SPONSOR: University of Washington

TITLE: Anti-PD-1 Therapy in Combination with Platinum Chemotherapy for Platinum Resistant Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

IND NUMBER: CDER 131988

EudraCT NUMBER (Studies in Europe only):

CONTACT INFORMATION:

Principal Investigator:
John B. Liao, MD, PhD
University of Washington
Gynecologic Oncology
850 Republican Street
Box 358050
Seattle, WA 98109
Phone: 206-221-1513
FAX: 206-221-5529
Email: johnliao@uw.edu

Study/Regulatory Coordinator/Contact:
Jennifer S. Childs, MPH, CCRP
University of Washington
Oncology
850 Republican Street
Box 358050
Seattle, WA 98109
Phone: 206-616-2305
FAX: 206-221-5529
Email: childj@medicine.washington.edu

Research Nurse:
Doreen Higgins, BSN, RN, OCN
University of Washington
Oncology
850 Republican Street
Box 358050
Seattle, WA 98109
Phone: 206-616-9538
FAX: 206-221-5529
Email: dhigg@medicine.washington.edu

University of Washington Pharmacy:

University of Washington Medical Center
Investigational Drug Services
1959 NE Pacific Street
Box 356015, Room EA-146
Seattle, WA 98195
Phone: 206-598-6054
FAX: 206-598-4901
Email: idssam@u.washington.edu
Main Email: uwmcids@u.washington.edu

Statistician:

James Y. Dai, PhD
Fred Hutchinson Cancer Research Center
Public Health Sciences Division
Biomathematics & Biostatistics
1100 Fairview Avenue North
PO Box 19024
Seattle, Washington 98109-1024
Phone: 206-667-6364
Email: jdai@scharp.org

1.0 TRIAL SUMMARY

Abbreviated Title	Combination MK-3475 plus platinum chemotherapy in platinum resistant ovarian cancer
Trial Phase	*I/II*
Clinical Indication	Platinum resistant ovarian, fallopian tube and primary peritoneal cancer
Trial Type	Single arm non-randomized
Type of control	Historical
Route of administration	MK-3475 = IV; Carboplatin = IV
Trial Blinding	Open label
Treatment Groups	Single arm
Number of trial subjects	27
Estimated enrollment period	*January 1, 2017 – June 30, 2018*
Estimated duration of trial	*January 1, 2017-- June 30, 2019*
Duration of Participation	Up to 2 years (or until progression of disease or toxicity)

2.0 TRIAL DESIGN

2.1 Trial Design

This will be a phase I/II single arm, non-randomized clinical trial designed to examine the clinical response rate of platinum and MK-3475 in platinum pretreated ovarian, fallopian tube, and primary peritoneal cancer subjects. Subjects who had an initial response to platinum-based (cisplatin or carboplatin) chemotherapy and who have progressed within 6 months of completing platinum-based chemotherapy and have subsequently received at least one non-platinum therapy regimen will be eligible to enroll. We will explore the sensitizing effect of this treatment on with platinum chemotherapy retreatment. In addition, safety, the role of PD-L1 expression, and survival benefit of this therapy will be examined.

A total of 27 eligible subjects will be enrolled to this study. All study subjects will receive treatment consisting of 21 day cycles, which will continue for up to 2 years or until progression or toxicity (whichever comes first). CT scans will be performed at screening (if not done within 30 days of first treatment), and then before cycles 4 and 8, then every three months per standard of care.
Treatment Cycle (21 days):

- Day 1: 200mg of MK-3475 IV
- Day 8: Carboplatin AUC 2 IV
- Day 15: Carboplatin AUC 2 IV

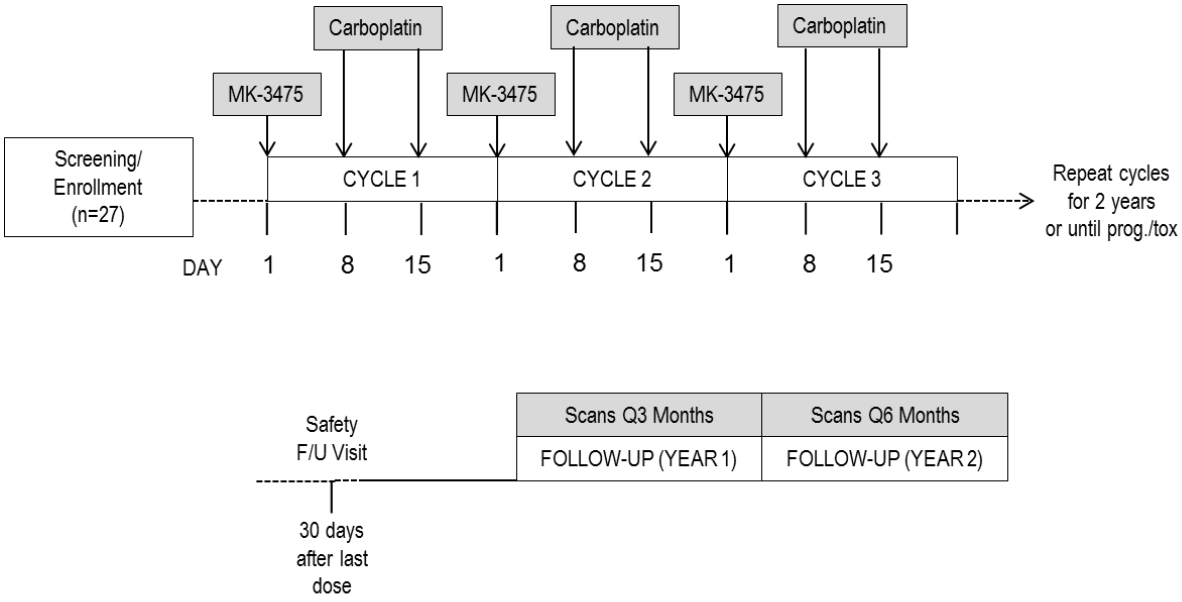
Primary endpoints: Response rate and PFS at 6 months (Cycle 8) assessed by RECIST v1.1.

Secondary endpoints: Adverse events evaluated by CTCAE v4.0, PD-L1 expression of primary tumor blocks, overall survival, assess best overall response (BOR) and progression free

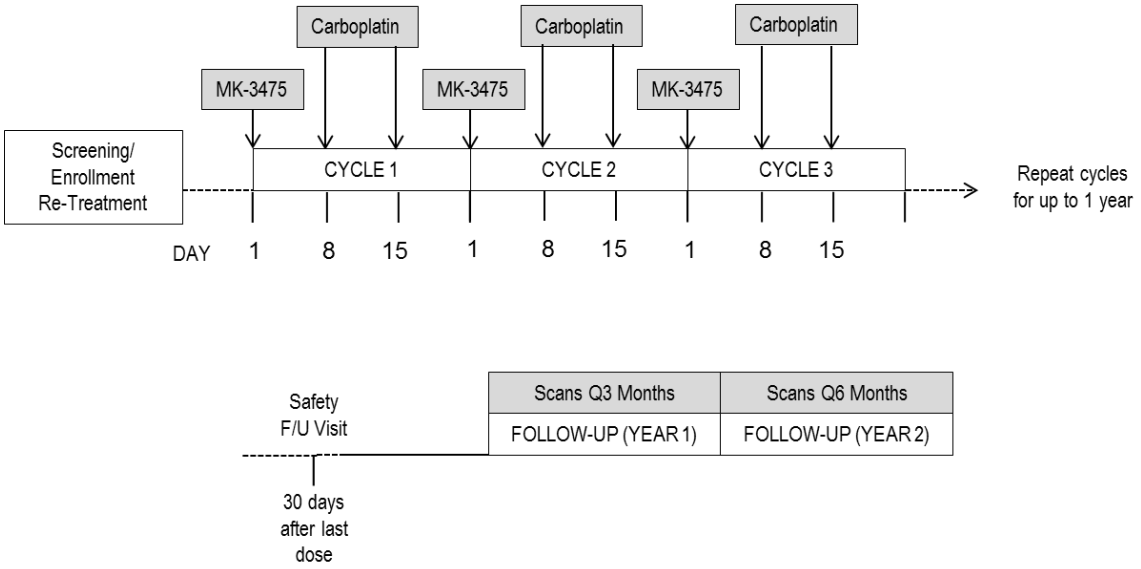
survival (PFS) time according to RECIST 1.1, assess the immune-related BOR and immune-related PFS using irRECIST (Immune-related Response Evaluation Criteria In Solid Tumors) derived from RECIST 1.1

2.2 Trial Diagram

2.2.1. Study Schema



2.2.2. Study Schema: Re-treatment



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the clinical response rate of platinum chemotherapy and MK-3475 in platinum chemotherapy pretreated ovarian, fallopian tube, and primary peritoneal

Hypothesis: MK-3475 and platinum chemotherapy will improve upon second line chemotherapy for ovarian, fallopian tube, and primary peritoneal cancers.

(2) **Objective:** To examine whether retreatment with platinum chemotherapy in platinum resistant ovarian, fallopian tube, and primary peritoneal cancers improves progression free survival by concurrent administration of MK-3475.

Hypothesis: MK-3475 can re-sensitize platinum resistant ovarian, fallopian tube, and primary peritoneal cancers to respond to platinum chemotherapy

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To assess the safety and tolerability of concurrent administration of MK-3475 with platinum chemotherapy in patients with platinum resistant recurrent ovarian, fallopian tube, and primary peritoneal cancers.

Hypothesis: MK-3475 can be used safely in combination with weekly platinum chemotherapy in patients with platinum resistant ovarian, fallopian tube, and primary peritoneal cancer.

(2) **Objective**: To determine the relationship between PD-L1 expression and response to the combination of MK-3475 and platinum

Hypothesis: PD-L1 expression measured by immunohistochemical staining in tumor correlates with treatment response.

(3) **Objective**: To assess the overall survival of patients treated with the combination of MK-3475 and platinum

Hypothesis: Combination treatment with MK-3475 and platinum improves PFS and OS compared to historical controls.

3.3 Exploratory Objective

(1) **Objective:** To explore whether treatment with MK-3475 and platinum alters soluble factors in sera, peripheral immune responses and immune cell profile.

Hypothesis: MK-3475 and platinum therapy in combination will enhance tumor immunogenicity and peripheral responses that reverse an immunosuppressive phenotype

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses,

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

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The mainstay of ovarian cancer chemotherapy has long been platinum-based agents. The majority of patients will achieve a response with initial treatment.[1] Unfortunately, recurrent ovarian cancer inevitably becomes resistant to platinum-based chemotherapy. Response rates to any cytotoxic agent in a platinum resistant recurrence are modest. Single cytotoxic agents employed include paclitaxel (21% response rate), pegylated liposomal doxorubicin (20% response rate), topotecan (19% response rate), and gemcitabine (9% overall response rate). A randomized phase 3 trial comparing pegylated liposomal doxorubicin to patupilone showed a mean PFS of 12 weeks and a OS of 13 months in both arms, which is unfortunately emblematic of the recent trials studying agents in platinum resistant disease.[2] Combination chemotherapy has not shown consistent benefits and NCCN guidelines do not support any combination in this setting except with bevacizumab. The extra value of a second agent has never been tested against platinum alone in a randomized trial.[3] While it is the inclination of many oncologists to approach a platinum resistant recurrence with a non-platinum regimen, there is evidence that even in a platinum resistance recurrence, retreatment with single platinum agent can yield a 23% response rate that is not inferior to platinum combinations also used in this setting. It is hypothesized that successful retreatment with platinum chemotherapy may be related to the duration of a platinum free interval, which may be prolonged with the use of non platinum agents,[4] however there are no trials that directly test this hypothesis and the biologic rationale supporting this is unclear. At our own institution, we will retreat with platinum after a platinum resistant recurrence has been diagnosed and have found similar response rates.

Ovarian cancer is immunogenic. The ability of the immune system to recognize ovarian cancer is associated with improved prognosis. The form of immunity associated with this improved prognosis is known; T cell infiltrates in ovarian cancers are shown to be associated with improved prognosis in a number of studies. The full prognostic significance of T-cell infiltration in ovarian cancers rivals optimal surgical cytoreduction.[5] The presence of intratumoral T cells was an independent prognostic factor for PFS and OS by multivariate analysis. These findings have been validated in several subsequent studies, and point to the specific importance of cytotoxic CD8+ T-cells.[6-12]

Subsequently, a number of factors that may influence the intraepithelial lymphocyte count in ovarian cancers have been studied. The evidence continues to mount pointing to the importance of the PD-1/PD-lL in ovarian cancer. The expression level of PD-L1 in paraffin embedded tumors has been shown to be significantly associated with prognosis by multivariate analysis. In addition there is a significant inverse correlation seen between PD-L1 expression and intraepithelial CD8+ T cell count, suggesting that PD-L1 on ovarian cancer cells may suppress antitumor CD8+ T cells.[13] The expression of PD-L1 in human ovarian cancer has also been shown to promote peritoneal dissemination suggesting that PD-L1 blockage may be

a viable strategy for treating metastatic ovarian cancer.[14] Furthermore, 93% of ovarian cancers have been reported to have PD-1 positive tumor infiltrating lymphocytes. [15]

While cytotoxic chemotherapy has traditionally been viewed as being immunosuppressive, recent studies have shown that specific agents may possess significant immune stimulatory effects.[16] Platinum agents in particular have been shown to stimulate effector antitumor responses through the modulation of the PD-1 receptor.[17, 18] Blockade of the PD-1/PDL-1 interaction in 15 ovarian cancer patients with platinum resistant disease has been recently reported to yield a response rate of 23% and disease control rate (CR+PR+SD) of 54%.[19] Ovarian cancer patients with platinum resistant relapses treated with a weekly platinum based regimen have shown to yield serum levels of IL-2 and interferon gamma associated with CD8+ cytotoxic T cell activity.[20] Studies combining PD-1 blockade with platinum chemotherapy in ovarian cancer mouse models have been shown to significantly increase the tumor control compared to the use of each agent alone, both in our own preliminary data and those reported by other investigators.[21]

We hypothesize that therapies targeting the PD-1/PD-L1 pathway may synergize with platinum chemotherapy agents and allow ovarian cancers that have become clinically resistant to platinum to be successfully retreated with this agent.

4.2.2 Rationale for Dose Selection/Regimen/Modification

MK-3475

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses

to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Carboplatin

Carboplatin when used in combination chemotherapy regimens for ovarian cancer has been shown to be well tolerated with an AUC 2 dose per week.[22] In addition, the dose intensity of platinum in the treatment of ovarian cancer has not shown to offer significant survival advantage in randomized trials.[23] Carboplatin will be infused at an AUC of 2, with the dose calculated using the Calvert equation.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR + 25)

Thus, in this regimen, the carboplatin dose will be:
Carboplatin dose (mg) = (2.0) x (GFR + 25)

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

NOTE: THE DOSE OF CARBOPLATIN WILL BE RECALCULATED FOR EACH CYCLE.

Dose of carboplatin will be monitored over time to determine if concurrent administration of MK-3475 alters carboplatin dose.

Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

For each subject, tumor response will be performed by CT scan or MRI imaging of chest abdomen and pelvis. CT scan of chest will be performed if MRI is used. RECIST 1.1 criteria and irRECIST (Immune-related Response Evaluation Criteria In Solid Tumors) criteria will be used to determine response.

Both PFS and OS will be measured. While OS remains the most objective clinical measure, because ovarian cancer is a heterogeneous disease, PFS as a surrogate endpoint has been proposed and reported in a number of trials for this disease.[24]

4.2.2.2 Biomarker Research

There are currently no universally accepted biomarkers to that can identify patients mostly likely to respond to either MK-3475 or carboplatin as a single agent in this population of patients. We will examine whether expression of PD-L1 in tumor, mutations in cancer associated genes, serum antibody responses against tumor associated antigens, and changes in immunomodulatory cells can be associated with response in this combination. We will also assess whether these markers are associated with PFS, OS, and toxicities.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Ovarian, fallopian tube, or peritoneal cancer patients who had a complete response to primary treatment with platinum based chemotherapy, have progressed within 6 months of completing platinum-based chemotherapy, and have subsequently received at least one non-platinum-based therapy.

5.1.2 Subject Inclusion Criteria

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

1. Have a diagnosis of ovarian, fallopian tube, or primary peritoneal cancer patients who had a complete response to primary treatment with platinum based chemotherapy, have progressed within 6 months of completing platinum based chemotherapy and have subsequently received at least one, non-platinum-based, therapy.

2. Have relapsed, refractory, or progressive disease following last line of treatment.

3. Have estimated life expectancy of at least 3 months.

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

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

6. Have measurable disease with at least 1 unidimensional lesion based on RECIST 1.1.

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

8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 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.	

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

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

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy within 4 weeks of the first dose of treatment.

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

    - Short-term administration of systemic steroids (i.e., for allergic reactions or the management of irAEs) is allowed

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

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

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

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

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

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

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

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

10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

11. Has an active infection requiring systemic therapy.

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

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

14. Is pregnant or breastfeeding, or expecting to conceive 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.

15. Clinically significant cardiovascular disease.

16. Known severe hypersensitivity reactions to monoclonal antibodies or carboplatin ≥ Grade 3, any history of anaphylaxis, or uncontrolled asthma.

17. Has received prior therapy with pembrolizumab.

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

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

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.

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Carboplatin*	AUC 2**		IV infusion	Day 8, 15 of each 3 week cycle	Standard
*Given per standard of care **Calculated by use of the Calvert formula					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of dose to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

Carboplatin is commercially available both from Bristol-Myers Squibb as well as generic manufacturers. Please refer to link to carboplatin prescribing information (Appendice 13.4).

5.2.1.2 Dose Modification

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays).

Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

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

Subjects will permanently discontinue drug for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	1. Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If
	Grade 4	Permanently discontinue		

General instructions:

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

				sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
	Grade 2	Withhold		

General instructions:

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

Nephritis and Renal dysfunction	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Carboplatin

Standard dose adjustments for carboplatin during treatment may be made based on changes in hepatic and renal function.

Some of the adverse events expected with carboplatin treatment are listed below.

1. Hematologic: Myelosuppression is the major dose-limiting toxicity

2. Hepatic toxicity: Elevated alkaline phosphatase, total bilirubin, and AST have been observed.

3. Allergic reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely anaphylaxis with bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

4. Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms

5. Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.

6. Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

*See link to FDA-approved package insert (Appendice 13.4) for a comprehensive list of adverse events associated with carboplatin.

5.2.2 Timing of Dose Administration

Trial drug should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Carboplatin may be administered up to 3 days before or after scheduled day due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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 contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Carboplatin AUC 2 will be administered as a 30 minute IV infusion (-5 min/+10 min) on days 8 and 15 of a 21 day cycle. Carboplatin is considered to have moderate emetic risk and administrations of antiemetics will follow NCCN guidelines Version 1.2015.

http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pd

For the management of Day 1, option A will be preferred:

Serotonin (5-HT3) antagonist + Steroid (category 1) ± NK-1 antagonist · Serotonin (5-HT3) antagonist (Select one):

Day 1 antiemetic management:

Serotonin (5-HT3) antagonist Select one: Option A.	**+ Steroid (category 1)**	**± NK-1 antagonist**
Dolasetron 100 mg PO once	Dexamethasone 12 mg PO/IV once	Aprepitant 125 mg PO once
Granisetron 2 mg PO or 1 mg PO BID, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24h transdermal patch applied 24-48 h prior to first dose of chemotherapy		Fosaprepitant 150 mg IV once
Ondansetron 16-24 mg PO once or 8-16 mg IV once		
Palonosetron 0.25 mg IV once (preferred)		

For Days 2 and 3, option A will be preferred with 5-HT3 antagonist monotherapy used first line and NK1 antagonist without steroid used second line. Option C Olanzapine will be used third line:

Day 2 and 3 antiemetic management:

First line treatment **Serotonin (5-HT3) antagonist** **Option A**	**Second line treatment (without steroid use)** **NK-1 antagonist**	**Third line treatment**
Dolasetron 100 mg PO on days 2, 3	Aprepitant 125 mg PO daily on days 2, 3	Olanzapine 10 mg PO daily on days 2, 3
Granisetron 2 mg PO or 1 mg PO BID, or 0.01 mg/kg (max 1 mg) IV daily on days 2, 3	Fosaprepitant used day 1	
Ondansetron 8mg PO BID or 16 mg PO daily or 8-16 mg IV daily on days 2, 3		

5.2.3 Trial Blinding/Masking

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

5.2.4 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

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

5.3 Randomization or Treatment Allocation

Not applicable.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. Medications administered during a hospitalization, not related to study treatment, will be reviewed and recorded only if clinically significant to the study. 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 or initiation of new treatment should be

recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs Events of Clinical Interest (ECIs) as defined in Sections 5.2.4 and7.2.

5.4.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail.

- **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.

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is 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.		

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-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.

5.6.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.6.4 Use in Nursing Women

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

5.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days or prior to initiation of new treatment for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7.1 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 7.1.5.5.

5.8 Subject Replacement Strategy.

Up to 4 patients may be replaced if patients withdraw or are withdrawn from the trial prior to completing their first cycle.

5.9 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Phase		Treatment Cycles[a, g]								End of Treatment	Post-Treatment		
Treatment Cycle/Title:		Main Study Screening[h] (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles: 5	6	7	8	Discon[e]	Safety Follow-up[e]		Survival Follow-Up[b]
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon		Every 12 weeks after discona
Administrative Procedures														
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration (Day 1)			X	X	X	X	X	X	X	X				
Carboplatin Administration (Day 8, 15)			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X		X
Survival Status														X
Clinical Procedures/Assessments														
Review Adverse Events[k]			X	X	X	X	X	X	X	X	X	X[d]		
Full Physical Examination		X	X	X	X	X	X	X	X	X	X			
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
PT/INR and aPTT		X			X			X			X			
CBC with Differential		X	X	X	X	X	X	X	X	X	X			
CA125			X	X	X	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel		X	X	X	X	X	X	X	X	X	X			

Trial Period:	Screening Phase		Treatment Cycles[a, g]								End of Treatment	Post-Treatment		
Treatment Cycle/Title:		Main Study Screening[h] (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon[e]	Safety Follow-up[e]		Survival Follow-Up[b]
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon		Every 12 weeks after discona
Urinalysis		X												
ANA, T3, FT4 and TSH			X		X			X			X			
Efficacy Measurements														
Tumor Imaging[c]		X				X				X[c]			X	X
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival Tissue Availability[l, m]		X												
Correlative Studies Blood Collection[f, i]			X			X		X						

Trial Period:	Screening Phase		Treatment Cycles[a, g]								End of Treatment	Post-Treatment		
Treatment Cycle/Title:		Main Study Screening[h] (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles: 5	6	7	8	Discon[e]	Safety Follow-up[e]		Survival Follow-Up[b]
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon		Every 12 weeks after discona

[a] Treatment Cycles: Up to 24 months for this study

[b] Follow-Up Visits (Post Discontinuation): Year 1 patients will be followed with CT scan approximately every three months per standard of care; Year 2 patients will be followed with CT scan approximately every 6 months per standard of care

[c] Tumor Imaging: : CT scan or MRI (if MRI is used then CT scan of chest required) of the chest, abdomen and pelvis may be done at screening or 30 days prior to study treatment and again prior to cycles 4 and 8 then will be repeated approximately every 3 months per standard of care

[d] Adverse events will be collected for 30 days or prior to initiation of new treatment. Serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1

[e] If subject initiates a new anticancer 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 (Section 7.1.1.6.3). Discontinuation Visit and Safety Follow Up may be the same visit.

[f] Correlative blood draw is up to 200mls; this blood will be used for correlative analysis (PBMC, serum, DC phenotyping, etc.)

[g] Re-treatment procedures will last for 1 year (Section 7.1.5.5).

[h] The screening visit and Cycle 1 could happen on the same day

[i] After Cycle 6; correlative blood draws will occur every six cycles (prior to cycles 12, 18, and 24)

[j] Has been deleted, no longer an active instruction.Through subject self reporting and clinician observation. Events may be clarified from previous medical records

[l] Tissue slides are shipped to QualTek for PDL1 analysis. The QualTek manual which details shipping can be found in the "Lab Certification" Binder

[m] We will obtain archival tumor, for immunohistochemical staining. Patients who have not been tested for germline mutations in BRCA1 and BRCA2 will be tested.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 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.

7.1.1.4.2 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 and ECI should be recorded as defined in Sections 5.4.2 and7.2.

7.1.1.5 Treatment Schedule

Subjects will receive repeat cycles of combination pembrolizumab and carboplatin for 2 years or until progression of disease or toxicity.

7.1.1.5.1 Research Treatment

Pembrolizumab will be administered on Day 1 of the treatment cycle.

7.1.1.5.2 Carboplatin Administration

Carboplatin is administered on Days 8 and 15 of the treatment cycle per standard of clinical care.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up Visit/Discontinuation Visit every effort is to be made to 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.

7.1.1.7 Assignment of Screening Number

The University of Washington will screen all potential subjects entering the study. We have a system that allows us to identify and follow a potential subject going through the screening process.

This system allows us to track the number of subjects we have screened for a specific study, where in the screening process a subject is at a given time, and those that did not make it to study treatment enrollment.

7.1.1.8 Assignment of Randomization Number

The University of Washington will assign a Unique Patient Number (UPN) to each subject at the time of signing study enrollment and the start of study procedures. This UPN does not hold any patient identifiers and will be used for Case Report Form documentation and research specimens for the correlative science.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject on Day 1 of each cycle to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Lab values are to be reviewed for Days 1, 8, 15 and documented in the database as adverse events, if applicable (clinically significant). Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms described in Table 6.

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

For subjects who are hospitalized, due to their disease, the PI will review their records and determine what events, procedures, and medications shall be documented in the study record.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

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

7.1.2.3 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 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.5 Tumor Imaging and Assessment of Disease

A CT scan or MRI (if MRI is used then CT scan of chest required) of the chest, abdomen and pelvis will be performed days prior to trial (if not done within 30 days of first treatment) in order to document the baseline status of tumor using RECIST 1.1 target and non-target lesions. Baseline screening scan does not need to be repeated if performed within 4 weeks prior to first treatment.

For each subject, tumor response will be assessed by CT scan or MRI. Scans performed prior to cycle 1need to be repeated at subsequent visits as outlined in Section 6.0 (prior to cycles 4 and 8, then approximately every three months per standard of care). Lesions detected at baseline need to be followed using same imaging methodology.

Due to data from cancer immunotherapy trials showing that despite new lesions that may appear at the beginning of treatment, total tumor burden may not increase substantially, and tumor regressions and stabilization may occur later, we will also use the proposed irRECIST (Immune-related Response Evaluation Criteria In Solid Tumors) criteria in addition to RECIST 1.1 to assess responses.[25]

7.1.2.6 Tumor Tissue Availability/Collection and Correlative Studies Blood Sampling

The identification of biomarkers that can predict response and allow the identification of patients most likely to benefit from therapy represents a significant gap in the treatment of recurrent ovarian cancer given the toxicity profiles and low response rates of the agents available. The expression of PD-L1 in tumor has been shown in melanomas, non-small cell lung carcinoma, renal carcinoma, colorectal carcinoma, and prostate cancer to be most closely correlated with response to anti-PD-1 blockade.[26] We will obtain archival tumor, for immunohistochemical staining. The median time to response reported for MK-3475 in

melanoma is 12 weeks.[27] Expression of PD-L1 will be correlated with response, OS, and PFS and toxicities.

Although ovarian cancer is immunogenic, the phenotype of the immune response is important to improved survival. Comprehensive multifactorial immune analysis resulting in immune profiles have been proposed a way to identify biomarkers for response of immune therapies in ovarian cancer.[28] Both regulatory T cells and myeloid derived suppressor cells have been reported have a negative impact on ovarian cancer outcomes.[29, 30] Control of these immunomodulatory elements may be possible with immune-base therapies. Upregulation of PD-1 on regulatory T cells has been shown to suppress CD8+ immune response through the PD-1/PD-L1 interaction.[31] We will collect peripheral blood mononuclear cells (up to 200 mls) before treatment and after 3 and 5 cycles to perform flow cytometry analysis on the regulatory T cell population and MDSC populations. We will also assess the percentage of regulatory T cells that have upregulated PD-1. Monocyte derived dendritic cells exposed to platinum chemotherapy during maturation have been shown to induce higher T cell proliferation and produce higher levels of interferon gamma and IL-2 compared to untreated DC.[18] Therefore, we will also assess DC phenotype at baseline and after cycles 3 and 5. We will correlate these findings with response rates, OS, PFS, and toxicities.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		ANA
	Chloride		CA-125
	Glucose		Blood for correlative studies
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

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.

7.1.4 Sample Collection and Storage.

Samples will be labeled with a unique patient identifier (without PHI). The samples will be processed within 24 hours, logged into our specimen tracking system and stored in a temperature monitor freezer.

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. 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 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

The trial is open label.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

During this time we are collecting source documents to be used to assess the subject's eligibility to the study.

7.1.5.1.1 Screening Period

There is not a set screening period for this study. Subjects must meet the eligibility requirements prior to initiation of study treatment.

7.1.5.2 Treatment Period

The treatment period is 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study drug, whichever is later, or until progression of disease. Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect. Subjects with disease progression may continue study drug per discretion of PI.

7.1.5.3 Post-Treatment Visits

Once a subject discontinues the study (either early or after study completion) we will perform a follow-up safety evaluation approximately 30 days after last treatment. We will continue collect tumor imaging reports approximately every 12 weeks per standard of care post the discontinuation of study until death, withdrawal of consent, or the end of the study, whichever occurs first.

In addition, survival data will be collected every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.4 Safety Follow-Up

The mandatory Safety Follow-Up evaluation 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 should be recorded. Subjects with an AE of Grade > 2 related to study treatment will be followed until the resolution of the AE to baseline or grade 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 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Safety follow up may be done at the Discontinuation/End of Treatment visit.

7.1.5.4.1 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 every 12 weeks will be assessed for survival status until death, withdrawal of consent, becoming lost to follow-up or the end of the study, whichever occurs first.

7.1.5.5 Second Course Phase (Re-treatment 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 24 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 5.1.2
- 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 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- 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 are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

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

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

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

All adverse events will be recorded from the time the consent form is signed through End of Treatment/Discontinuation visit. Adverse events will be collected on day 1 of each cycle through subject self reporting and clinician observation. Events may be clarified from previous medical records. Lab values are to be reviewed for treatment days 1, 8, 15 and documented in the database as adverse events, if applicable. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

For purposes of this trial, an overdose 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 the Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

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

7.2.3.1 Serious Adverse Events

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

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

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

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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

reported within one business day to the Sponsor and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

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 215 661-6229) at the time of submission to FDA.

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 221-6229)Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - 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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. Additional adverse events:

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

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

7.2.4 Evaluating Adverse Events

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

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

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

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

7.2.4.1 Pembrolizumab Expected Adverse Events

Likely (≥10% of patients)	Less likely (≥5%)	Rare but serious (≥0.2%)
• Anemia • Fatigue • Itching • Cough • Nausea • Decreased appetite • Diarrhea • Shortness of breath • Arthralgia • Rash • Constipation • Headache • Vomiting • Weakness • Fever • Back pain • Swelling (limbs)	• Fatigue • Decreased appetite • Hypothyroidism • Thyroiditis • Itching • Diarrhea • Arthralgia • Weakness • Nausea • Myalgia • Vitiligo	• Pneumonitis* • Diarrhea • Colitis • Fever • Autoimmune hepatitis • Hyper thyroidism • Shortness of breath • Nausea • Low sodium in blood • Adrenal insufficiency • Pneumonia • Immune-mediated myocarditis • Stevens-Johnson Syndrome (SJS) • Toxic Epidermal Necrolysis (TEN) • Encephalitis • Scarcoidosis • Myasthenic syndrome • Graft vs. host disease (GVHD) in patients with a history of allogenic hematopoietic stem cell transplant (HSCT). Sometimes this condition can lead to death. • If you have had a solid organ transplant, you may experience rejection of the transplanted organ. • Arthritis (inflammation of the joints which may include joint pain, stiffness and/or swelling)

7.2.4.2 Carboplatin Expected Adverse Events

Likely (>20% of patients)	Less likely (4-20%)	Rare but serious (<3%)
• Hair loss • Vomiting, nausea • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, fatigue, or may require blood transfusions • Bruising, bleeding • Belly pain	• Diarrhea, Constipation • Numbness and tingling in fingers and toes • Allergic reaction: which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Changes in taste • Changes in vision	• Damage to organs which may cause hearing and balance problems

7.2.4.3 Potential Overlapping Toxicities

The combination of pembrolizumab and carboplatin could cause side effects we do not know about yet. When recording adverse events we will be making every attempt to distinguish which study treatment contributes to the adverse event: (1) pembrolizumab, (2) carboplatin, (3) both pembrolizumab and carboplatin or (4) neither of the treatments.

From the tables above there are some common side effects for pembrolizumab and carboplatin.

Likely (≥10% of patients)	Less likely (≥5%)	Rare but serious (≥0.2%)
• Anemia • Fatigue • Nausea • Diarrhea • Shortness of breath • Constipation • Vomiting	• Fatigue • Diarrhea • Nausea • Constipation • Allergic reaction: which may cause shortness of breath	• Diarrhea • Nausea • Shortness of breath

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL CONSIDERATION AND ANALYSIS PLAN

8.1 Sample size and power

Assume the response rate for the platinum re-treatment therapy in platinum pre-treated ovarian, fallopian tube, and primary peritoneal cancer patients is 23%. One of the primary objectives of this phase I/II trial is to test whether a new combinatory therapy (platinum + anti-PD1

antibody) can achieve a higher response rate (RR). We hypothesize that the true clinically significant response rate for the new therapy is 40~50%. The following table shows the sample size required to have either 80% or 90% power to declare statistical significance at level 0.05 for a true response rate at 40%, 45%, or 50%. A sample size of 27 patients will be required to have 80% power when the true response rate of the new combinatorial therapy is around 50%.

Response Rate of the new Therapy	**Power 80%**	**Power 90%**
40%	66	88
45%	41	54
50%	27	37

Furthermore, it is desirable to determine the response rate of the new combinatory therapy with sufficient precision. We can compute the standard error (SE) of the estimated response rates as the measure of precision for a range of true response rates. For the true response rate being in the range of 40%-50%, the SE does not vary much (0.07~0.09), and so there is adequate precision to detect the targeted response rate at 40-50%.

The median progression-free survival time is another efficacy endpoint of interest. Suppose the median progression-free survival time is 17, 20, or 23, and for the target sample size 27, the power to detect a statistically significant improvement in median progression-free survival time assuming accrual time is 1 year and the follow-up time is 1 year is listed in the following table. This table shows that our targeted sample size provides good power to detect 40% or more improvement in median progression-free survival time.

The median PFS in historical control	40% improvement in the new therapy	60% improvement in the new therapy
17 weeks	0.68	0.89
	0.66	0.88

20 weeks		
23 weeks	0.65	0.89

8.2 Statistical analysis plan

Clinical characteristics of the study cohort at the time of initial diagnosis will be tabulated, including age, stage, surgical optimality, and disease status after initial platinum therapy. The clinical characteristics and outcome of platinum-resistant patients will be also tabulated when retreated with the combinatory therapy.

The RR is the primary efficacy variable. The point estimate and the 95% exact confidence intervals will be reported for RR. The comparison with the historical control rate will be conducted by examining whether the 95% confidence internal covers the historical control rate. Additional analyses will be conducted to evaluate in logistic regression models the odds ratio of response rate on predictors such as platinum-free interval, time to progression after previous platinum treatment, number of prior platinum regimens etc. Other efficacy endpoints, which included progression free survival (PFS) and overall survival (OS), were also analyzed. Time-to-event variables were analyzed using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function with 95% CIs at specific time points (using Greenwood's formula for the standard error) were computed. Comparisons with the historical control PFS and OS will be conducted by examining whether the 95% confidence internal covers the historical control proportions.

The safety population included all patients who received at least one dose of study medication. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

The number and the percentage of patients who are removed from the study or altered dose regimen due to adverse effects will be reported.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 7 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1. Institutional Review Board

In accordance with federal regulations, an Institutional Review Board that complies with the regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study.

10.2. Study Team Roles and Responsibilities

Dr. Liao, the PI, will be responsible for the oversight of the research. Dr. Liao is responsible for ensuring that all information and documentation related to the conduct and safety of the study is disseminated to the proper agencies in the proper timeframe. In addition, Dr. Liao will delegate study responsibilities to qualified and trained research staff.

Research physicians/sub-investigators will be responsible for conducting consent conferences. Research physicians/physician extenders may perform assessment as per the delegation log.

Research Nurses/Coordinators will be responsible for initial screening and scheduling patient visits. The Research Coordinators will ensure that the clinical data is entered into the database in a timely manner, so as to have real time data to review and report any safety concerns trends. They will also be responsible for maintaining regulatory documentation to the various agencies involved with this research and ensure that all research team members are following the protocol and all regulations.

All clinical research staff are required to complete the following training:

1. Human Subjects Protections
2. HIPAA
3. Good Clinical Practice

New staff will also be required to review any existing standard operating procedures. This review will be documented that they understand the information. Existing staff will also be trained on new standard operating procedures and this training will also be documented on a Training Log for monitors to review at a site visit, if inclined.

10.3 Confidentiality

All eligible patients will be assigned a UPN that will not contain any personally identifying information, such as name, initials, medical record number, social security number, etc. To maintain confidentiality, we protect the link between the patients' personal identifying information and UPN number by limiting who has access to the patients' chart documentation. Only delegated clinical research staff has access to the data, which remain locked at all times when not in use.

All hard copy research records collected on potential and enrolled patients are stored in a locked filing cabinet that can only be accessed by approved clinical research staff when not in use. This staff includes: PI/study physician(s), and designated clinical research staff. These are also the only people that have access to the link between the patients' personal identifying information and their assigned UPN codes.

In terms of the protections and security of electronic clinical data, it is being performed by the University of Washington Information Technology (UW IT) Services. The UW IT information

security policy is to protect University of Washington (UW) information and information systems. It also ensures compliance with UW policy and state and federal regulations.

10.4 Compliance with Financial Disclosure Requirements

We will comply with the Financial Conflict of Interest Policy (GIM 10) mandated by the Office of Sponsored Programs of University of Washington.

http://www.washington.edu/research/osp/gim/gim10.html

10.5 Compliance with Law, Audit and Debarment

We will follow the terms of the signed contract and any subsequent amendments.

10.6 Compliance with Trial Registration and Results Posting Requirements

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

10.7 Quality Management System

Our group has extensive experience running investigator initiated Phase I and II clinical trials. We have established collection materials and database which we are capable of entering, tracking and reporting clinical trial information, laboratory samples, and reporting requirements. We meet regularly to discuss active clinical trials in terms of recruitment, adverse events or any other issue that might arise. In addition, all clinical staff are trained in HIPAA, Human Subjects and GCP.

10.7.1 Data Management

10.7.2 Collection

We have developed collection methods (case report form and source documentation) to capture study specific data. This includes, but in not limited to the capture of a patients prior disease treatment, clinical laboratory values, adverse events, medications and post enrollment treatments.

10.7.3 Database

10.7.3.1. Deviation Tracking

We have developed a deviation tracking tool within our database, which allows us to track the deviation, reporting requirements and study and regulatory outcomes.

This report can easily be pulled for reporting purposes.

10.7.3.2 Auditing

We perform regular internal audits and track the results. By doing this we are able to determine a trend in data collection methods and allow for improvements in data collection instruments or training.

The database incorporates a robust data auditing and tracking feature that documents any data change made to an existing record in the study database, who made the data changes, and when the update was made. The module also tracks the creation and deletion of any records in individual tables and the user who deleted or added the record

10.7.3.3 Long Term Follow Up

We have the ability to develop report(s) that allow us to determine when a subject is due to for a study procedure (i.e. imaging or survival data).

10.7.4 Security

The database is password protected. Passwords are changed every 90 days. Access privileges are obtained when a new employee is hired. If something is developed or requires new privileges then access will be assessed at that time.

If there is a change in a clinical research staff responsibilities access will reassessed at that time. However, once someone has access privileges they can maintain this until they leave their position.

10.7.5 Systems Backup

The database is stored on a HIPAA compliant secure server with access granted only to the Tumor Vaccine Group. The database is backed-up on tape and stored off-site and the tape is handled according to HIPAA regulations.

11.0 MONITORING

12.0 PLAN

12.1 Institutional Study Monitoring:

Institutional support of trial monitoring will be in accordance with the FHCRC/UW Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring

conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/UW Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

12.2 Medical Monitor

The Medical Monitor, Ron Swensen, M.D., will review data with the P.I., designee, and/or other members of the clinical team, approximately every 6 months. All patients are reviewed for adverse events. Conduct of the study is reviewed and changes/clarifications can be requested/discussed with the Medical Monitor

13.0 APPENDICES

13.1 ECOG Performance Status

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

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

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

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

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

* As published in the European Journal of Cancer:

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

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

13.4 Carboplatin Package Insert

http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_03_05_Carboplatin%20label%201-9-04%20FDA.pdf

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