+ responses in 13 evaluable patients, recruitment will be expanded with this treatment regimen to up to an additional 21 evaluable patients.

12 STATISTICAL CONSIDERATIONS

A Simon Optimum Two-Stage design will be used with a Type I error rate alpha equal to 0.10 and a Type II error rate beta equal to 0.20. The null hypothesis is an objective response rate (irCR + irPR) of 10% or lower. The alternative hypothesis is an objective response rate of 25% or higher. With these design parameters, the first stage will consist of 13 patients. If there are 2 or more responses in 13 patients, up to an additional 21 evaluable patients will be recruited for a maximum sample size of 34 evaluable patients. If there are 6 or more responses in up to 34 evaluable patients the null hypothesis will be rejected. If there are 5 or fewer responses 34 evaluable patients the null hypothesis will not be rejected. It is estimated that it may be necessary to enroll up to 40 patients to accrue 34 response evaluable patients.

Kaplan-Meier methods and associated confidence intervals will be used to analyze PFS and OS. All subjects assessed for progression will contribute to this analysis. The clinical benefit rates (irCR + irPR + irSD) will be analyzed by tabulating the observed counts and proportions together with exact binomial confidence intervals.

Tumor tissue will be analyzed for the correlation of biomarkers to response rate.

1) Tissues analyzed for correlation of tumor mutational burden will be categorized as high, medium and low burden.
2) Tissues analyzed for correlation of PD-L1 expression will be categorized as high or low.
3) Tissues analyzed for correlation to proliferative index will be categorized as Ki-67 20-55% or Ki-67 > 55%.

Fisher's exact test will be used to analyze each of these biomarkers. Two sided p-values < 0.05 will be regarded as statistically significant.

Safety will analyzed by tabulating adverse events.

13 REGISTRATION GUIDELINES

When the clinical research coordinator (CRC) or study coordinator (SC) identifies a potential study patient, they MUST contact the Research Compliance Office at the Huntsman Cancer Institute (by

email at compliance@hci.utah.edu) to confirm that a slot is available prior to initiating the consent process.

After a patient has consented to participate in the study and all screening procedures have been completed, the CRC/SC will review eligibility with the properly delegated enrolling physician who will sign a copy of the eligibility checklist (section 5). This, along with all de-identified documentation supporting eligibility, will be sent to the RCO at HCI for verification.

Eligible patients will be registered on study at the University of Utah – Huntsman Cancer Institute and applicable subsites via the OnCore system by the CRC/SC. **Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.**

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the principal investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The CRC/SC and Research Compliance Office should be notified of cancellations as soon as possible.

Once the RCO confirms the patient's eligibility and notifies the CRC/SC, the patient can be registered by emailing a completed Clinical Trials Office Patient Registration Form to the RCO at CTORegistrations@hci.utah.edu. The RCO will then return the completed form (including patient number and cohort/dose level) to the coordinator after which time the patient can begin treatment.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

14 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

15 SPECIAL INSTRUCTIONS

15.1 Pathology review for PD-L1 analysis at central laboratory

Formalin fixed paraffin embedded (FFPE) tissue samples will be sent for PD-L1 IHC analysis at screening if samples are available. Fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimens will not be accepted for PD-L1 IHC analysis. If a patient does not have archival tissue available and a fresh biopsy is required for Ki-67 testing (see 15.3), tissue will be sent for PD-L1 analysis if adequate tissue is available after Ki-67 testing has been performed. This is optional when tissue is available for evaluation.

If the patient consents to this testing, screening tissue samples will be sent to QualTek Molecular Laboratories.

Please reference the Qualtek lab manual for more information.

15.2 Pathology review for tumor mutational burden analysis

Screening tissue analyzed for correlation of tumor mutational burden will be performed locally per treatment center's standard protocol. If not performed previously and not clinically indicated at the time of screening, TMB will not be required.

15.3 Pathology review for Ki-67 antibody staining

Patients must have existing Ki-67 results from archival tissue or available tissue for Ki-67 testing. If no archival tissue is available the subject must agree to a fresh biopsy for testing to qualify for the study.

Screening tissue Ki-67 immunohistochemistry will be performed locally per treatment center's standard protocol.

15.4 Correlative Studies

15.4.1 Tissue Specimens for PD-L1 IHC analysis

- 5 unstained slides cut at 4 microns thickness.

15.4.1.1 Fresh tissue biopsy (if archival tissue is not available for Ki-67 testing)

- 1-2 cores with an 18 gauge needle.
- .

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

16.2 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

16.3 Human Subjects Protections

16.3.1 Participation of Children

Patients must be at least 18 years of age to participate.

16.3.2 Participation of Subjects Unable To Give Consent

Patients unable to give consent will be allowed to participate if a legally authorized representative (as defined by Utah state laws and the policy of the IRB) consents on their behalf.

16.4 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

16.5 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All phase II studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as toxicities for patients on treatment and within a 30 day follow-up window.

16.6 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting.

16.6.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The collection of adverse events will begin after the first dose of study treatment and end 30 days post the last dose of study treatment.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v.4 (grade 1-5)
2. Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational and commercial drugs are described in the Drug Information (section 3) and the most recent Investigator Brochure or the FDA-approved product labels. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

16.6.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin after the first dose and end 90 days after the last dose of study treatment or until a new cancer treatment is initiated, whichever happens the soonest.

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

16.7 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and LSK BioPartners, Inc., according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

For multisite studies: the HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office. The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety update, including external safety reports, manufacturer's reports and updates to the investigator's brochure.

FDA Notifications:

Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:

- Serious
- Unexpected

- Definitely, Probably or Possibly Related to the investigational drug

Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.

All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.

The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements. The RCO will also ensure the complete, accurate, and timely reporting of the event to the FDA.

The Regulatory Coordinator will submit the report as an amendment to the IND application.

All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

External sites should abide by local IRB requirements for submission of SAEs

Drug Manufacturer Notifications:

SAEs should be reported to Merck Global Safety within 2 working days of first knowledge or notification of event.

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 by HCI as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220 or AER_mailbox@merck.com) at the time of submission to FDA.

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

16.8 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events thought to be related to Pembrolizumab are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the HCI Principal Investigator and research compliance office and within 2 working days of first knowledge or notification of event to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220 or AER_mailbox@merck.com)

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 16.7 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the HCI and to Merck Global Safety within 2 working days of first knowledge or notification of event

16.9 Definition of an Overdose for this Protocol and Reporting of Overdose to HCI 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. 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. (Attn: Worldwide Product Safety; FAX 215 993-1220 or AER_mailbox@merck.com)

16.10 Reporting of Pregnancy and Lactation to HCI Sponsor, IRB, DSMC and 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) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but

not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor, DSMC and IRB and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220 or AER_mailbox@merck.com)

16.11 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

16.12 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

16.13 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

16.14 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16.15 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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