A PHASE II STUDY OF PEMBROLIZUMAB AND DYNAMIC PD-L1 EXPRESSION IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER (SCLC)

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Etoposide, commercial

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List of Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BWH	Brigham and Women's Hospital
cGy	centigray (unit)
CR	Complete Response
CRF	Case Report Form
CT	Computed-Tomography
CTL	Cytotoxic T cell
CTO	Clinical Trials Office
CXR	Chest X-ray
DF/HCC	Dana-Farber/Harvard Cancer Center
DFCI	Dana-Farber Cancer Institute
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FNA	Fine-needle aspiration
GCPs	Good Clinical Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDH	Isocitrate dehydrogenase
IRB	Institutional Review Board
mAb	Monoclonal Antibody
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
NSCLC	Non-small cell lung cancer
NYULMC	New York University Langone Medical Center
OR	Objective Response
OS	Overall Survival
PBMC	Peripheral blood mononuclear cells
PCC	Perlmutter Cancer Center
PCI	prophylactic cranial irradiation
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase (also known as AST)
SGPT	Serum Glutamic-Pyruvic Transaminase (also known as ALT)
TCR	T cell receptor
TIMC	Tumor Imaging Metrics Core Facility
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Cell
WES	whole-exome sequencing

Study Synopsis

1. RATIONALE

SCLC provides an opportune setting to evaluate the potential importance of variability in PD-L1 expression and its influence on optimizing timing and efficacy of checkpoint inhibition. All extensive-stage SCLC patients are treated with chemotherapy and recent data suggests added benefit to consolidation thoracic radiation[10]. A prior study of patients with known PD-L1 expression showed a 35% response rate. That study used archival specimens and found a 29% PD-L1 positivity rate (at 1% level) suggesting that the expression level and prevalence could be higher (and response rate/outcome therefore potentially better) in patients who have previously had chemotherapy or radiation.

The proposed study seeks to evaluate pembrolizumab therapy initiated at different times during the course of SCLC treatment: a) up front, in conjunction with initiation of chemotherapy, b) starting after one cycle of chemotherapy, c) starting after completion of 1st line chemotherapy (4-6 cycles), d) starting after completion of consolidation thoracic radiation therapy and/or PCI. Treatment with pembrolizumab will be preceded by biopsy for evaluation of PD-L1 expression with correlative evaluation of changes in PD-L1 expression (relative to diagnostic biopsy) and changes in other tissue- and blood-based biomarkers and immune markers.

2. OBJECTIVES

Primary Objective:

- To determine PD-L1 expression status in subjects with SCLC and assess changes in expression with chemotherapy and radiation

Secondary/Exploratory objectives:

- To evaluate progression-free survival with the addition of pembrolizumab to standard therapy
- To evaluate overall survival with the addition of pembrolizumab to standard therapy
- To evaluate response rates by RECIST 1.1 and irRECIST with the addition of pembrolizumab to standard therapy
- To evaluate soluble PD-L1 and circulating cytokines before, during, and after therapy with pembrolizumab
- To evaluate mutational burden, gene expression profiling, and immune profiling from pre-treatment biopsies before therapy with pembrolizumab
- To evaluate immune markers of response and resistance in pre-treatment (and post-treatment) tumor biopsies.

3. TREATMENT PLAN

Each cohort will consist of 15 patients. All patients will be treated with up to 6 cycles of cis/carboplatin + etoposide. Eligible patients for consolidation thoracic radiotherapy will complete this within 6 weeks following completion of chemotherapy. All patients will be required to have pre-treatment biopsies prior to initiation of pembrolizumab for evaluation of PD-L1 expression and other correlative evaluations (within 4 weeks of start). Cohorts B-D will ALSO be required to submit a diagnostic biopsy specimen (prior to any treatment) for intra-subject comparison of PD-L1 expression between biopsies.

Cohort A will start pembrolizumab at the same time as starting standard chemotherapy with carboplatin + etoposide and receive all three drugs. Cohort B will start pembrolizumab after one cycle of cis/carboplatin/etoposide and receive all three drugs for the remaining cycles. Cohort C will consist of subjects who are not candidates for consolidation thoracic radiotherapy (thoracic RT) or prophylactic cranial irradiation (PCI) but who have completed 1st line therapy with 4-6 cycles of chemotherapy—these subjects will start pembrolizumab after completion of chemotherapy. Cohort D will consist of patients who have completed 4-6 cycles of carboplatin + etoposide as well as consolidation thoracic radiotherapy and/or PCI-- these subjects will start pembrolizumab after completion of chemotherapy and radiation.

Pembrolizumab will be continued until progression following completion of standard treatment for all cohorts or for up to 2 years of therapy total.

4. TRIAL PROCEDURES
Prior to treatment, a screening period of 28 days will consist of baseline CT and MRI scans as indicated, complete blood count, complete metabolic profile, TSH, blood for research studies as outlined below, and pulmonary function tests.

Day 1 of each cycle will include MD/NP visit, labwork as above, and treatment..

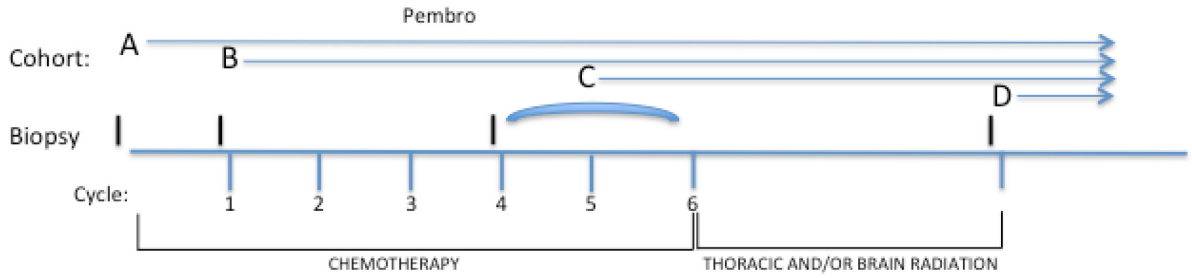
For cohorts A and B, in which pembrolizumab is given in combination with platinum and etoposide, initial enrollment will include only 3 participants. Once these three participants have been enrolled to either cohort A or B, enrollment will be halted until these participants have cleared cycle 1. An additional 3 participants (into either cohort A or B) may be enrolled if no DLTs are seen. If < 2 DLT's are seen in the first 6 particpants, enrollment to the rest of the cohort will proceed. If $\geq$ 2 DLTs are seen, enrollment will be halted and discussion of dosing change amongst the investigators will occur prior to further enrollment. Based on safety data to date with other platinum-based regimens, we do not anticipate interactions that would necessitate dosing change.

Because there is limited data on the combination of pembrolizumab with radiotherapy, for cohorts A and B, pembrolizumab dosing will be held 2 weeks prior to the start of radiation (i.e radiotherapy could start at completion of last cycle of pembrolizumab) and resumed 2 weeks after completion of radiation (resulting in 2 missed doses of pembrolizumab)

5. TREATMENT REGIMEN
- All participants will be treated with cisplatin (75 mg/m2) or carboplatin (AUC 6) + etoposide 100 mg/m2 IV every 3 weeks for up to 6 cycles (minimum of 4 cycles, maximum of 6).
- Pembrolizumab will be dosed at 200 mg IV fixed dose every 3 weeks until progression or for up to 2 years of therapy.
- Thoracic radiotherapy will be given per institutional standards (dose and duration may vary for individual participants).

6. CORRELATIVE STUDIES
Diagnostic biopsy specimens (20 slides) from all participants will be evaluated for PD-L1 expression on tumor cells as well as within the tumor microenvironment. For cohorts B-D, an additional mandatory biopsy specimen will also be evaluated and compared to the diagnostic biopsy specimen. Optional post-treatment biopsies will also be collected. All tumor specimens will be evaluated for PD-L1, CD3, FOXP3, TIM3, LAG3 and other immune biomarkers if sufficient tissue available. Next-gen sequencing-based genotyping and gene expression profiling using nanostring will be performed from pre-treatment biopsies from all participants. A subset who have fresh tissue samples collected will also have immune profiling and whole-exome sequencing performed. All participants will have blood samples collected pre, during, and post-treatment for evaluation of soluble PD-L1 and cytokine profiling as well as possible sequencing.

SCHEMA



Pembrolizumab therapy starts at different time points for each cohort

A) concurrent with cycle 1 chemotherapy
B) after cycle 1 (concurrent therapy)
C) after completion of 4-6 cycles of chemotherapy (maintenance monotherapy)
D) after thoracic radiation+/- prophylactic cranial irradiation (maintenance monotherapy)

Biopsies:

a) Cohort A will have single required diagnostic biopsy

b) Cohort B will have diagnostic biopsy and required pre-treatment with pembrolizumab biopsy (after cycle 1 chemotherapy)

c) Cohort C will have diagnostic biopsy and required pre-treatment with pembrolizumab biopsy (after completion of 4-6 cycles chemotherapy)

d) Cohort D will have diagnostic biopsy and required pre-treatment with pembrolizumab biopsy (after completion of chemotherapy and radiation).

Core biopsy prior to pembrolizumab required for all cohorts in addition to diagnostic biopsy for cohorts B-D (Diagnostic biopsy must be core or greater to allow for paired biopsy comparisons).

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

1.1.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) is an aggressive tumor that represents approximately 13% of all lung cancer in the US [1]. This disease has a dismal outcome that has improved only marginally in the last 30 years [2]. Although it is a chemotherapy- and radiotherapy-sensitive tumor, SCLC continues to show very high rates of relapse and metastasis, resulting in a very poor outcome. The high propensity for metastases and poor outcomes in this tumor type underscores the need to develop therapies with more durable benefit and that may block not only tumor growth, but also invasion and the development of distant metastases. In fact, given the overall poor outcomes, only two stages are clinically used: limited-stage (that which is defined as disease confined to a radiation field), for which both chemotherapy and thoracic radiation are used; and extensive-stage (widespread metastases) for which palliative chemotherapy is the standard treatment.

Historically, the treatment with the best data for efficacy and tolerance has been platinum + etoposide, which was shown to have equivalent efficacy to older regimens such as cytoxan, adriamycin, and vincristine or cytoxan, epirubicin, and vincristine but with better tolerability[3-5]. Cisplatin + irinotecan was shown to be superior in a Japanese trial[6] but repeat trials in the U.S. did not demonstrate superiority although both appeared to be efficacious[7-9]. In the U.S., carboplatin + etoposide (or cisplatin + etoposide) remains a standard of care for treatment of extensive-stage SCLC.

Prophylactic cranial irradiation (PCI) is currently recommended as a consideration by the NCCN guidelines[10] based on a European study suggesting survival benefit[11] but more recent data presented at ASCO 2015 from Japan suggests that when MRI monitoring is incorporated, there is no survival benefit[12], so it is currently not a clear-cut standard of care.

More recently, another study from Slotman and colleagues suggested that there is survival benefit to consolidation thoracic radiotherapy following good response with minimal extra-thoracic disease[13] and this is now an emerging standard of care. However, in this study, which also incorporated PCI, the 2 year survival was still a dismal 13%, suggesting more durable systemic approaches are needed.

2. PD-1 inhibition in cancer

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.

Immunotherapies involving checkpoint inhibition have opened a new door in cancer therapy with promising single agent activity seen in multiple tumor types and durable responses seen ([14-17]). In some cases, prolonged tumor control has been seen long after cessation of the inhibitory therapy and re-induction of responses can be generated with re-introduction of therapy [18].

1.2 Pembrolizumab

Pembrolizumab (Keytruda, MK-3475, previously known as SCH 900475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab contains the S228P stabilizing mutation and have no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. 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.

1.2.1 Non-clinical pharmacology

MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. MK-3475 also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T cells.

Using anti–murine PD-1 surrogate antibodies, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti–PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU), and combination therapy results in increased complete tumor regression rates in vivo. Studies also revealed that immunosuppressive doses of dexamethasone included in combination with agents used in standard-of-care treatment for

NSCLC do not reduce the anti-tumor efficacy of an anti–murine PD-1 surrogate antibody. **For complete information, please refer to the current Investigator's Brochure.**

1.2.2 Nonclinical Pharmacokinetics

After single-dose IV administration at 0.3, 3, or 30 mg/kg in Cynomolgus monkeys, decline of serum concentration followed multiphasic kinetics. Anti–drug antibodies (ADAs) were detected in most of the treated animals. Clearance (CL) and terminal half-life ($t_{1/2}$) appeared to be dose-dependent in the dose range tested with $t_{1/2}$ varying from 4 to 10 days.
In the 1-month repeat-dose (once weekly) GLP toxicity study at 6, 40, or 200 mg/kg in Cynomolgus monkeys, ADAs were detected in most of the low-dose (6 mg/kg) treated animals. The systemic exposure over the 7-day dosing interval ($AUC_{0\text{-}7\ days}$) was sex-independent and increased with increasing dose. The mean $t_{1/2}$ values in individual ADA-negative animals ranged from 15.7 to 22.3 days across doses. **For complete information, please refer to the current Investigator's Brochure.**

1.2.3 Clinical Pharmacokinetics

Pembrolizumab has been/is being studied in many different clinical trials across many tumor types, with the largest pool of information from patients with melanoma or non-small cell lung cancer (NSCLC). The observed PK profile of pembrolizumab was typical when compared with other immunoglobulin G (IgG) mAbs with a half-life (t1/2) of approximately 3 weeks.
A prior phase I study including coevaluated pembrolizumab at different dose levels (1, 3, and 10 mg/kg) and dose schedules (2-3 weeks). There was no indication of dose dependency of t1/2 in the 3 dose groups. A dose-related increase in exposure was observed from 1 to 10 mg/kg.
The long t1/2 supports a dosing interval of every 2 weeks or every 3 weeks**. For complete information, please refer to the current Investigator's Brochure.**

1.3 Clinical Efficacy

There are now extensive data on efficacy in both melanoma and NSCLC from multiple clinical trials summarized in detail in the current investigator's brochure. The significant response rate in melanoma following ipilimumab led to pembrolizumab approval in this setting in September 2014[16]. Since then, pembrolizumab has been shown to be superior to ipilimumab in untreated patients as well[19].

In non-small cell lung cancer (NSCLC), pembrolizumab has also had encouraging and durable activity, although there PD-L1 expression appears to predict for a higher chance of durable response[20]. Specifically, for patients with the highest levels of tumor cell expression of PD-L1 ($\geq$50%), there was a 45% chance of response and clearly superior progression-free and overall survival compared to patients who had 0% expression or 1-49% expression. This study utilized fresh tumor biopsies to account for any variability in expression that could be caused by prior therapy.

In addition, pembrolizumab has already been demonstrated to have activity in small cell lung cancer from a basket studying requiring PD-L1 positivity at a 1% level from archival tumor tissue samples[21]. This study showed a 35% response rate—however 157 patients were screened in order to enroll 20 patients (partly due to time frame to evaluation of PD-L1 and clinical deterioration as well as <29% PD-L1 positivity rate. It is unknown whether PD-L1 is truly a biomarker predictive of response in this setting.

1.4 Rational for Dose Selection

The current dose established from multiple prior studies is a flat dose of 200 mg every 3 weeks. 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.

1.5 Cisplatin/Carboplatin and Etoposide

Cisplatin + etoposide or carboplatin + etoposide are standard of care for 1st line therapy for SCLC, please refer to product label for further information.

1.6 Rationale

Immunotherapies involving checkpoint inhibition have opened a new door in cancer therapy with promising single agent activity seen in multiple tumor types and durable responses seen ([14-17]). In some cases, prolonged tumor control has been seen long after cessation of the inhibitory therapy and re-induction of responses can be generated with re-introduction of therapy [18].

In non-small cell lung cancer (NSCLC), a tumor type with few effective therapies and generally dismal outcomes, and one where immunotherapies have historically not been successful, marked single agent activity has been seen with inhibition of programmed death receptor 1 (PD-1) on immune cells or inhibition of programmed death receptor ligand 1 (PD-L1) [15,17,22]. Notably, PD-L1 appears to be expressed in 25-50% [23] of NSCLC tumors with expression seen both on tumor cells and within the tumor microenvironment on tumor-associated macrophages. While the relationship of expression (and on which cells) to therapeutic response is still being defined, there seems to be clearly higher activity of such inhibitors in NSCLC in the setting of PD-L1 expression within the tumor or tumor microenvironment, with 37-80% response rates in tumors that express PD-L1 compared with 0-14% in tumors that don't [14,24,25].

PD-L1 positivity is defined differently by different companies making these types of drugs. Different antibodies and methodologies are used and different specimens (archival vs. fresh) have been used to define positivity which is why there is a wide range of prevalence seen. There is less data on whether PD-L1 positivity is common in other thoracic malignancies such as small cell lung cancer (SCLC) and it is thought that the rate of positivity may be much lower in SCLC[26], although this determination is based solely on archival tissue evaluation.

Because PD-L1 is a dynamic biomarker, it is hard to compare results from archival vs. fresh tissue. For instance, it is thought that chemotherapy, radiation, and targeted therapy can modulate the expression of PD-L1 although there is little published data in this regard. Chemotherapy, radiation, and targeted therapy can all result in tumor lysis and this process itself may stimulate immune activation against tumors. If treatments modulate PD-L1 expression, it may suggest an opportunity for all patients to benefit from PD-1/PD-L1 targeted drugs if trials are designed with the right timing in mind.

SCLC provides an opportune setting to evaluate the potential importance of variability in PD-L1 expression and its influence on optimizing timing of checkpoint inhibition. All extensive-stage SCLC patients are treated with chemotherapy and recent data suggests added benefit to consolidation thoracic radiation[10]. A prior study of patients with known PD-L1 expression showed a 35% response rate. That study used archival specimens and found a 29% PD-L1 positivity rate (at 1% level) suggesting that the expression level and prevalence could be higher (and response rate/outcome therefore potentially better) in patients who have previously had chemotherapy or radiation.

The proposed study seeks to evaluate pembrolizumab therapy initiated at different times during the course of SCLC treatment: a) up front, in conjunction with initiation of chemotherapy, b) starting after two cycles of chemotherapy, c) starting after completion of 1st line chemotherapy, d) starting after completion of consolidation thoracic radiation therapy. Treatment with pembrolizumab will be preceded by biopsy for evaluation of PD-L1 expression with correlative evaluation of changes in PD-L1

expression (relative to diagnostic biopsy) and changes in other tissue- and blood-based biomarkers and immune markers.

1.6.1 Rationale for combination of pembrolizumab with chemotherapy for cohorts A and B

The combination of PD-1 inhibition with chemotherapy is attractive for several reason. First, if chemotherapy creates tumor lysis that can lead to the uptake and presentation of tumor antigens that can promote immune responses, the combination of then blocking the PD-1 checkpoint may offer synergy in boosting the immune response. This idea will be explored in cohort B, where participants will have received 1 cycle of chemotherapy prior to entering study. Second, if PD-1 inhibition can augment the immune response initially, this may allow for synergistic killing of cancer cells from two sides (CD8 cells and direct cytotoxic activity of chemotherapy) upfront. This idea will be explored in cohort A, where pembrolizumab and chemotherapy are combined upfront. Finally, if initial exposure to chemotherapy or radiation can upregulate PD-L1 expression, this may signal a timeframe during which PD_1 inhibition can be most effective (an idea which will be explored in this study in cohorts B-D).

The safety and efficacy of pembrolizumab with platinum-based regimens is actively being explored including in KEYNOTE-021, which is a study in non-small cell lung cancer combining pembrolizumab with carboplatin + paclitaxel (+/- bevacizumab) and carboplatin + pemetrexed. Other studies have combined other anti PD-1/PD-L1 antibodies with similar platinum doublets. To date, there have not been clearly adverse safety signals seen and no clear reason to think that a combination with platinum + etoposide would be different given known toxicity profiles of these agents or pembrolizumab. In order to establish safety, however, an initial cohort of 3 participants will be enrolled and once safety has been determined, an additional 3 participants will be enrolled. If safety is adequate in these 6 participants, enrollment will continue, but if not, combination therapy will be re-evaluated (see section 5.3.1 for details).

1.7 Correlative Studies Background

Immunohistochemistry:
PD-L1 has been studied extensively in studies of pembrolizumab and other PD-1/PD-L1 inhibitors with mixed results, although this has been attributed to variability in different assays and in different definitions of positivity. In NSCLC, pembrolizumab activity was significantly better in patients who had high levels of TUMOR cell expression of PD-L1[20] although the data are more mixed for nivolumab[27]. Atelolizumab had higher activity either in the setting of high tumor cell expression or immune infiltrate expression with improved outcomes in those settings.

There is less data on whether PD-L1 positivity is common in other thoracic malignancies such as small cell lung cancer (SCLC) and it is thought that the rate of positivity may be much lower in SCLC, although this determination is based solely on archival tissue evaluation primarily from surgical resections[26]. There is some data that immune infiltrate may be more prevalent in SCLC and the relative importance of PD-L1 expression in each of these compartments remains to be determined for SCLC.

SCLC is also unique compared to both NSCLC and melanoma in that it demonstrates robust response rates to both chemotherapy and radiation, both of which could modulate PD-L1 expression. Therefore, PD-L1 expression and the degree of immune infiltrate could change in response to therapy and influence the effectiveness of anti-PD-1 therapy.

This study will evaluate cohorts of patients receiving pembrolizumab prior to any therapy (cohort A), after 1-2 cycles of chemotherapy (cohort B), after completion of 1st line chemotherapy (cohort C), and after completion of radiotherapy (cohort D) to evaluate changes in PD-L1 expression as assessed by immunohistochemistry compared to pre-treatment samples. In addition, CD3 immunostaining will be performed to evaluate the degree of immune infiltrate in tumor specimens pre- and post- chemotherapy or radiotherapy. Finally, other markers of immune suppression will be simultaneously evaluated in all specimens. Dr. Luis Chirboga of NYU has developed a quantitative immunofluorescence platform that

can simultaneously measure up to 7 markers. This assay is currently being optimized on lung cancer specimens and will be used as the methodology of evaluation in this study. The current optimized markers are PD-1, PD-L1, CD3, CD8, CD163, and IDO1.

DNA sequencing
Neoantigen load has been proposed as an important biomarker of potential senstivity to PD-1 and PD-L1 inhibition in multiple tumor types[28], and compared to other malignancies, small cell lung cancer has a high mutational burden due to the very high association with heavy smoking. Given the reported lower level of PD-L1 expression in SCLC, mutational burden may be a relatively more important biomarker in this setting.

We will plan to conduct whole-exome sequencing on a subset of patients in collaboration with the Broad Institute.

Gene Expression
Inflammatory or immune-related gene expression signatures have been suggested to serve as predictors of clinical benefit beyond PD-L1 expression in multiple tumor types treated with pembrolizumab[29,30] and will be evaluated using nanostring in pre-treatment biopsies on this study.

Immune profiling in tumor biopsies is actively under evaluation at the Belfer Center for Applied Cancer Science at DFCI and in Kwok-Kin Wong's lab at NYU to understand correlates of response and resistance. Preliminary data has been generated in both mesothelioma and NSCLC and we are currently generating data from SCLC samples as well using fresh tissue that is dissociated and subject to flow cytometry using antibodies specific for the following human markers: CD3 (HIT3a; UCHT1), CD8 (RPA-T8), CD14 (M5E2; MphiP9), CD24 (ML5), CD45 (HI30), CD56 (B159), CCR7 (150503), EpCAM (EBA-1), HLA-DR (G46-6), PD-1 (EH12.1), and IgG1 isotype control (MOPC-21) from BD Biosciences (San Jose, CA); CD3 (UCHT1), CD4 (RPA-T4), CD14 (M5E2), CD15 (W6D3), CD16 (3G8), CD19 (HIB19), CD20 (2H7), CD21 (Bu32), CD25 (BC96), CD27 (M-T271), CD33 (WM53), CD38 (HIT2), CD40L (24-31), CD45 (HI30), CD45RA (HI100) , CD45RO (UCHL1), CD56 (HCD56; 5.1H11), CD66b (G10F5), CD69 (FN50), CD83 (HB15e), CD123 (6H6), CD160 (BY55), CD163 (GHI/61), CTLA-4 (L3D10), CXCR5 (J252D4), EpCAM (9C4), HMGB1 (3E8), IgM (MHM-88), Ki-67 (Ki-67), PD-1 (EH12.2H7), PD-L1 (29E.2A3), PD-L2 (24F.10C12), TIM-3 (F38-2E2), NKG2D (1D11), NKp46 (9E2), IgG2a isotype control (MOPC-173), IgG2b isotype control (MPC-11), and IgG1 isotype control (MOPC-21) from BioLegend (San Diego, CA); Pan-cytokeritin (C11) and PD-L1 (E1L3N) from Cell Signaling Technologies (Danvers, MA); CD45 (2D1), FOXP3 (236A/E7), and IL-10 (236A/E7) from Affymetrix/eBioscience (San Diego, CA); LAG3 (polyclonal) and isotype control (polyclonal) from R&D Systems (Minneapolis, MN).

Soluble PD-L1 analysis from peripheral blood samples has been extensively studied in melanoma in Steve Hodi's lab, Dana Farber Cancer Institute and is now being evaluated in all tumor types under the Center for Immuno-Oncology core facility.

Circulating tumor DNA
Dr. Love and colleagues in concert with the Broad Institute initiatives under Dr. Garraway have demonstrated that accurate and powered WES of circulating tumor cells (CTCs) is both possible and likely useful clinically[74]. This was first established in experimental and analytical workflows for census-based sequencing of single CTCs and then validated in patients with metastatic prostate cancer. The approach is currently being validated in other tumor types including SCLC. This same approach is also being extended to the sequencing of tumor-derived cfDNA and we have preliminary data demonstrating consistent adequate purity and yield of tumor-derived DNA for WES from SCLC samples.

Blood sample collections will occur at baseline for all participants, prior to the start of immunotherapy for cohorts A and B, and at the time of progression for all participants. Each blood sample would be processed for cfDNA, and germline DNA. The extraction of cfDNA and germline DNA will be performed from frozen aliquots of plasma and white blood cells, respectively. The yields and purities of cfDNA will be assessed prior to WES with ultra-low-pass (ULP) sequencing. It has been recently demonstrated

that the yield and purity of cfDNA from a set of previously collected SCLC plasma samples is adequate for sequencing (25-30%) with variance in the quantity through the course of therapy. In addition to evaluating genomic alterations and neoantigen profile changes as a result of exposure to therapy in DNA extracted from blood, the findings will be compared to parallel sequencing analysis done on tissue biopsies from the same subjects to compare similarities and any potential differences. This analysis will help us to determine whether cfDNA sequencing may be a possible substitute for tissue-based sequencing which would be critical particularly in this tumor type given the difficulty in obtaining adequate tissue for molecular analysis. We will also evaluate quantitative changes in tumor-derived cfDNA through the course of therapy to determine correlation with tumor burden.

1.8 Research Risks & Benefits

1. Risk of Study Drug

Pembrolizumab

Very common, side effects seen in (> 20% chance this will happen):

- Itching of the skin
- Loose or watery stools
- Cough

Common, side effects seen in (≥ 10% to 20% chance this will happen):

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

Uncommon,side effects seen (>1% to < 5% chance this will happen)

- Inflammation of the lungs so you may feel short of breath and cough.
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection.

Rare, side effects seen in (<1% chance this will happen)

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating,, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling

If you have had an allogenic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of transplant you have had.

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2. Other Risks of Study Participation

Additional risks to study participation include breach of confidentiality and risks associated with blood draw. Privacy procedures in place and good clinical practice guidelines are followed for the study to minimized risks associated with research procedures and participation. The risks associated with blood draw include weaknesses, redness, pain, bruising, bleeding or infection at the needle site.

3. Potential benefits

The potential benefits to subjects with study participation are improved overall survival. The information obtained from this research may help others with this disease in the future.

2 Study Objectives

2.1 Primary Objectives

Primary Objective:

- To determine PD-L1 expression status in subjects with SCLC and assess changes in expression following chemotherapy and radiation in pre-specified cohorts of SCLC.
  - A—subjects who are chemotherapy and radiation naïve
  - B--subjects who have had 1 prior cycle of 1st line chemotherapy with cisplatin or carboplatin + etoposide for extensive-stage SCLC
  - C—subjects who have completed 4-6 cycles of chemotherapy with cisplatin/carboplatin + etoposide and are not going to receive further radiation therapy
  - D—subjects who have completed 4-6 cycles of cisplatin/carboplatin + etoposide and consolidation thoracic radiation therapy (with or without the addition of prophylactic cranial irradiation

2.2 Secondary Objectives

- To evaluate median and progression-free survival at 3 and 6 months with the addition of pembrolizumab to standard therapy
- To evaluate median overall survival and overall survival at 6 months with the addition of pembrolizumab to standard therapy
- To evaluate response rates at 6 and 12 weeks by RECIST 1.1 and irRECIST with the addition of pembrolizumab to standard therapy
- To evaluate safety profile of pembrolizumab in combination with standard therapy for small cell lung cancer.

2.3 Exploratory Objectives

- To evaluate soluble PD-L1, circulating cytokines, and circulating T cell repertoire before, during, and after therapy with pembrolizumab and their relationship to clinical benefit with

pembrolizumab therapy.

- To evaluate genetic changes using nextgen sequencing (oncopanel) and gene expression changes using nanostring before, during, and after therapy with pembrolizumab and determine relationship, if any, to clinical benefit with pembrolizumab. If feasible, will also perform whole-exome sequencing on a subset of tumor biopsies to evaluate mutational burden prior to treatment with pembrolizumab and determine relationship to clinical benefit.

3 Study Design

3.1 General Design

This is a phase II study of pembrolizumab therapy initiated at different times during the course of SCLC treatment: **a)** up front, in conjunction with initiation of chemotherapy, **b)** starting after one cycle of chemotherapy, **c)** starting after completion of 1st line chemotherapy, and **d)** starting after completion of consolidation thoracic radiation therapy.

Treatment with pembrolizumab will be preceded by biopsy for evaluation of PD-L1 expression at baseline prior to any treatment (cohort A); after short-term exposure to chemotherapy (cohort B); after completion of chemotherapy (cohort C, which will include both patients with chemotherapy-sensitive disease (stable/continued response) and those with chemotherapy-refractory disease (progression within 60 days of completion of treatment with carboplatin-etoposide); and after exposure to radiation therapy (cohort D). These timed biopsies will permit correlative evaluation of changes in PD-L1 expression (relative to diagnostic biopsy) and changes in other tissue and blood based immune markers before, during, and after therapy.

3.2 Primary Study Endpoints

- To determine PD-L1 expression status in subjects with SCLC and assess changes in expression with chemotherapy and radiation
  --We will evaluate PD-L1 expression as determined by immunohistochemistry in pre-treatment and archival samples.

3.3 Secondary Study Endpoints

- To evaluate progression-free survival with the addition of pembrolizumab to standard therapy
  - endpoint: to evaluate median progression-free survival in overall population with stratification by cohort as compared to historical control of 5.4 months[31]
- To evaluate overall survival with the addition of pembrolizumab to standard therapy
  - Endpoint: to evaluate median overall survival in overall population with stratification by cohort as compared to historical control of 9.5 months.[31]
- To evaluate response rates by RECIST 1.1 and irRC (as adapted to RECIST 1.1[32]) with the addition of pembrolizumab to standard therapy (for cohort A only)
  - Endpoint: response rate at 6 and 12 weeks after initiation of pembrolizumab therapy as measured by RECIST 1.1 and irRC (as adapted to RECIST 1.1[32])

3.4 Exploratory Objectives

- To evaluate soluble PD-L1, circulating cytokines and immune profiling, before, during, and after therapy with pembrolizumab and their relationship to clinical outcome. Given that these assays are still being optimized and we don't know what pattern of circulating factors will be observed in SCLC (for instance, 5 different isoforms of soluble PD-L1 are seen in melanoma, Steve Hodi, personal communication), descriptive statistics will be used for assessment of serial measures of circulating markers.

- To evaluate gene expression using nanostring and tumor genotype using next-generation sequencing and whole-exome sequencing (WES) and determine relationship, if any, to clinical benefit with pembrolizumab (WES will be performed on a subset of samples if tissue is available). Again, given unknown findings for SCLC, descriptive statistics will be used to assess relationship of mutational pattern to outcome.

4 Subject Selection and Withdrawal

Participants will include patients with extensive-stage small cell lung cancer undergoing standard treatment with platinum-etoposide combination chemotherapy. One cohort of participants will be enrolled PRIOR to the start of chemotherapy and receive pembrolizumab along with chemotherapy from the start of therapy (cohort A). A second cohort of participants will be eligible to enroll after 1 prior cycle of chemotherapy (cohort B) and will receive pembrolizumab along with continued chemotherapy. A third cohort will be eligible to enroll after completion of 1st line chemotherapy (cohort C) and will receive pembrolizumab as maintenance therapy. A fourth cohort will be eligible to enroll after completion of consolidation thoracic radiation (cohort D) and will receive pembrolizumab as maintenance therapy.

4.1 Eligibility/Inclusion Criteria

1. Participants must have histologically confirmed small cell lung carcinoma not amenable to initial concurrent radiotherapy (extensive-stage disease).

2. Participants may have evaluable or measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 7.0 for the evaluation of measurable disease.

3. Participants in cohort B must have completed 1 cycle of systemic chemotherapy. Therapy with the combination must start no sooner than 3 weeks from the last dose of chemotherapy and no later than 5 weeks from the last dose of chemotherapy. Participants in cohort B must not have had progression of disease prior to the start of therapy.

4. Participants in cohort C must have completed systemic therapy (4-6 cycles cisplatin or carboplatin + etoposides) and NOT be a candidate for consolidation thoracic radiotherapy or PCI. Participants in cohort C must initiate therapy with pembrolizumab within 6 weeks of the last dose of chemotherapy (therapy must not start within 2 weeks from the last dose). Participants in cohort C must not have had progression of disease prior to the start of therapy.

5. Participants in cohort D must have completed systemic therapy AND have completed either consolidation thoracic radiotherapy or PCI or both completed either consolidation thoracic radiotherapy or PCI or both. Participants in cohort D must initiate therapy with pembrolizumab within 6 weeks of the last dose of radiation. Therapy must not start within 2 weeks from the

last dose. **Consolidation radiotherapy dose must NOT be more than 3000 cGy**. Participants in cohort D must not have had progression of disease prior to the start of therapy.

6. Age > 18 years.

7. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

8. Life expectancy of greater than 3 months.

9. Participants must have normal organ and marrow function during screening and on Cycle 1, day 1 as defined below:

Table 1 Adequate Organ Function Laboratory Values

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

10. Availability of a diagnostic or pre-chemotherapy tissue biopsy is required (cytologic specimens or bone biopsies not accepted). This biopsy must be within 6 weeks of starting initial therapy. A minimum of 20 5 μm slides or block is required.

11. Participants in cohorts B-D must be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen within 4 weeks to initiation of treatment and AFTER the last dose of any prior therapy.

12. Participants with treated brain metastases are allowed. Radiation must be completed at least 2 weeks prior to pembolizumab dosing and participants must not require ongoing steroids. Participants with untreated brain metastases that are all <5 mm with no clinical symptoms or vasogenic edema may be allowed on study on a case-by-case basis on discussion with sponsor. These participants will require MRI monitoring every 6 weeks to ensure stability.

13. The effects of pembrolizumab on the developing human fetus are unknown. For this reason and because the chemotherapy and radiation also used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) or be surgically sterile prior to study entry and for the duration of study participation. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

14. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of chemotherapy, radiation, and pembrolizumab administration.

15. Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

1. Participants in cohort A may not have had prior therapy for their disease. Participants in cohort B may not have had more than 1 cycle of systemic therapy (cisplatin or carboplatin + etoposide). Participants in cohort C and D should not have had more than one prior regimen of chemotherapy.

2. For participants entering cohorts C or D, prior treatment-related toxicities should have resolved to grade 1 or baseline (with the exception of anemia (as per inclusion criteria, alopecia, and neuropathy (≤ grade 2 allowed).

3. Participants who have had a CR after pre-study therapy are not eligible for study.

4. No thoracic radiation > 3000 cGy allowed.

5. Prior radiation or surgery must have completed at least 2 weeks prior to initiation of therapy and all toxicities or complications from these must have resolved to baseline or grade 1 prior

to starting therapy (with the exception of anemia (as per inclusion criteria, alopecia, and neuropathy (≤ grade 2 allowed).

6. No stroke, myocardial infarction, or major surgery within 3 months of starting on therapy.

7. Participants who are receiving any other investigational agents or have received investigational therapy or any anti-cancer monoclonal antibody (mAB) within 4 weeks prior to the 1st dose of pembrolizumab.

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

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

10. Has known history of non-infectious pneumonitis which required steroids, or any evidence of current, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

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

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

14. History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab, cisplatin, carboplatin, or etoposide.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

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

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

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

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

20. 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.*

21. Has a known additional malignancy that is progressing or requires active treatment or has required active treatment within the last 2 years. Exceptions include basal cell carcinoma of

the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer or in situ bladder cancer.

22. Has a paraneoplastic syndrome other than SIADH (hyponatremia).

23. Evidence of interstitial lung disease

4.3 Inclusion of Women and Minorities

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

4.4 Subject Recruitment

Target Enrollment for this study is 60 patients. Each cohort will consist of 15 patients. The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of these populations.

Patients will be recruited from physicians at the NYULMC Perlmutter Cancer Center (PCC). Consenting, screening, and treatment take place at the NYULMC PCC under the supervision of the Overall PI. Prospective subjects receive detailed information about this study its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They also receive the informed consent document to read. All questions are answered by the Principal Investigator.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.
2. Determine patient eligibility See Section 4.1 and Section 4.2
3. Submit registration to NYULMC Perlmutter Cancer Center CTO
4. Receive registration confirmation from the Research Coordinator at NYU Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient by the research coordinator, which will be distributed to the study team upon registration.

Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows the established procedures of the NYULMC PCC CTO.

4.4.1 Informed Consent

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions

or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. For these patients the consent letter and all other information will be administered orally and a witness, not related to the research project, will be present while the oral presentation is given. A short form will be utilized for the subject to sign in his/her name and the translator and/or witness must sign the short form. The translator will also sign the main consent form.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form

4.4.2 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

4.4.3. Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Overall Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's six month Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six month review to their IRB of record at the time of continuing review.

4.4.4. Patient Informed Consent at Additional Sites

The Principal Investigator at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for this research study. It is NYULMC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials, unless Fellows are listed as co-investigators.

The Investigator must ensure that each participant, is fully informed about the nature and objectives of the study and possible risks associated with participation. All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative (if applicable), and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

All parties will ensure protection of participant personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, NYULMC PCC will maintain high standards of confidentiality and protection of participant personal data.

The informed consent form must be in compliance with ICH/GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the NYU IRB and Merck before use.

4.5 Registration Procedures

4.5.1. General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.
Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrolment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office. The following materials must be submitted to the Research Coordinator for registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 24 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be distinguished to the study team upon registration.

Pretreatment evaluation will therefore be as directed by standard clinical practice. Eligible subjects will be entered on study by the study coordinator.

All patients will be required to sign a written informed consent prior to being registered on this study. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered on study. Subjects must not start any protocol procedures prior to registration.

Issues that would cause treatment delays should be discussed with the Overall Principal Investigator.

4.5.2 Patient Registration at Other Participating Institutions

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is NYULMC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

Enrollment at additional sites can occur once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYULMC Perlmutter Cancer Center Clinical Trials Office. Once, all required documents are provided to NYULMC PCC Clinical Trials Office an activation notification will be sent to the PI and research coordinator at that site.

Central registration for this study will take place at NYULMC PCC.

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYULMC PCC Research Coordinator and forward a copy of the signed consent to NYULMC PCC Clinical Trials Office within 24 hours.

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 24 hours of research coordinators receipt of all of the above documents. Once eligibility is verified, a unique subject study number will be issued within 24 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYULMC PCC Clinical Trials Office will return a signed eligibility confirmation worksheet with the subject's unique study number. The subject will not be identified by name. This is the point, at which, the patient is considered on the study.

Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator, Joshua Sabari, MD. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled.

4.6 Early Withdrawal of Subjects

4.6.1 When and How to Withdraw Subjects

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

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

Every effort should be made to obtain information on subjects who withdraw from the study. The date the participant was removed, must be documented.

4.6.2 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10 –Adverse Event reporting. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of

restarting treatment if they meet the criteria specified in Section 6.6.10.6. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 6.6.10.3 and then proceed to the Follow-Up Period of the study (described in Section 6.6.10.4.

5 Study Drug

5.1 Description

Pembrolizumab (Keytruda, MK-3475, previously known as SCH 900475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

5.2 Trial Treatment

The treatment to be used in this trial is outlined below:

Table 2 Trial Treatment

Cohort	Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
A and B[1]	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
	carboplatin OR	AUC 6	Q3W	IV infusion	Day 1 of each 3 week cycle	Standard care
	cisplatin	75 mg/m2	Q3W	IV infusion	Day 1 of each 3 week cycle	Standard of care
	Etoposide	100 mg/m2	Q3W	IV infusion	Days 1, 2, 3 of each 3 week cycle	Standard of care
C	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
D	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

[1]for cohort A, the number of total cycles of chemotherapy will be 4-6 total, while pembrolizumab will continue as long as disease has not progressed or patient not removed from study for other reasons for up to 2 years. For cohort B, patients should have received 1 cycle platinum + etoposide prior to entry onto study, so the total number of cycles during study will be 3-5 (such that the TOTAL number of cycles on or off study is a MINIMUM of 4 and a MAXIMUM of 6).

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

5.3 Treatment Regimen

Pembrolizumab will be administered every 3 weeks, with 21 consecutive days defined as a treatment cycle. For cohort A, pembrolizumab will be administered together with ALL cycles of chemotherapy (4-6 total cycles). For cohort B, pembrolizumab will be administered together with cycles during study which may be 3-5 additional cycles. Specifically, participants in cohort B should have received 1 prior cycle of chemotherapy. These patients should be continued on the same treatment regimen while on

study to a TOTAL of 3-5 cycles of chemotherapy (on and off study). For cohorts C and D, pembrolizumab will be administered as monotherapy (see below).

Cisplatin (75 mg/m2) or carboplatin (AUC 6) will be administered every 3 weeks, with 21 consecutive days defined as a treatment cycle. Either cisplatin or carboplatin will be administered together with etoposide 100 mg/m2 given on days 1, 2, and 3 as per institutional standards of care. Criteria for treatment and dose modifications for each of these drugs will occur as per institutional standards of care.

Platinum and etoposide treatments will be given only in cohorts A and B. Cohorts C and D will have pembrolizumab monotherapy following completion of standard therapy.

Cohort A: pembrolizumab + carboplatin or ciplatin + etoposide X 4-6 cycles followed by pembrolizumab monotherapy for up to 2 year (34 cycles post-combination therapy).

Cohort B: Participants may have received 1 cycle of prior therapy. They will be continued on the SAME treatment regimen (carboplatin or ciplatin + etoposide) together with pembrolizumab for up to a TOTAL of 4-6 cycles (including cycles prior to study). Treatment with the combination should start no sooner than 3 weeks and no later than 5 weeks from the start of the last cycle of chemotherapy. Maintenance pembrolizumab will continue following completion of combination therapy for up to 2 years (34 cycles post-combination therapy).

FOR COHORTS A AND B ONLY: Initial enrollment will include only 3 participants, who may be enrolled into either cohort A or B. Once these three participants have cleared cycle 1, an additional 3 participants may be enrolled into either cohort A or B if no DLTs are seen. If < 2 DLT's are seen in the first 6 participants, enrollment to the rest of the cohorts will proceed. If $\geq$ 2 DLTs are seen, enrollment will be halted and discussion of dosing change with Merck and the overall PI will occur prior to further enrollment. Based on safety data to date with other platinum-based regimens, we do not anticipate interactions that would necessitate dosing change, so there will not be pre-specified dose reductions planned. Cohorts A and B will be pooled for the purposes of DLT evaluation as the treatment regimen after study initiation is identical.

Cohort C: participants will have previously received 4-6 cycles of platinum-based therapy and have stable disease. In addition, these patients must not be candidates for further consolidation thoracic radiotherapy or PCI. Pembrolizumab treatment should start no sooner than 2 weeks and no later than 6 weeks from the start of the last cycle of chemotherapy. Therapy will continue for up to 34 cycles (2 years).

Cohort D: participants will have previously received 4-6 cycles of platinum-based chemotherapy and thoracic radiation therapy or PCI or both. Pembrolizumab treatment should start no sooner than 2 weeks and no later than 6 weeks from the start of the last dose of radiation. Therapy will continue for up to 34 cycles (2 years).

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 1.8.1. Appropriate dose modifications are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

All patients will be required to have a tissue biopsy within 3 weeks of study entry and after completion of prior therapy (see section 6.6.7.1). For cohort A, this time frame could be up to 6 weeks.

5.3.1 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicities are defined as any hematologic or non-hematologic toxicity of grade 3 or above possibly attributable to drug that does not resolve within 12 weeks with or without steroids (and steroids

must be able to be tapered to <10 mg po qd within that time frame). Although the DLT period is officially the 1st two cycles, if any participant experiences a grade 3, 4, or 5 toxicity, they will be closely monitored. If those participants are not able to resume treatment within 6 weeks (2 cycles), enrollment into cohorts A and B will be halted to allow for a full 12 week evaluation prior to further enrollment.

For cohorts A and B only: initially 3 participants will be enrolled. When those three participants have completed the DLT evaluation period (2 cycles), if 0 of 3 have experienced a DLT (defined as hematologic or non-hematologic toxicity of grade 3 or above possibly attributable to drug that does not resolve within 12 weeks with or without steroids), the study may continue to enroll an additional 3 participants for DLT monitoring. If 1 of 3 participants experiences a DLT, an additional 3 participants will be enrolled and followed. If > 2 participants experiences a DLT (either when 3 or when 6 enrolled), further enrollment will be halted for discussion between Merck and the overall PI to determine whether additional enrollment should continue or if dose modifications should be made. If no more than 1 of 6 participants experiences a DLT, full enrollment of the cohort may proceed.

Management and dose modifications associated with the above adverse events are outlined below.

Number of Participants with DLT during initial 3 participant enrollment	Continuation Decision Rule
0 out of 3	Enroll 3 additional participants and monitor for DLT.
≥2	Further enrollment will be stopped until discussions re: dose modification between Merck and overall PI determine whether further dose levels should be explored.
1 out of 3	Enter at least 3 more participants and monitor for DLT. • If 0 of these 3 participants experience DLT, proceed with complete enrollment of the cohort. • If 1 or more of this group suffer DLT, then further enrollment will be stopped until discussions re: dose modification between Merck and overall PI determine whether further enrollment should continue and if dose modification is required.

5.3.2 Dose Delays/Dose Modifications

Dose delays and modifications of cisplatin or carboplatin and etoposide should follow institutional standards (namely, that participants meet re-treatment criteria prior to re-initiation of therapy and may be dose-reduced per institutional standards). However, if dosing of chemotherapy that occurs concurrently with pembrolizumab is held (cohorts A and B), then that day's dosing of pembrolizumab should also be held. If dose –delay of chemotherapy for hematologic or other laboratory toxicity results in a > 4 week delay in therapy, chemotherapy should be discontinued and pembrolizumab may continue as monotherapy. Exceptions to this may be reviewed on a case-by-case basis with sponsor.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related

toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.8.3 for supportive care guidelines, including use of corticosteroids.

Table 3. Toxicity Management and Dose Reduction/Delay/Discontinuation

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled

interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

If dosing interruption or delay occurs, when treatment is restarted, the cycle should restart (exceptions may be discussed with the overall study Sponsor (PI)) and the schedule of assessments going forward should be in accordance with the new start date of that cycle.

5.4 Pre-Treatment Criteria

5.4.1 Cycle 1, Day 1

Participants should meet treatment criteria for platinum and etoposide per institutional standards. For participants entering cohorts C or D, prior treatment-related toxicities should have resolved to grade 1 or baseline (with the exception of anemia (Grade 2 allowed), alopecia, and neuropathy (grade 2 allowed).

5.4.2 Subsequent Cycles

Participants should meet treatment criteria for platinum and etoposide per institutional standards.

5.5 Agent Administration

5.5.1 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion on day 1 of every 21 day cycle.

After completion of chemotherapy, pembrolizumab will be administered as monotherapy for up to a total of 34 cycles (2 years of monotherapy).

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).
The Pharmacy Manual for pembrolizumab contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.5.2 Cisplatin or carboplatin and etoposide.

Cisplatin, carboplatin, and etoposide should be administered as per institutional standards.

Cisplatin 75 mg/m^2 will be administered as an IV infusion per institutional standards on day 1 of every 21 day cycle for up to 6 cycles for cohort A and for up to 5 cycles for cohort B (total number of cycles of chemotherapy on and off study should not total more than 6)

Carboplatin AUC 6 will be administered as an IV infusion per institutional standards on day 1 of every 21 day cycle for up to 6 cycles for cohort A and for up to 5 cycles for cohort B (total number of cycles of chemotherapy on and off study should not total more than 6)

Etoposide 100 mg/m^2 will be administered as an IV infusion per institutional standards on day 1, day 2, and day 3 of every 21 day cycle for up to 6 cycles for cohort A and for up to 5 cycles for cohort B (total number of cycles of chemotherapy on and off study should not total more than 6).

5.5.3 Availability

Pembrolizumab is provided by Merck and study drug to each site will be supplied directly by Merck.

5.5.4 Preparation

Following reconstitution with sterile water for injection, Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) 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.

If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible, Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS unless instructed by NYULMC PCC in writing. Refer to pharmacy manual for further details.

5.5.5 Timing of Administration

Pembrolizumab will be administered at least 30 minutes prior to premedication for the chemotherapies.

Trial treatment should be administered on Day 1 (or days 1, 2, and 3 for etoposide) of each cycle after all procedures/assessments have been completed.

All trial treatments will be administered on an out-patient basis.

For subjects who experience disease progression, investigators may elect to interrupt treatment by deferring the decision to continue/discontinue treatment in the trial until confirmation of disease progression per RECIST 1.1 at least 28 days from the date of imaging demonstrating disease progression. Subjects for whom disease progression is not confirmed on subsequent imaging may resume treatment.

5.5.5.1 Pembrolizumab dose interruption for planned radiation as part of initial treatment

For cohorts A and B, dosing may be interrupted for consolidation thoracic radiation and/or prophylactic cranial irradiation.

Radiation treatments should be confined to a period of 3 weeks (i.e. if both consolidation thoracic radiation and prophylactic cranial irradiation are planned, they should be done concomitantly). Radiation should commence no less than 2 weeks and no more than 4 weeks from the last dose of pembrolizumab. Pembrolizumab should be restarted no less than 2 weeks and no more than 6 weeks after completion of radiation.

5.5.6 Infusion-related reactions

Infusion –related reactions to cisplatin or carboplatin and etoposide should follow the guidelines below. If etoposide cannot be used again, etoposide phosphate may be substitute.

Table 4 Infusion Reaction Treatment Guidelines for MK-3475

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.5.7 Other treatments

For participants on cohorts A and B who may be candidates for consolidation thoracic radiation or PCI after the completion of initial platinum-based therapy, pembrolizumab dosing should be halted 2 weeks prior to initiation of radiation and restarted no earlier than 2 weeks post-completion of radiation. For participants on this study, the total dose of thoracic radiation should not exceed 3000 cGy given in 10 fractions.

5.6 Administration

Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter. 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). Please refer to the pharmacy manual for further details.

5.7 Subject Compliance Monitoring

Subjects who are significantly non-compliant with protocol required visits, assessments, and dosing instructions may be withdrawn from the study by the investigator and/or sponsor. The investigator and/or sponsor have the right to discontinue a subject from study treatment or withdraw a patient from the study at any time.

5.7.1 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

5.7.2 Participant replacement strategy

Participants in this study will not be replaced unless if there is not sufficient tissue to evaluate the primary endpoint (PD-L1 expression) from either archival or pre-treatment biopsies from at least 12 participants. Tissue evaluation will be ongoing in real time to determine adequacy of assessment. Initial tissue adequacy assessment from diagnostic biopsy specimens will be required prior to starting on therapy to minimize this risk.

5.8 General Concomitant Medication and Supportive Care Guidelines

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

5.8.1 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.

5.8.2 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:

Immunotherapy not specified in this protocol
Chemotherapy not specified in this protocol
Investigational agents other than pembrolizumab
Radiation therapy not specified in this protocol

Note: palliative radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion after discussion with sponsor.

- 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 Sponsor.

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

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

5.8.3 Supportive Care Guidelines

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

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event and should be discussed with the overall PI.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

5.9 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment with platinum + etoposide may continue for UP TO 6 TOTAL CYCLES (on and off therapy) but may be stopped at 4 cycles at investigator discretion based on tolerability. Treatment may be stopped at any time if one of the below criteria applies. Pembrolizumab may continue for up to 34 cycles (2 years) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply UNLESS THERE IS ISOLATED CNS PROGRESSION (Section 5.11.2). The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Joshua Sabari, MD, 212-731-5662 .

5.9.1 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.

It must be reported immediately to the regulatory specialist, research coordinator, and NYUPCCsafetyreport@nyumc.org in accordance with the procedures described below. Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication. This will be reported to the IRB if necessary.

The outcome of the pregnancy will be reported to Merck without delay and within 2 working days 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).

When a pregnancy has been confirmed, the following procedures should occur:

- The investigator must notify the sponsor immediately.
- The study drug must be discontinued immediately.
- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.

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 NYULMC. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to NYULMC and to Merck and followed as described above and in Section 10.2.2).

5.9.2 Use in Nursing Women

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

5.10 Diet/Activity/Other Considerations

5.10.1 Diet

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

5.10.2 Contraception

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

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

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

5.11 Duration of Follow up

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Protocol Flow Chart) and Section 6.6.9 Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 10.3). Subjects who discontinue for reasons other than progressive

disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. The total study duration will be 3 years or until death of all participants.

5.11.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 6.6.9.6.

Participants will be followed for one year after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.11.2 Treatment beyond isolated CNS progression

If there is isolated CNS progression for which participants may be treated with radiation (i.e. participants who did not receive PCI but then experienced isolated CNS progression), treatment with pembrolizumab may be continued following radiation.

Radiation should commence no less than 2 weeks and no more than 4 weeks from the last dose of pembrolizumab. Pembrolizumab should be restarted no less than 2 weeks and no more than 6 weeks after completion of radiation.

5.12 Ordering

Each individual site will be responsible for ordering and maintaining drug supply of pembrolizumab from Merck, Sharp, and Dohme.

5.13 Receiving, Storage, Dispensing and Return

5.13.1 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

5.13.2 Receipt of Drug Supplies

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.
Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

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

5.13.3 Storage and Stability

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

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.

5.13.3.1 Compatibility

- 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

5.13.4 Dispensing of Study Drug

5.13.4.1 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Pembrolizumab (MK-3475) Powder for Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C). Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F)) for up to 24 hours. Refer to pharmacy manual for further details.

5.13.5 Return or Destruction of Study Drug

Unused pembrolizumab (MK-3475) Powder for Solution for Infusion or Solution for Infusion vial(s) shall be returned to the designated facility for destruction.

- For US clinical sites, return to: Fisher Clinical Services, Return and Destruction Center, 700B Nestle Way, Breinigsville, PA 18031

Solution remaining in a used vial should be discarded as Chemotherapeutic Waste according to local procedures of the institution.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

5.14 Standard Agents

Cisplatin, carboplatin, and etoposide will be purchased commercially as they are for standard of care. Storage, handling, administration, accounting, and destruction will be as per institutional standards.

6 Study Procedures

The Trial Flow Chart - Section 7 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

6.2 Inclusion/Exclusion Criteria

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

6.3 Medical History

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

6.4 Prior and Concomitant Medication Review

6.4.1 Prior Medications

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

6.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs should be recorded as defined in Section 10.3

6.4.3 Prior chemotherapy

The investigator or qualified designee will record all chemotherapy cycles and doses given prior to study entry as well as reported response to prior therapy. For cohort C, CT scan to assess initial response will be collected and evaluated by RECIST 1.1 criteria as for scans ON-STUDY and recorded in screening documentation.

6.5 Disease Details

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

6.5.1 Prior Treatment Details

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

6.5.2 Subsequent Anti-Cancer Therapy Status

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

6.6 Clinical Procedures/Assessments

6.6.1 Adverse Event (AE) Monitoring

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

Please refer to section 10.2 for detailed information regarding the assessment and recording of AEs.

6.6.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and directed physical exam for other visits. Clinically significant abnormal findings should be recorded as medical history.

6.6.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 7.0). Vital signs should include temperature, pulse, respiratory rate, height, weight and blood pressure.

6.6.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG performance status (see Section 7.0) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.6.5 Tumor Imaging and Assessment of Disease

CT scan or MRI (as indicated) will be performed at baseline (within 28 days of initiation of treatment) and after every 2 cycles. Brain MRI should be performed during screening. All scans will be subjected to RECIST 1.1 evaluation and modified RECIST (ir RECIST 1.1)

Participants in cohorts A and B should have brain MRI performed during standard planned radiologic assessment at the completion of chemotherapy.

Participants in cohort C and participants in cohort A and B who do not have brain metastases after completion of chemotherapy and DO NOT undergo prophylactic cranial irradiation should have brain MRI performed every 12 weeks during planned radiologic assessments (after completion of chemotherapy).

6.6.6 Pulmonary Function Tests

A baseline set of pulmonary function tests including DLCO will be obtained during screening.

6.6.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

6.6.7.1 Tumor Tissue Collection

For cohort A, an archival (diagnostic) tissue biopsy obtained within six weeks of study start (minimum 20 5 um slides) will be required. For cohorts B-D, an archival (diagnostic) tissue biopsy (minimum 20 5 um slides) will be required (prior to initiation of any treatment). In addition, for cohorts B-D, a new core tissue biopsy (minimum 3 cores from lung tissue, minimum 4 cores from any other site) will be required prior to study entry.

A minimum of 4 participants in each cohort (B-D) will be required to have fresh tissue sampling from which FNA will be also obtained for immune profiling at the Belfer Institute. For those participants, FNA will be immediately placed into RPMI media and hand-couriered to the Belfer Institute (Patrick Lizotte at DFCI) or to the Wong laboratory at NYU. The remaining core biopsies of fresh tissue will be formalin-fixed and paraffin-embedded as per institutional standards for further evaluation with IHC or tumor DNA/RNA extraction for sequencing or nanostring and shipped to the Overall PI, Dr. Joshua Sabari (see also section 6.7.2.1).

Optional core biopsies will be obtained at the time of tumor progression from participants who consent to this procedure. A minimum of 3 cores will be required.

6.6.7.2 Correlative Studies Blood Sampling

10 ml of blood for evaluation of soluble PD-L1 (and possibly for additional cytokine profiling) will be obtained at screening, cycle 2 day 1, every other cycle day 1 thereafter, and at the time of progression.

6.6.8 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Screening assessments other than scans should take place within 21 days of study entry.
Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)
Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests to be performed during screening

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

[a] Perform on women of childbearing potential only during screening and after every 4 cycles. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

[b]During screening only and as clinically indicated thereafter.

[c] TSH to be obtained every 2 cycles and T3/T4 to be obtained at screening and if TSH abnormal thereafter.

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

6.6.9 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.0 - Study Procedures.

6.6.9.1 Screening Period

The screening period includes 21 days for pre-study assessments except for scans and consent forms which must be completed within 28 days.

6.6.9.2 Treatment Period

The treatment period consists of up to 34 cycles (2 year) of treatment with pembrolizumab in addition to up to 5 (cohort B) or 6 (cohort A) cycles of chemotherapy. Cohort A and B patients may also have treatment with pembrolizumab interrupted for consolidation thoracic radiation and/or prophylactic cranial irradiation as indicated. Re-treatment after cessation of pembrolizumab following a CR will also continue for up to 1 year (See section 6.6.9.6).

6.6.9.3 Post-treatment visits—Safety Follow-up

For participants who progress on therapy or after completion of therapy, a safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 6.6.9.6) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

6.6.9.4 Post-treatment visits—Follow up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 27 months (the maximum time of treatment + 3 months), the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 6.6.9.5 Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.
Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.9.6 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Participants treated in the second course phase should follow the schedule of assessments as for maintenance pembrolizumab cycles in section 7.0.

6.6.9.5 Survival Follow-up

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

6.6.9.6 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

    OR

    - Had SD, PR or CR and stopped pembrolizumab treatment after 12 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 4.1.9
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.10.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject 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.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.
Visit requirements will be the SAME as those for all cycles of maintenance pembrolizumab as outlined in Study Calendar/Protocol Flow Chart in section 7.

6.7 Biomarker, Correlative, and Special Studies

6.7.1 Biomarker/Correlative Studies

The studies described below are all ancillary/exploratory in nature and are designed to determine whether protein expression, mutational burden, gene expression, soluble PD-L1 or immune cell profiling can be associated with clinical benefit or resistance.

6.7.1.1 Immunohistochemistry

PD-L1 has been studied extensively in studies of pembrolizumab and other PD-1/PD-L1 inhibitors with mixed results, although this has been attributed to variability in different assays and in different definitions of positivity.

There is less data on whether PD-L1 positivity is common in other thoracic malignancies such as small cell lung cancer (SCLC) and it is thought that the rate of positivity may be lower in SCLC, although this determination is based primarily archival tissue evaluation primarily from surgical resections[26]. There is some data that immune infiltrate may be more prevalent in SCLC and the relative importance of PD-L1 expression in each of these compartments remains to be determined for SCLC. A recent basket study of pembrolizumab which included SCLC patients found a 28.6% rate of positivity of PD-L1 (on at least 1% of tumor cells) from archival specimens[21].

SCLC is also unique compared to both NSCLC and melanoma in that it demonstrates robust response rates to both chemotherapy and radiation, both of which could modulate PD-L1 expression. Therefore, PD-L1 expression and the degree of immune infiltrate could change in response to therapy and influence the effectiveness of anti-PD-1 therapy.

This study will evaluate cohorts of patients receiving pembrolizumab prior to any therapy (cohort A), after 1-2 cycles of chemotherapy (cohort B), after completion of 1st line chemotherapy (cohort C), and after completion of radiotherapy (cohort D) to evaluate changes in PD-L1 expression as assessed by immunohistochemistry compared to pre-treatment samples. In addition, CD3 immunostaining will be performed to evaluate the degree of immune infiltrate in tumor specimens pre- and post- chemotherapy or radiotherapy.

Finally, other markers of immune suppression will be simultaneously evaluated in all specimens. Dr. Luis Chirboga of NYU has developed a quantitative immunofluorescence platform that can simultaneously measure up to 7 markers. This assay is currently being optimized on lung cancer specimens and will be used as the methodology of evaluation in this study. The current optimized markers are PD-1, PD-L1, CD3, CD8, CD163, and IDO1. PD-L1 IHC will also independently be done at NYU using the 22C3 antibody optimized on a Ventana Platform as per Neuman T et al, Journal of Thoracic Oncology 2016.

6.7.1.2 Collection of Specimens

For cohort Archival tissue from a biopsy obtained within six weeks of study start (minimum 20 5 um slides, 25 preferred) will be required (this sample could be archival tissue from a diagnostic biopsy although if insufficient material is available, a fresh tissue biopsy should be obtained). For cohorts B-D, an archival (diagnostic) tissue biopsy (minimum 20 5 um slides, 25 preferred) will be required (prior to initiation of any treatment). In addition, for cohorts B-D, a *new* core tissue biopsy (minimum 3 cores from lung tissue, minimum 4 cores from any other site) will be required prior to study entry. All biopsies will be performed at individual sites where participants are enrolled.

A minimum of 4 participants in each cohort (B-D) will be required to have fresh tissue sampling from which FNA will be also obtained (in addition to core biopsies) for immune profiling at the Belfer Institute. For those participants, FNA will be immediately placed into RPMI media and hand-couriered to the Belfer Institute (Patrick Lizotte) or to the Wong laboratory at NYU (identical SOP's for immunophenotyping exist at both institutions. for processing.The remaining core biopsies will be formalin-fixed and paraffin-embedded as per institutional standards for further evaluation with IHC or tumor DNA/RNA extraction for sequencing or nanostring and shipped to the Overall PI, Dr. Joshua Sabari (see also Section 6.7.2.1).

Optional core biopsies will be obtained at the time of tumor progression from participants who consent to this procedure. A minimum of 3 cores will be required.

A block or minimum of 20 5 um slides (formalin-fixed, paraffin embedded (FFPE)), (25 preferred) will be requested from both archival (diagnostic) biopsy specimens and pre-treatment biopsy specimens.

6.7.1.3 Collection of Specimen, Handling, Shipping, sites performing IHC
Specimens will be collected by the clinical research coordinator (CRC) from each participating site and shipped directly to the coordinating CRC at DFCI at room temperature (5-10 5 um slides). Immunostaining will be performed at the DF/HCC Histopathology core facility (located in the Brigham and Women's Hospital) under the direction of Dr. Scott Rodig with interpretation by Dr. Rodig or his delegate.

Samples should be shipped at ambient temperature to the following address:
NYU Center for Biospecimen Research and Development (CBRD)
Alexandria Center for Life Science
430 East 29th Street, Lab 424
New York, NY 10016
CBRD Phone: 646-501-4268
Phone: 646-501-0438
Fax: 646-754-9658

6.7.2 DNA sequencing

Neoantigen load has been proposed as an important biomarker of potential senstivity to PD-1 and PD-L1 inhibition in multiple tumor types[28], and compared to other malignancies, small cell lung cancer has a high mutational burden due to the very high association with heavy smoking. Given the reported lower level of PD-L1 expression in SCLC, mutational burden may be a relatively more important biomarker in this setting.

We will plan to conduct whole-exome sequencing on a subset of patients in collaboration with Dr. David Barbie and Dr. Eli Van Allen of the Broad Institute.

6.7.2.1 Collection of Specimens
7-10 5 um slides (formalin-fixed, paraffin embedded (FFPE)) from both archival (diagnostic) biopsy specimens and pre-treatment biopsy specimens will be used to isolate tumor DNA in the Center for Advanced Molecular Diagnostics (CAMD) at BWH. A subset of samples (those from which we have the most tissue, up to 20 total) will be subjected to both whole-exome sequencing (WES) in collaboration with Dr. Van Allen at the Broad Institute

Samples should be sent at ambient temperature to the overall study PI at the below address; so that we can determine feasibility of sequencing with Dr. Andre Moreira of pathology (NYU) and then distribute samples accordingly (to the Broad Institute, BWH path, and BWH molecular path):

NYU Center for Biospecimen Research and Development (CBRD)
Alexandria Center for Life Science
430 East 29th Street, Lab 424
New York, NY 10016

CBRD Phone: 646-501-4268
Phone: 646-501-0438
Fax: 646-754-9658

6.7.2.2 Collection of Specimen, Handling, Shipping, site performing sequencing

Specimens will be collected by the clinical research coordinator (CRC) from each participating site and shipped directly to the coordinating CRC at NYU at room temperature.

WES will be performed at the Broad Institute under the direction of Dr. Eli Van Allen on a subset of specimens (20 tissue and 20 blood). Whole-exome sequencing will be performed at the Broad Institute in accordance with IRB sanctioned practices involving Protected Health Information (PHI). De-identified data will be maintained on a secure server and the results of these research tests will not be shared with study subjects.

6.7.3 Gene Expression

Inflammatory or immune-related gene expression signatures have been suggested to serve as predictors of clinical benefit beyond PD-L1 expression in multiple tumor types treated with pembrolizumab[29,30] and will be evaluated in a subset of pre-treatment biopsies (20) on this study. Tumor-derived RNA from 5-8 5 um slides will be used for Nanostring using the nCounter Human PanCancer Immune Profiling kit, to be performed in the DF/HCC genomics core facility. Interpretation/analysis will be performed in collaboration with Dr. Van Allen on a subset of specimens (20).

6.7.4 Immune profiling

Immune profiling in tumor biopsies is actively under evaluation at the Belfer Center for Applied Cancer Science at DFCI and at the Wong laboratory at NYU to understand correlates of response and resistance. Preliminary data has been generated in both mesothelioma and NSCLC and we are currently generating data from SCLC samples as well. To date, data in other tumor types has suggested that the best cell collection is obtained from FNA samples.

6.7.4.1 Collection, Handling, Shipping, and Site Performing analyses

FNA samples from DF/HCC sites will be obtained in parallel from at minimum 4 pre-treatment biopsies per cohort and transferred to RPMI medium immediately. These samples will then be couriered (from MGH) or taken directly to the Belfer Institute for Applied Cancer Science at the Harvard Institute of Medicine (hand-carried by CRCs at DFCI and BIDMC) for processing (Attn: Patrick Lizotte). At NYU, samples will be hand-couriered to the Wong laboratory (Smilow 1210).

6.7.5 Blood biomarkers

Soluble PD-L1 analysis from peripheral blood samples has been extensively studied in melanoma in Steve Hodi's lab at DFCI and is now being evaluated in all tumor types under the Center for Immuno-Oncology core facility. Blood may also be used for the evaluation of cytokine profiles and exosomal profiling as these assays are developed. Finally, in order to evaluate genomic changes (particularly with regard to neoantigen profile) that may occur as a result of exposure to chemotherapy and radiation, in addition to evaluating tissue samples pre/post therapy, we will also collect blood for evaluation of circulating free DNA and for samples where there is adequate DNA pre and post therapy, we will subject a subset of these samples (up to 15) to whole-exome sequencing for evaluation of genomic change and neontigen profile change. A sample of whole blood for germline comparison will also be collected.

6.7.5.1 Collection, Handling, Shipping, and Site Performing analyses for circulating markers

Blood samples for potential cytokine, cell profiling, and soluble PD-L1 analysis will be drawn at the time of venipuncture during routine clinic visits. 10-20 ml blood (minimum of 10 ml) will be drawn into EDTA-containing tubes, and plasma will be separated from the cellular component by centrifugation over Ficoll. The separated PBMCs will be allocated into plastic freezing tubes, catalogued, and frozen at -70°C in 10% DMSO using standard methods available for future assays. Note: the period from draw to freezing of samples must be less than 3 hours.

Samples should be shipped on dry ice to:

NYU Center for Biospecimen Research and Development (CBRD)
Alexandria Center for Life Science
430 East 29th Street, Lab 424
New York, NY 10016
CBRD Phone: 646-501-4268
Phone: 646-501-0438
Fax: 646-754-9658

6.7.5.2 Collection, Handling, Shipping, and Site Performing analyses for circulating free DNA

For cf DNA samples, blood will be collected in 10 cc EDTA tubes, barcoded, and processed within 3 hours of blood draw. We have previously confirmed that white blood cells remain stable during this period of time and thus, do not affect the purity of tumor-derived cell-free DNA. 1mL of whole blood will be banked from each tube and frozen at -80C in a 2d-barcoded tube until further processing. The remaining blood will be subjected to two rounds of centrifugation (2,000 x g for 10 min followed by 15,000 x g for 10min). Plasma will be removed and frozen at -80C in another 2d-barcoded tube until further processing. All samples are registered in our laboratory information management system and tracked throughout the process. Extractions of cell-free DNA and germline DNA will be performed from banked plasma and whole blood, respectively, using an automated liquid handler. Liquid handling systems will also be used for the subsequent steps of quantification, normalization, and library construction. Sequencing on the Illumina HiSeq will be used to assess the purity of tumor-derived cell-free DNA. Samples with sufficient purity of tumor-derived cell-free DNA will be nominated for hybrid capture of the entire human exome and sequenced on the Illumina HiSeq.

Samples should be shipped on dry ice to:

The Broad Institute
Attn: Blood Biopsy Group
75 Ames Street
Lab 4045
Cambridge MA, 02142

7 Study Calendar/Protocol Flow Chart

Baseline evaluations are to be conducted within 21 days prior to start of protocol therapy. Scans and x-rays must be done $\leq$28 days prior to the start of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Study Calendar/Protocol Flow Chart Cohort A and B

	Screening (days --28 to 0)	C1[a]	C2	C3-6[b]	Maintenance Pembro[c] C1-34	End of Treatment	Post-Treatment			Second Course phase (Retreatment)
Pembrolizumab		A	A	A	A		Safety Follow-up	Follow-up	Survival follow-up	A
Cisplatin or Carboplatin[1]		B	B	B						
Etoposide[2]		C	C	C						
Informed consent	X									X[h]
Demographics	X									
Medical history	X									X
Concurrent meds	X	X	X	X	X	X				X
Details of prior therapy for cohort B	X									
Physical exam	X	X	X	X	X	X		X[g]		X
Vital signs	X	X	X	X	X	X		X[g]		X
Height	X	X	X	X	X	X				X
Weight	X	X		X	X	X				X
Performance status	X	X		X	X	X		X[g]		X
CBC w/diff, plts[d]	X	X	X	X	X			X[g]		X
Serum chemistry[e]	X	X	X	X	X			X[g]		X
EKG	X									
Adverse event evaluation	X	X	X	X	X	X	X	X[g]	X[l]	X
Tumor measurements/radiologic evaluation[f]	X			X	X	X		X[g]		X
Pulmonary Function Tests	X									
B-HCG	X[e]									X[e]
Tumor biopsy (archival)[i]	X									
Tumor biopsy (pre-treatment)[j]	X									
Tumor biopsy (post-treatment), optional						X[h]				
Blood samples for correlative studies		X[k]	X[k]		X[k]	X[k]				X[k]

[a]Pembrolizumab will be given on day 1 of each cycle. Carboplatin or cisplatin will be given on day 1 of each cycle. Etoposide will be given on days 1, 2, and 3 of each cycle.

[b]Cohort A participants will be treated with combination chemotherapy + pembrolizumab for a minimum of 4 and a maximum of 6 cycles. Cohort B participants will be treated for a minimum of 3 and a maximum of 5 cycles of combination therapy if they had only one cycle prior to study and a minimum of 2 or maximum of 4 if they had 2 cycles of therapy prior to study.
[c]Continued maintenance pembrolizumab will be given on day 1 of each cycle after completion of chemotherapy with 1st dose 3 weeks after last cycle day 1 up through a maximum of 17 cycles following completion of chemotherapy. Interruption of therapy for planned radiation may occur as detailed in sections 5.5.5.1 and 5.11.1
[d]See Table 5 for details.
[e]See Table 5. BHCG, Free T4, T3, PT/PTT, uric acid will be drawn at screening only and thereafter as clinically indicated.'
[f]Radiologic assessment should include chest/abdomen/pelvis CT scan at baseline following by CT scan or MRI as appropriate to follow known areas of disease. Participants who have untreated brain metastases should have brain MRI at every scheduled radiologic assessment. For participants who DO NOT have baseline brain metastases, brain MRI should be performed on the planned radiologic assessment after completion of chemotherapy. For participants who do not have brain metastases after completion of chemotherapy and DO NOT undergo prophylactic cranial irradiation, brain MRI should be performed every 12 weeks following the completion of chemotherapy. Other radiologic assessments should occur every 6 weeks (within 7 days prior to every other cycle—prior to cycle 3, 5, 7, 9, etc).
[g]In the follow-up phase, exam, VS, laboratory assessments, and radiologic assessments should occur every 6 weeks for up to 18 weeks and then every 12 weeks thereafter.
[h]Participants who proceed to second course phase of treatment (re-treatment after progression with no intervening therapy) should sign consent for second-course phase and meet eligibility requirements prior to initiation of treatment. During treatment, assessments (laboratory, radiographic, blood collection) should follow schedule of maintenance pembrolizumab cycles. At the time of SECOND PROGRESSION, end-of –treatment, safety follow-up, and survival follow-up assessments should be as for 1st progression.
[i]Archival biopsy with adequate tissue REQUIRED prior to starting on study (minimum 20 5 um slides)
[j]Pre-treatment biopsies should be fresh biopsies for at minimum 4 participants in each cohort. For these participants, FNA in addition to core-needle biopsy (minimum 3-4 cores—see section 6.6.7.1 for specific requirements. For all participants, biopsies should be within 4 weeks of starting treatment with pembrolizumab and AFTER the last dose of prior therapy.
[k]Blood samples will be drawn at the time of venipuncture during routine clinic visits. See section 6.7.4 for details.
[l]Safety-follow up evaluation should occur within 30 days of end of treatment.

Study Calendar/Protocol Flow Chart For Cohorts C and D

	Screening (days -- 28 to 0)	Maintenance Pembro C1-34	End of Treatment	Post-Treament			Second Course phase (Retreatment)
Pembrolizumab[a]		A		Safety Follow-up	Follow-up	Survival follow-up	A
Informed consent	X						X[f]
Demographics	X						
Medical history	X						X
Concurrent meds	X	X	X				X
Details of prior therapy and response	X						
Physical exam	X	X	X		X[g]		X
Vital signs	X	X	X		X[g]		X
Height	X	X	X				X
Weight	X	X	X				X
Performance status	X	X	X		X[g]		X
CBC w/diff, plts[b]	X	X			X[g]		X
Serum chemistry[c]	X	X			X[g]		X

EKG	X						
Pulmonary Function Tests	X						
Adverse event evaluation	X	X	X	X	X[g]	X[l]	X
Tumor measurements/radiologic evaluation[d]	X	X	X		X[e]		X
B-HCG	X[c]						X[e]
Tumor biopsy (archival)[g]	X						
Tumor biopsy (pre-treatment)[h]	X						
Tumor biopsy (post-treatment), optional			X[h]				
Blood samples for correlative studies		X[k]	X[k]				X[k]

[a]Pembrolizumab will be given on day 1 of each cycle. Dosing may be interrupted for planned or palliative radiation as per section 5.5.5.1 and 5.11.1
[b]See Table 5 for details.
[c]See Table 5. Free T4, T3, PT/PTT, uric acid will be drawn at screening only and thereafter as clinically indicated.'
[d]Radiologic assessment should include chest/abdomen/pelvis CT scan at baseline following by CT scan or MRI as appropriate to follow known areas of disease. For participants in cohort C (who do not have brain metastases after completion of chemotherapy and DO NOT undergo prophylactic cranial irradiation) brain MRI should be performed every 12 weeks following the completion of chemotherapy. Other radiologic assessments should occur every 6 weeks (within 7 days prior to every other cycle—prior to cycle 3, 5, 7, 9, etc). .
[e]In the follow-up phase, exam, VS, laboratory assessments, and radiologic assessments should occur every 6 weeks for up to 18 weeks and then every 12 weeks thereafter.
[f]Participants who proceed to second course phase of treatment (re-treatment after progression with no intervening therapy) should sign consent for second-course phase and meet eligibility requirements prior to initiation of treatment. During treatment, assessments (laboratory, radiographic, blood collection) should follow schedule of maintenance pembrolizumab cycles. At the time of SECOND PROGRESSION, end-of –treatment, safety follow-up, and survival follow-up assessments should be as for 1st progression.
[g]Archival biopsy with adequate tissue REQUIRED prior to starting on study (minimum 20 5 um slides)
[h]Participants who proceed to second course phase of treatment (re-treatment after progression with no intervening therapy) should sign consent for second-course phase and meet eligibility requirements prior to initiation of treatment. During treatment, assessments (laboratory, radiographic, blood collection) should follow schedule of maintenance pembrolizumab cycles. At the time of SECOND PROGRESSION, end-of –treatment, safety follow-up, and survival follow-up assessments should be as for 1st progression.
[j]Pre-treatment biopsies should be fresh biopsies for at minimum 4 participants in each cohort. For these participants, FNA in addition to core-needle biopsy (minimum 3-4 cores—see section 6.6.7.1 for specific requirements. For all participants, biopsies should be within 4 weeks of starting treatment with pembrolizumab and AFTER the last dose of prior therapy.
[k]Blood samples will be drawn at the time of venipuncture during routine clinic visits. See section 6.7.4 for details.
[l]Safety-follow up evaluation should occur within 30 days of end of treatment.

8 Measurement of Effect

8.1 Antitumor Effect—Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 6 weeks during therapy (and for 1st 18 weeks after therapy completion) followed by re-evaluation every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response (preferably at 6 weeks or next planned assessment).

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

8.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up

8.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol

should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 µCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

8.1.4 Response Criteria

8.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is

the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

8.1.4.4 Evaluations of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

8.1.6 Survival outcomes

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

8.2 Other Response Parameters

In addition to RECIST 1.1, irRECIST (a modification of irRC to use RECIST 1.1 criteria (Nishino et al.) will be independently assessed as a measure of response and outcome measurement.

8.2.1 Disease Parameters

Disease assessments (assessments of target, non-target, and non-measurable lesions) and methodology of assessment follows RECIST 1.1 and is as detailed in section 8.1.2 and 8.1.3.

8.2.2 Response Criteria

The major differences in response criteria are as outlined here but please refer to Nishino et al, 2013 for further details:

New Measurable lesions
In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

Measurement of total tumor burden
The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine
the Total Measured Tumor Burden (TMTB) at follow-up.

Non-target lesions
The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

Measurement of response

irCR: complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. irPR: decrease of ≥ 30% in TMTB relative to baseline
non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
irSD: failure to meet criteria for irCR or irPR in the absence of irPD.
irNN: no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
irPD: minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
irNE: used in exceptional cases where insufficient data exists.
irND: in adjuvant setting when no disease is detected (not applicable here).

For further details, see Nishino et. Al. 2013.

9 Statistical Plan

SCLC provides an opportune setting to evaluate the potential importance of variability in PD-L1 expression and its influence on optimizing timing of checkpoint inhibition. All extensive-stage SCLC patients are treated with chemotherapy and recent data suggests added benefit to consolidation thoracic radiation[10].
The proposed study seeks to evaluate pembrolizumab therapy initiated at different times during the course of SCLC treatment: a) up front, in conjunction with initiation of chemotherapy, b) starting after one cycle of chemotherapy, c) starting after completion of 1st line chemotherapy, d) starting after completion of consolidation thoracic radiation therapy and/or PCI. Treatment with pembrolizumab will be preceded by biopsy for evaluation of PD-L1 expression with correlative evaluation of changes in PD-L1 expression (relative to diagnostic biopsy) and changes in other tissue- and blood-based biomarkers and immune markers. The study is based on the following hypotheses:

1) PD-L1 expression is dynamic and can increase with exposure to chemotherapy and/or radiation
2) PD-L1 expression influences efficacy of pembrolizumab=
3) Pembrolizumab can improve outcomes in SCLC

9.1 Sample Size, Accrual Rate and Study Duration

Though the plan is to enroll 15 participants to each of the 4 cohorts, we anticipate that there may be some dropout due to inability to continue therapy or undergo biopsy. We therefore inform our statistical calculations under the assumption that 12 participants in each group will yield results for analysis.
The number 15 chosen as a minimum number for evaluation for the following 3 reasons:
1) The prevalence of PD-L1 expression in SCLC is not well-characterized. In one basket study of pembrolizumab that enrolled ONLY patients who were PD-L1 positive, the rate of positivity among those screened was 28.6% (other factors may have had a selection bias in those who were screened for study), which would estimate that <4/12 patients would have positive PD-L1 expression from a diagnostic biopsy. We have NO information regarding the potential changes that may occur as a result of exposure to chemotherapy and radiation. Attempts at retrospective evaluation have been unsuccessful as below.

2) After screening > 220 SCLC patients for retrospective analyses of paired equivalent biopsies at DFCI, we were able to find exactly 3 pairs with adequate and comparable tissue which was one of the prompts to design this prospective trial. Most SCLC biopsies contain extensive crush artifact or often have scant tissue and the adequacy of prospectively collected tissue samples is also uncertain making it difficult to make statistical assumptions.

3) It is anticipated that it may be difficult to compare the pre and ON/POST treatment samples due to treatment effect as there is a high rate of response to therapy with both chemotherapy and radiation (therefore there may be extensive treatment effect or minimal tumor in biopsies done after exposure to

chemotherapy), but we won't know how difficult until the study is done because of the rarity of these on-treatment biopsies to know how tissue specimens will compare.

These considerations are the reason that the endpoint was built around the feasibility of getting comparable specimens for assessment of change in PD-L1 expression (i.e. being able to accurately measure from both to actually evaluate change).

Comparisons of paired biopsies will be conducted using the one-sample Wilcoxon signed rank test, which has 88% power to test that the mean of paired differences in 10% vs. 0% while testing at the 2-sided 0.05 level and assuming an effect size of 1.0. We plan to estimate event-time distributions of progression-free survival and overall survival using the Kaplan-Meier method, and any comparisons (for example, between groups defined by baseline PD-L1 expression level) will be made using the logrank test. Multivariable Cox models will be fitted to adjust for any known prognostic factors and landmark analyses may be conducted to explore any association between post-baseline PD-L1 expression levels and outcomes. Comparisons of baseline PD-L1 expression levels and response will be made either using Fisher's exact test (should a reasonable cutpoint defining 'positivity' in PD-L1 expression level be identified during this study) or Wilcoxon rank sum test.
We will analyze the data of circulating cytokines, and circulating T cell repertoire before, during, and after therapy with pembrolizumab and their relationship to clinical benefit with pembrolizumab therapy. Many of the statistical methods described above will apply, but we may also fit repeated measures models to data that is collected longitudinally. Identification of genetic changes using nextgen sequencing (oncopanel) and gene expression changes using nanostring before, during, and after therapy with pembrolizumab to determine relationship, if any, to clinical benefit with pembrolizumab.

10 Safety and Adverse Events

10.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

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

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

- fatal
- life-threatening

- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

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

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

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

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

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

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

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

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

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.1.1 Expected Toxicities

10.1.1.1 Adverse Event List(s) for Pembrolizumab

Please refer to investigator brochure for pembrolizumab for a complete list of expected toxicities. Please refer to section 5.8.3 (Table 3) for a list of immune-related toxicities and guidance for supportive care management.

Very common, (> 20% chance this will happen):

- Itching of the skin
- Loose or watery stool
- Cough

Common, side effects seen (≥ 5% to 20% chance this will happen):

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

Uncommon, side effects seen (1% to 5% chance this will happen):

- Inflammation of the lungs so you may feel short of breath and cough.
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection.

Rare, side effects seen (< 1% chance this will happen):

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating,, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling

If you have had an allogenic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include

diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of transplant you have had.

-

It is possible that you will have an allergic reaction to the infusion. This can cause dizziness or feeling faint (due low blood pressure), flushing, rash, fever, shortness of breath, or nausea at the time of receiving your infusion or just after. You may also experience pain at the site of infusion.

10.1.1.2 Adverse Event Lists(s) for Other Agent(s)

For risks associated with cisplatin, carboplatin, or etoposide, please refer to the product label for each.

10.2 Recording of Adverse Events

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

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

Progression of the cancer under study is not considered an adverse event.

All adverse events 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.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the study lead (Dr. Sabari), NYULMC PCC CTO, DSMC, and NYU IRB within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

10.2.2 Reporting of Pregnancy and Lactation to the Overall PI and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) 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 should be followed to the completion/termination of the pregnancy if feasible. 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 study lead (Dr. Sabari), NYULMC PCC CTO, DSMC, NYU IRB and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

Immediate Reporting of Adverse Events to the Sponsor and to Merck

Serious Adverse Events:
A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the overall PI and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the overall PI and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to pembrolizumab that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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

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

10.3.1 Investigator reporting: notifying the study sponsor, NYU IRB, and PCC Clinical Trials Office, and Merck

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.
- Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor, without delay and within 2 days of identification, any pregnancy occurring in a female subject or female partner of a male subject, during the study or within 120 days of the last dose of the study drug. Any complication of pregnancy affecting a female study subject or female partner of a male study subject, and/or fetus and/or newborn must be reported as an SAE.

Additionally, an FDA Form 3500A (MEDWATCH Form) must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

Sponsor contacts (NYULMC):

NYULMC PCC CTO: NYUPCCsafetyreports@nyumc.org

And

Joshua Sabari, MDPerlmutter Cancer Center at NYU Langone Health
160 E. 34th St, 8th Floor
New York, NY 10016
Phone: 212-731-5662
Email: Joshua.sabari@nyumc.org

Follow-up report: within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both NYULMC PCC and NYU IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

10.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

The NYU IRB address is:

NYU IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

10.3.3 Sponsor reporting: *Notifying the FDA*

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  – associated with the use of the study drug
  – unexpected,
  – fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  – associated with the use of the study drug,
  – unexpected, and
  – serious, but not fatal or life-threatening
  -or-
  – a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  – suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

Email: NYUPCCsafety@nyumc.org
Tel: 212-263-4427

10.3.4 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above in section 8.3.3. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

10.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

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

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

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

Table 6 Evaluating Adverse Events
An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	

	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

10.4.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB or to Merck. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
	Neutropenia	3 or 4		Chemotherapy	
	Anemia	3		Chemotherapy	
	Thrombocytopenia	3 or 4		Chemotherapy	Without bleeding

10.4.2 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

10.4.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

10.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (Section 12 Study Monitoring, Auditing, and Inspecting). The Data Safety and Monitoring Committee (DSMC) will review the study twice a year. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10.5.1 Data and Safety Monitoring Plan

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2011 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULMC PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by DSMC quarterly (from the date the first patient is enrolled), at dose escalation point and subsequent cohort activation, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc.

Other external sites will be monitored and informed of other adverse events by the medical monitor within 7 days of toxicities and within 3 business days of SAE. Scheduled conference calls will be conducted after 3 patients are enrolled and at each dose escalation point. Additional conference calls will be scheduled as indicated based on the recommendations from the medical monitor, the Overall PI of this study.

11 Data Handling and Record Keeping

11.1 Confidentiality

The research team will maintain clinical and laboratory data in a manner that ensures patient confidentiality. All study personnel have passed human subject protection courses. Tissue samples sent to collaborators outside of NYU PCC will only be labeled with an assigned protocol subject identification

number without patient identifiers. Systems used for electronic data capture are compliant with HIPAA and applicable local regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for specific study personnel, CTO quality assurance specialists, and authorized representatives of regulatory agencies as described in the informed consent document. Samples sent to commercial labs or collaborating labs as per study protocol will be coded. Samples remaining after completion of the study will be destroyed once this study is completed. None of the samples collected will be used to create a repository for future research studies.

11.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

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

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

11.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into Velos. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

11.4 Data and Source Documentation

Velos, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned research coordinator, and CTO quality assurance specialists will have access to the database. Velos is the primary data collection instrument for the study. All data requested in Velos must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

11.5 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 3 years after formal closure of the study.

12 Study Monitoring, Auditing, and Inspecting

12.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO and Merck of any audit requests by health authorities, and will provide Merck Pharmaceuticals with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will provide extensive monitoring for this trial, including real-time review of all electronic CRFs to verify adherence to the protocol; the completeness,

accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

12.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and Institution compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institution compliance and quality assurance offices. The investigator will contact the PCC CTO immediately if contacted by a regulatory agency about an inspection at the center.

13 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the NYU Institutional Review Board (IRB) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULMC PCC CTO.

14 Study Finances

14.1 Funding Source

Funding for conducting this trial will be provided by Merck Pharmaceuticals. The investigational agent (Pembrolizumab) will be provided to subjects enrolled on this study by Merck Pharmaceuticals.

14.2 Conflict of Interest

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

14.3 Subject Stipends or Payments

No patient or subject will receive payments or stipends for participation in this research study. Merck Pharmaceuticals may provide coverage for test and/or procedures that are a part of the research study, if it is not covered by the subject's insurance.

15 Publication Plan

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

16 References

1. Pillai RN, Owonikoko TK: Small cell lung cancer: therapies and targets. Semin Oncol 41:133-42, 2014
2. Byers LA, Rudin CM: Small cell lung cancer: where do we go from here? Cancer 121:664-72, 2015
3. Sundstrom S, Bremnes RM, Kaasa S, et al: Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 20:4665-72, 2002
4. Fukuoka M, Furuse K, Saijo N, et al: Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 83:855-61, 1991
5. Roth BJ, Johnson DH, Einhorn LH, et al: Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 10:282-91, 1992
6. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85-91, 2002
7. Lara PN, Jr., Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 27:2530-5, 2009
8. Hanna N, Bunn PA, Jr., Langer C, et al: Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24:2038-43, 2006
9. Zatloukal P, Cardenal F, Szczesna A, et al: A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease. Ann Oncol 21:1810-6, 2010
10. Kalemkerian GP, Akerley W, Bogner P, et al: Small cell lung cancer. J Natl Compr Canc Netw 11:78-98, 2013
11. Slotman B, Faivre-Finn C, Kramer G, et al: Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357:664-72, 2007
12. T S, T T, T Y, et al: Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): Results of a Japanese randomized phase III trial, ASCO Annual Meeting Abstract 7503. Chicago, IL, 2014
13. Slotman BJ, van Tinteren H, Praag JO, et al: Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 385:36-42, 2015
14. Powderly JD, Koeppen H, Hodi FS, et al: Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. Presented at the ASCO Annual Meeting 2013, Chicago, IL,

15. Topalian SL, Hodi FS, Brahmer JR, et al: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443-54, 2012

16. Hamid O, Robert C, Daud A, et al: Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 369:134-44, 2013

17. Spigel DR, Gettinger SN, Horn L, et al: Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Presented at the ASCO Annual Meeting 2013, Chicago, IL, 2013

18. Lipson EJ, Sharfman WH, Drake CG, et al: Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res 19:462-8, 2013

19. Robert C, Schachter J, Long GV, et al: Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 372:2521-32, 2015

20. Garon EB, Rizvi NA, Hui R, et al: Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372:2018-28, 2015

21. Ott P, Fernandez M, Hiret S, et al: Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. J Clin Oncol 33, 2015 (suppl; abstr 7502)

22. Brahmer JR, Tykodi SS, Chow LQ, et al: Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366:2455-65, 2012

23. Velcheti V, Schalper KA, Carvajal DE, et al: Programmed death ligand-1 expression in non-small cell lung cancer. Lab Invest, 2013

24. Garon EB, Balmanoukian A, Hamid O, et al: Preliminary clinical safety and activity of MK-3475 monotherapy for the treatment of previously treated patients with non-small cell lung cancer (NSCLC) Presented at the World Conference on Lung 2013, Sydney, Australia, 2013

25. Grosso JF, Horak CE, Inzunza HD, et al: Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538). Presented at the ASCO Annual Meeting 2013, Chicago, IL,

26. Schultheis AM, Scheel AH, Ozretic L, et al: PD-L1 expression in small cell neuroendocrine carcinomas. Eur J Cancer 51:421-6, 2015

27. Gettinger SN, Horn L, Gandhi L, et al: Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 33:2004-12, 2015

28. Rizvi NA, Hellmann MD, Snyder A, et al: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348:124-8, 2015

29. V S, K M, YJ B, et al: Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475

. J Clin Oncol 33, 2015 (suppl; abstr 3026)

30. TY S, B B, J W, et al: Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients. J Clin Oncol 33, 2015 (suppl; abstr 6017)

31. Rossi A, Di Maio M, Chiodini P, et al: Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 30:1692-8, 2012

32. Nishino M, Giobbie-Hurder A, Gargano M, et al: Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 19:3936-43, 2013

17 Attachments

17.1 Appendix A Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.2 Appendix B Pharmacy Manual

PHARMACY MANUAL

PEMBROLIZUMAB (MK-3475)

Merck Sharpe & Dohme, Corp

TABLE OF CONTENTS

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17.3 2. Trial Treatment

Trial Treatment Table

Table 2 Trial Treatment

Cohort	Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
A and B1	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
	carboplatin OR	AUC 6	Q3W	IV infusion	Day 1 of each 3 week cycle	Standard care
	cisplatin	75 mg/m2	Q3W	IV infusion	Day 1 of each 3 week cycle	Standard of care
	Etoposide	100 mg/m2	Q3W	IV infusion	Days 1, 2, 3 of each 3 week cycle	Standard of care
C	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
D	Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

1for cohort A, the number of total cycles of chemotherapy will be 4-6 total, while pembrolizumab will continue as long as disease has not progressed or patient not removed from study for other reasons for up to 2 years. For cohort B, patients should have received 1 cycle platinum + etoposide prior to entry onto study, so the total number of cycles during study will be 3-5 (such that the TOTAL number of cycles on or off study is a MINIMUM of 4 and a MAXIMUM of 6).

18. 3. Drug Preparation-- Pembrolizumab (MK-3475) Powder for Solution for Infusion, 50 mg/vial

18.1. 3.1 DRUG PRODUCT

- Pembrolizumab **(MK-3475) Powder for Solution for Infusion, 50 mg/vial**

- Pembrolizumab (MK-3475) Powder for Solution for Infusion is a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use Type I glass vial containing 50 mg of pembrolizumab (MK-3475). The product is preservative-free, white to off-white powder and free from visible foreign matter.

- Pembrolizumab (MK-3475) Powder for Solution for Infusion is reconstituted with 2.3 mL sterile water for injection (WFI) to yield a 2.4 mL solution containing 25 mg/mL of pembrolizumab (MK-3475) at pH 5.2 – 5.8.

Pembrolizumab (MK-3475) Powder for Solution for Infusion vial contains an excess fill of 10 mg (equivalent to 0.4 mL of reconstituted solution) to ensure the recovery of label claim of 50 mg pembrolizumab (MK-3475) per vial (equivalent to 2 mL of reconstituted solution).

18.2 3.2 STABILITY AND HANDLING OF DRUG PRODUCT

- Pembrolizumab (MK-3475) Powder for Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C). Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F)) for up to 24 hours.

- Following reconstitution with sterile water for injection, Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) 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.

- If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible, Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

- Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS unless instructed by the SPONSOR in writing.

- 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 reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion.

- In addition, reconstituted vials and/or 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 vials and/or 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 reconstituted 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**.
- **DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.**

Any deviation from the guidance listed in this manual, must be discussed with sponsor

18.3 3.3 DOSE CALCULATION

<u>200 mg Fixed Dose</u>

- **Required Number of vials = 4 vials (50 mg/vial)**
- **8 mLs Total**

18.4 3.4 RECONSTITUTION OF DRUG PRODUCT (POWDER FOR SOLUTION FOR INFUSION, 50 MG/VIAL)

- 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 reconstitution is not permitted
- Remove the cap from the seal. **Do not decrimp the vial**.
- Insert a needle through the stopper of the pembrolizumab (MK-3475) Powder for Solution for Infusion vial(s) to release vacuum (if any). Leave the needle inserted in the stopper. If local standard operating procedures (SOPs) prohibit leaving a needle inserted in the stopper, this step can be skipped.
- If one WFI bottle is used to reconstitute one pembrolizumab (MK-3475) vial: Attach a 3 mL syringe to a needle. Insert the needle through the stopper of the sterile water for injection (WFI) bottle. Draw excess of 2.3 mL of WFI in the syringe and remove the syringe-needle assembly from the vial.
- If one WFI bottle is used to reconstitute more than one pembrolizumab (MK-3475) vials: Insert a needle through the stopper of the sterile WFI bottle. Attach a 3 mL syringe to the needle inserted in the sterile WFI bottle and draw excess of 2.3 mL of WFI in the syringe. Carefully detach the syringe without removing the needle from the WFI bottle. Repeat the process to fill additional syringes while keeping the needle inserted in sterile WFI bottle to minimize particle shedding from stopper. Use a new sterile WFI bottle after filling approximately 10 syringes.
- Attach a new needle to the filled syringe (if applicable). Remove excess air and WFI from the syringe-needle assembly while ensuring that there is 2.3 mL WFI still remaining in it.
- Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of pembrolizumab (MK-3475).

Caution: To avoid foaming, ensure that water is delivered along the walls of the vial and not directly squirted on the lyophilized powder.

- Remove the needle(s) from the stopper of pembrolizumab (MK-3475) vial.

- Slowly swirl the vial to allow reconstitution of the lyophilized powder. Allow up to 5 minutes for the bubbles to clear.

Caution: Do not shake the vials.

18.5 3.5 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.

- Reconstitute the required number of vials to prepare the infusion solution.

- 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 pembrolizumb (MK-3475) and normal saline required to prepare the infusion (admixture) bag

  Volume of reconstituted 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 reconstituted pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

- 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 reconstituted 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 2 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) (reconstituted solution) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

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

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

18.6 3.6 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 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 (ie., 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.

18.7 3.7 RETURN AND DISCARDING OF PEMBROLIZUMAB (MK-3475) VIALS

- Unused pembrolizumab (MK-3475) Powder for Solution for Infusion or Solution for Infusion vial(s) shall be returned to the designated facility for destruction.
    - For US clinical sites, return to: Fisher Clinical Services, Return and Destruction Center, 700B Nestle Way, Breinigsville, PA 18031
    - For all other sites, consult with local Merck subsidiary for facility address.
- Solution remaining in a used vial should be discarded as Chemotherapeutic Waste according to your local procedures.
- Any information on the label identifying the subject should be redacted prior to returning the study medication.

19. 4. Drug Preparation—Pembrolizumab (MK-3475) Solution for Infusion

19.1 4.1 DRUG PRODUCT

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial

Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free solution which is essentially free of extraneous particulates.

19.2 4.2 STABILITY AND HANDLING OF DRUG PRODUCT

- **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.
- 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 deviation from the guidance listed in this manual, must be discussed with sponsor**

19.3 4.3 DOSE CALCULATION

200 mg Fixed Dose

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

19.4 4.4 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 reconstituted pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

- 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 reconstituted 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

19.5 4.5 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

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-linefilter 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 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

19.6 4.6 RETURN AND DISCARDING OF PEMBROLIZUMAB (MK-3475) VIALS

- Unused pembrolizumab (MK-3475) Solution for Infusion vial(s) shall be returned to the designated facility for destruction.
  - For US clinical sites, return to: Fisher Clinical Services, Return and Destruction Center, 700B Nestle Way, Breinigsville, PA 18031
  - For all other sites, consult with local Merck subsidiary for facility address.

- Any information on the label identifying the subject should be redacted prior to returning the study medication.