Official Title	A Phase II Study of Anti-PD-1 (pembrolizumab) in Combination with Carboplatin to Prevent Progression after Serologic Detection of Recurrent Ovarian Cancer
NCT Number	NCT04387227
Document Type	Protocol and Statistical Analysis Plan
Document Date	7/15/2025

UNIVERSITY OF WASHINGTON

DEPARTMENT OF MEDICINE

DIVISION OF HEMATOLOGY & ONCOLOGY

Current Version Date: 06/26/2025
Previous Version Date: 11/14/2024

Protocol 150

A Phase II Study of Anti-PD-1 (pembrolizumab) in Combination with Carboplatin to Prevent Progression after Serologic Detection of Recurrent Ovarian Cancer

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1.0 TRIAL SUMMARY

Abbreviated Title	Combination pembrolizumab plus platinum chemotherapy in patients with serologic recurrence of ovarian cancer
Trial Phase	*II*
Clinical Indication	Platinum treated ovarian, fallopian tube and primary peritoneal cancer
Trial Type	Single arm non-randomized
Type of control	Historical
Route of administration	Pembrolizumab = IV; Carboplatin = IV
Trial Blinding	Open label
Treatment Groups	Single arm
Number of trial subjects	22 total (plus 4 possible replacements) with interim analysis at 15 patients
Estimated enrollment period	2 years
Estimated duration of trial	3 years
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 II, single arm, prospective, open label study designed to examine the clinical response rate of platinum and pembrolizumab in platinum pretreated ovarian, fallopian tube, and primary peritoneal cancer patients. Patients who have received and responded to front-line systemic chemotherapy with platinum-based (cisplatin or carboplatin) chemotherapy and are without radiographic evidence of disease but in whom CA-125 is increasing will be eligible to enroll. We will explore the sensitizing effect of platinum chemotherapy (one-time dose at start of study) with concurrent pembrolizumab continuing in preventing radiographic recurrence in these patients (Section 2.2.1 – Study Schema). In addition, safety, the role of PD-L1 expression, T cell activation, and survival benefit of this therapy will be examined.

A total of up to 26 (including 4 replacements) eligible patients will be enrolled to this study. All study participants will receive treatment consisting of six week cycles, which will continue for up to two years or until radiographic disease recurrence or toxicity (whichever comes first). Treatment may continue past the initial determination of disease progression per discretion of PI, unless they develop unacceptable toxicities that cannot be clinically managed. CT scans will be performed at screening (if not done within 30 days of first treatment), and then before cycles 3 and 5, then every three months per standard of care.

Treatment Cycle (Six weeks):

- Day -2: carboplatin IV, AUC 6 (two days prior to pembrolizumab-first cycle only)

- Day 1: pembrolizumab IV, 400 mg
- Thereafter pembrolizumab every six weeks +/- 3 days until radiographic evidence of progression by RECIST v.1.1

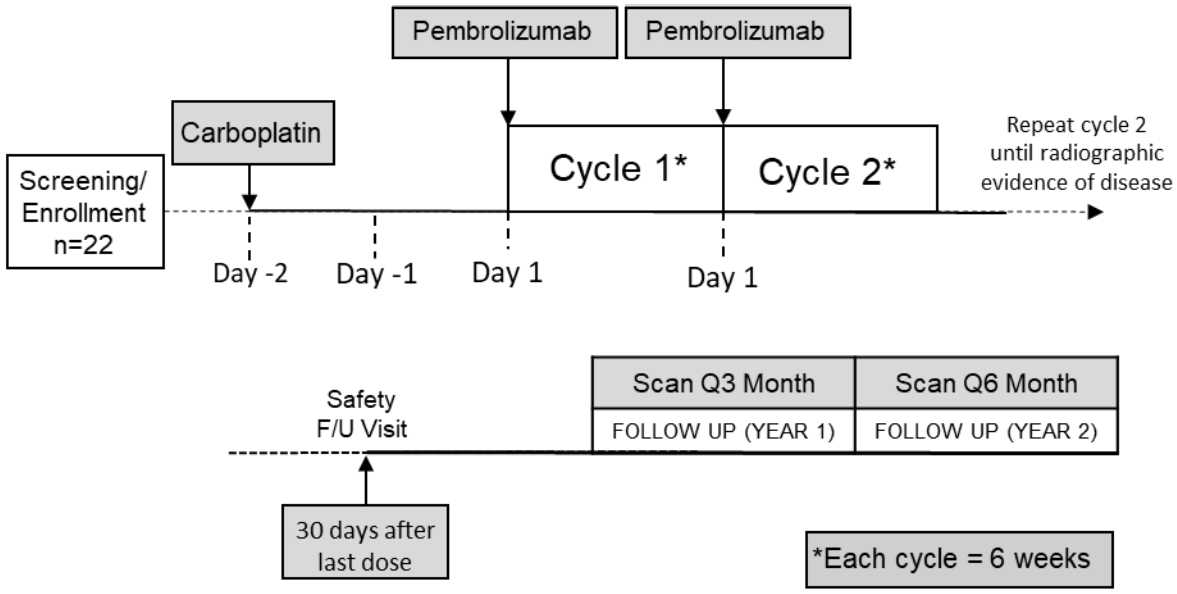
Primary endpoints: Rate of radiographic recurrence at 6 months and progression free survival

Secondary endpoints: PD-L1 expression, T cell activation, overall survival,

Exploratory endpoints: Rate of clinical progression

2.2 Trial Diagram

2.2.1 Study Schema



3.0 OBJECTIVES

3.1 Primary Objectives

1. To determine the ability of carboplatin and pembrolizumab to increase the rate of recurrence free survival in ovarian cancer patients with biochemical recurrences

2. To determine the ability of carboplatin and pembrolizumab to prolong progression free survival in ovarian cancer patients with biochemical recurrences

3.2 Secondary objectives

1. To determine the relationship between PD-L1 expression and response to carboplatin and pembrolizumab combination therapy

2. To determine the relationship between response to carboplatin and pembrolizumab combination therapy and T cell activation

3. To determine overall survival in ovarian cancer patients with biochemical recurrences treated with carboplatin and pembrolizumab

3.3 Exploratory objective

1. To determine the rate of clinical progression in ovarian cancer patients with biochemical recurrences

4.0 BACKGROUND & RATIONALE

4.1 Introduction

For the year 2019, in the United States alone, nearly 14,000 women are estimated to die of ovarian cancer and over 22,000 women will be diagnosed with ovarian cancer. In the majority of cases, the cancer presents at advanced stage, having already metastasized.[1] Although even advanced stage disease will often respond to surgery and cytotoxic chemotherapy and achieve a remission, the majority of patients will ultimately succumb to recurrent, chemoresistant disease.

4.1.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

4.1.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in ovarian cancer.

4.1.3 Immunity and targeting the PD-1/PD-L1 pathway in ovarian cancer

The presence of TILs in ovarian cancer is an independent prognostic factor for PFS and OS by multivariate analysis.[2] These findings point to the singular importance of cytotoxic CD8+ T-cells.[3-7] Interactions between PD-1 and PD-L1 have been shown to be important for tumor growth by suppressing T cells and antitumor responses. Agents targeting this pathway have already been approved as immunotherapies to treat a number of malignancies. The role of PD-1 and PD-L1 in ovarian cancer also appears important, but complex. PD-L1 expression has been associated with both cytolytic and regulatory subsets of tumor infiltrating lymphocytes.[8] 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.[9] 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.[10] Furthermore, 93% of ovarian cancers have been reported to have PD-1 positive tumor infiltrating lymphocytes.[11] Despite the weight of all this evidence, thus far monotherapy targeting PD-1 or PD-L1 has only shown very modest response rates in early phase clinical trials when used to treat recurrent ovarian cancer.[12-15]

4.1.4 Platinum chemotherapy and PD-1

While cytotoxic chemotherapy has traditionally been considered immunosuppressive, recent studies have shown that some 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 via PD-L1 and PD-L2.[17, 18] 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.[19] Studies combining PD-1 blockade with platinum chemotherapy in ovarian cancer mouse models show significant increases in tumor control compared to the use of each agent alone, both in preliminary data from our own laboratory and those reported by other investigators.[20] Biopsies obtained after neoadjuvant chemotherapy with platinum-based regimens in ovarian cancer patients have demonstrated higher levels of PD-L1 and a high proportion of T cells expressing both PD-1 and CTLA-4.[21] Data from our investigator initiated trial of pembrolizumab and carboplatin in heavily pretreated patients with platinum resistant recurrences (NCT03029598) shows improved responses by several metrics compared to pembrolizumab monotherapy.[22] 57% of evaluable patients (not selected for PD-L1 expression) in our study had a decrease in target lesions compared to KEYNOTE-028 where only 23% had any decrease at all in target lesions with pembrolizumab alone in PD-L1 positive patients.[14] In addition we have found that 65% of evaluable patients had stable disease as their best clinical response by RECIST 1.1 compared to only 27% reported in KEYNOTE-028. We also noted 2 patients who discontinued carboplatin after the first cycle due severe hypersensitivity reactions, but were still able to achieve sustained disease stabilization with pembrolizumab alone.

4.1.5 Response and tumor burden with anti-PD-1 therapy

Why anti-PD-1 therapy succeeds or fails in ovarian cancer is still poorly understood. However, some important discoveries from other malignancies may apply to ovarian cancer. One of these relates to tumor burden. Residual disease after cytoreductive surgery has shown prognostic significance for advanced ovarian cancer.[23] But in some patients with residual tumor remaining after primary surgery, the prognostic significance of CD8+ TIL is lost.[24] Tumor volume may be important in the success of PD-1 therapy as well since larger tumors may have more developed immunosuppressive environments. The success of pembrolizumab therapy in melanoma is related to the ratio of T cells to pretreatment tumor burden.[25] This effect has been seen in phase 1 monotherapy trials of agents targeting PD-1/PD-L1 in recurrent ovarian cancer as well, where response rates have been reported to be 15.0% in those tumor burden less than the median sum of the longest diameter lesion, 58 mm, compared to 5.7% those greater than 58mm.[13] This suggests that pembrolizumab may be most successful in ovarian cancers that have the lowest tumor burden, patients with the earliest recurrences. Unfortunately, patients with the smallest disease burden are often excluded from immunotherapy trials because they do not possess a tumor of sufficient size to qualify as a RECIST target lesion.[26]

4.1.6 Biochemical recurrence in ovarian cancer

Serum CA-125 is commonly used for cancer surveillance in ovarian cancer and elevations often precede symptoms or radiographic evidence of recurrence.[27, 28] Standard of care calls for either treatment with hormonal therapy or observation for these “biochemical” recurrences. Early treatment of recurrences is controversial and may not yield survival advantage.[29] Therapies with favorable toxicity profiles would be attractive in a niche where disease stabilization is highly desirable because patients are often asymptomatic. Disease stabilization and disease control rates are increasingly being reported for immunotherapies. Anti-PD-1 therapy in recurrent ovarian cancer has thus far shown only modest response rates, but higher rates of disease stabilization.[12-15]

In ovarian cancer the use of progression free survival as an endpoint due to feasibility issues in studying overall survival has been advocated.[30]

4.1.7 Predictive biomarkers for anti-PD-1 therapy

Biomarker defined disease has accelerated the approval of pembrolizumab.[31] Data from our trial also shows that PD-L1 expression in archival tissue may correlate with response. While the response rate to pembrolizumab monotherapy was reported to be only 11.5% in KEYNOTE-028 for PD-L1 positive patients, our trial combining pembrolizumab with carboplatin has shown 7 patients positive for PD-L1 (MPS≥5) in archival tissue by the same 22C3 antibody out of 23 evaluable patients.[22] All 7 PD-L1 positive patients achieved stable disease (4 of 7) or had partial responses (3 of 7).

4.2 Rationale for Dose Selection/Regimen/Modification

4.2.1. Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg Q6W.

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 in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200mg Q3W, and
- 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

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala et al, 2018]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- Pharmacokinetic (PK) simulations demonstrating that in terms of pembrolizumab exposures:

- Average concentration over the dosing interval (Cavg) (or area under the curve [AUC]) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations (Cmin) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
- Peak concentrations (Cmax) at 400mg Q6W are well below the Cmax for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

4.2.2 Carboplatin

Carboplatin will be infused at an AUC of 6 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) = (6.0) x (GFR + 25)

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

We have scheduled pembrolizumab to be given 2 days after carboplatin in this expansion cohort based on data demonstrating superior T cell proliferation after 48 hours compared to other cytotoxic chemotherapies and the importance of proliferating CD8 T cells in the peripheral blood to pembrolizumab responses in melanoma.[18, 25]

Carboplatin will be administered only in the first cycle to decrease potential toxicity. Hypersensitivity during retreatment with carboplatin is known and is most often seen in the second or third exposure in the second line of treatment, usually the eighth or ninth dose overall.[32] Since we are not proposing to use carboplatin for its cytotoxic properties, we will not re-dose after the first cycle of treatment with pembrolizumab. If a patient goes on to the re-treatment phase refer to Section 9.5.

4.3 Rationale for Endpoints

4.3.1 Efficacy Endpoints

1. For each patient, tumor measurements 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 will be used to establish measurable tumor to establish rate of radiographic progression at 6 months. Please also see Section 11.1.

2. 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.[33]

4.4 Biomarker Research

4.4.1 Immunohistochemistry of PD-L1

Patients will be consented so that archival tissue can be requested through the University of Washington's Department of Pathology/Outside Pathology if needed and sent for immunohistochemistry testing for PD-L1.

4.4.2 T cell assays from peripheral blood samples

The importance of TILs has been long established in ovarian cancer, but the utility of this T cell marker has been difficult to apply and study in practice because patients do not often get biopsies when a recurrence is suspected or diagnosed. Even if a biopsy were desired, the anatomic location and size of recurrences often preclude this on a technical basis. Peripheral T cells have been less studied for their prognostic significance. Immune responses that fail to eradicate tumor can lead to T cell dysfunction and exhaustion (T_{ex}).[37] Peripheral T cells are easily obtained and T_{ex} cells can be partially reinvigorated by anti-PD-1 therapy with pembrolizumab.[25] We propose to measure both T cell proliferation and activation markers.

5.0 PATIENT SELECTION

5.1 Diagnosis Status for Study Entry

Ovarian, fallopian tube, primary peritoneal cancer patients in complete remission undergoing cancer surveillance found to have elevated CA-125 two times the upper limit of normal for their institution but without measurable radiographic evidence of recurrence by RECIST 1.1.

Patients with FIGO stage III or IV and treated to a complete response to primary therapy without regard to platinum sensitivity or resistance will be eligible as per GOG 198.[38] While the main clinical determinant in treating recurrent ovarian cancer has long focused on whether patients recur within an arbitrary 6 months of a platinum-based combination, the utility of this definition has begun to be re-examined.[39] The biology of platinum resistance in ovarian cancer is not completely understood.[40] Platinum resistance is not an immutable state. Furthermore, the paradigm of platinum resistance was developed in the context of platinum versus other cytotoxic chemotherapies, but the landscape of cancer therapy has changed with the advent of biological and immune-based therapies.

5.2 Inclusion Criteria

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

a. Have a diagnosis of ovarian, fallopian tube, or primary peritoneal cancer who have received systemic chemotherapy including platinum-based chemotherapy.

b. Have a CA-125 that normalized after first-line therapy

c. CA-125 increased to more than twice the upper limit of normal or two times the nadir value after most recent second or later line of treatment.

d. Have no measurable disease based on RECIST 1.1. Ascites and pleural effusions are not measurable disease, if asymptomatic.

e. All patients who are having sex that can lead to pregnancy must agree to contraception for the duration of the study.

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

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

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

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

j. Demonstrate adequate organ function as defined below, all screening labs should be performed within 14 days of treatment initiation.

k. Adequate Laboratory values as follows:

i. Hematological

1. Absolute neutrophil count (ANC) ≥1,500/mcL.

2. Platelets ≥100,000/mcL.

3. Hemoglobin (Hgb) ≥ 9g/dL or ≥ 5.6mmol/L without transfusion or EPO dependency (within 7 days of assessment).

ii. Renal

1. Creatinine ≤ 1.5 X upper limit of normal (ULN) OR

2. Measured or calculated creatinine clearance ≥ 30 mL/min for subject with creatinine levels > 1.5 X institutional ULN.

iii. Hepatic

1. Total bilirubin ≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5ULN.

2. AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases.

iv. Coagulation

1. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤ 1.5X ULN unless patient is receiving anticoagulant therapy (as long as PT or PTT is within therapeutic range of intended use of anticoagulants)

2. Activated Partial Thromboplastin Time (aPTT) or PTT ≤ 1.5X ULN unless patient is receiving anticoagulant therapy (as long as PT or PTT is within therapeutic range of intended use of anticoagulants).

5.3 Exclusion Criteria

Exclusion from participating in the trial will occur if the patient:

a. 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.

b. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (if dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

d. Has symptomatic ascites or pleural effusions.
e. History of borderline or low malignant potential ovarian cancer.

f. Hypersensitivity to pembrolizumab or any of its excipients.

g. 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.

h. Has had prior chemotherapy, biologic therapy, targeted small molecule therapy, hormonal 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: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

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

i. 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.

j. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 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 14 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

k. 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.

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

m. Has an active infection requiring systemic therapy.

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

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

p. 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.

q. Clinically significant cardiovascular disease.

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

s. Has received prior therapy with pembrolizumab.

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

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

v. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.

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.

6.0 STUDY TREATMENT

Treatment to be used in this Study is outlined below in Table 1.

Table 1. Study Treatment

Drug	*Dose/ Potency*	*Dose Frequency*	*Dose Route*	*Treatment Period*	*Use*
Pembrolizumab	400 mg	Q6W	IV infusion	Day 1 each 6 week cycle	Experimental /Standard of Care
Carboplatin*	AUC 6**	Once	IV infusion	2 days prior to cycle 1	Standard
*Given per standard of care **Calculated by use of the Calvert formula					

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Study Flow Chart (Section 8.0). Trial interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Trial interventions will be administered on an outpatient basis.

6.1. 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 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 (Appendix D).

6.2 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).

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

Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician/physician extender discretion. Patients 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.

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 2.

Table 2 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
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	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
ventilatory support indicated	**Participant is permanently discontinued from further study drug intervention.**	
Appropriate resuscitation equipment should be available at the bedside and a physician/physician extender readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

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 may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants 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.

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

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

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroids and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	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 patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4 or recurrent Grade 3	Permanently discontinue		
AST/ALT elevation or increased bilirubin	Grade 2[a]	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[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer 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[d]		
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[d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All otherirAEs	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[e].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

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

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

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

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician/physician extender. 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)

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

Carboplatin
Standard dose adjustment for carboplatin may be made based on 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 (Appendix D) for a comprehensive list of adverse events associated with carboplatin.

6.3 Timing of Dose Administration
Study drug should be administered on Day 1 of each cycle after all procedures and assessments have been completed as detailed on the Study Flow Chart (Section 8.1). Study drug may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 400 mg will be administered as a 30 minute IV infusion every 6 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 6 will be administered per standard of care two days prior to pembrolizumab on cycle 1 only.

6.4 Blinding Method

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

6.5 Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than 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/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

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/combination treatment are provided in Table 3.

6.6 Attribution of Toxicity for pembrolizumab combination studies

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination or carboplatin alone or to pembrolizumab alone, for adverse events listed in Table 3, both interventions must be held according to the criteria in Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

6.7 Holding Study Interventions

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

6.8 Restarting Study Interventions

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

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combination of carboplatin and pembrolizumab may be restarted at the discretion of the investigator.[In these cases where the toxicity is attributed to

the combination or to carboplatin alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.]

6.9 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

6.9.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. 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 Section 10.2.2.

6.9.2 Prohibited Concomitant Medications

Throughout the duration of this study, patients should refrain from receiving the following medications or therapies:

- 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.

Participants 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. Participants may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial. Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

7.0 RESCUE MEDICATIONS & SUPPORTIVE CARE

7.1 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 T1DM 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 liothyronine, 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.

7.2 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 pro-gestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 10.1.2- 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.

7.3 Patient Withdrawal/Discontinuation Criteria

Patients 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 patient 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 9.3 – Other Procedures.

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

- The patient or legal representative (such as a parent or legal guardian) withdraws consent
- Confirmed RECIST 1.1 measurable radiographic disease
  - Treatment may continue past the initial determination of disease progression per discretion of PI, unless they develop unacceptable toxicities that cannot be clinically managed
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Sections 10 and Appendix B
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The patient is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 17 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Patients who stop pembrolizumab after 24 months may be eligible for additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 9.5
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 8.1 (Study Flow Chart) and Section 9.4 (Visit Requirements). After the end of treatment, each patient 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 10.2.1). Patients 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 patient will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.4 Participant Replacement

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

8.0 STUDY & ADMINISTRATIVE PROCEDURES

8.1 Study Flow Chart

Trial Period:	**Screening Phase**			**Treatment Cycles [a, g]**								**End of Treatment [f]**	**Post Treatment**	
Treatment Cycle/Title:		Main Study Screening[h]	-2	1	2	3	4	Repeated beyond 8 cycles 5	6	7	8	Discontinuation	Safety Follow-up[e]	Survival Follow-Up[b]
Scheduling Window (Days):					± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discontinuation	30 days post discontinuation	Every six months after discon
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Demographics and Medical History		X												
Archival Tissue Availability[j, k]		X												
Prior and Concomitant Medication Review		X		X	X	X	X	X	X	X	X		X	
Carboplatin Administration (Day -2)[l]			X											
Trial Treatment Administration (Day 1)				X	X	X	X	X	X	X	X			
Review Adverse Events				X	X	X	X	X	X	X	X		X	
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	
PT/INR and aPTT or PTT		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	
ANA, T3, FT4 and TSH				X		X			X				X	
Correlative Studies Blood Collection [f, i]				X		X			X			X[m]	X[m]	
Post-Study anticancer therapy status														X
Survival Status														X

[a] Treatment Cycles: Up to 17 6 week treatment cycles

[b] Follow-Up Visits (Post Discontinuation): Patients will be followed with CT scan 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 3 and 5 +/- 7 days then will be repeated approximately every 3 months per standard of care

[d] Adverse events will be collected for 30 days post treatment or prior to initiation of new treatment. Serious adverse events will be followed for 90 days after the end of treatment as described in Section 10.2.1

[e] Approximately 30 days post treatment or before the initiation of a new anti-cancer treatment 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 8.6.3). 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 Phase procedures (9 cycles for each retreatment) (Section 9.5)

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

[i] After Cycle 6; correlative blood draws will occur every six cycles

[j] Tissue slides are shipped to Discovery Life Sciences, LLC for PDL1 analysis. The Discovery Life Sciences, LLC manual details shipping requirements

[k] We will obtain archival tumor, for immunohistochemical staining

[l] Two days prior to administration of study drug. May be given per standard of care at patient's own clinic or as part of a study visit

[m] Correlative blood collection for Re-Treatment Phase only (this can be done either at EOT visit or 30 Day Safety Follow-Up)

8.2 Study Procedures

The Study Flow Chart - Section 8.1 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

8.3 Administrative Procedures

8.3.1. Informed Consent

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

8.3.2 General Informed Consent

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

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

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

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

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

8.3.3 Inclusion/Exclusion Criteria

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

8.3.4 Medical History

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

8.4 Prior and Concomitant Medications Review

8.4.1 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 patient within 28 days before starting the trial. Treatment for the disease for which the patient has enrolled in this study will be recorded separately and not listed as a prior medication.

8.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the patient during the trial. All medications related to reportable SAEs and ECI should be recorded as defined in Section 10.2.2 and Appendix B.

8.5 Research Treatment

8.5.1 Treatment Schedule

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

8.5.2 Pembrolizumab Administration

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

8.5.3 Carboplatin Administration

Carboplatin is administered per standard of care once, two days prior to the first dose of study drug.

8.6 Disease Details & Treatments

8.6.1 Disease Details

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

8.6.2 Prior Treatment Details

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

8.6.3 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 patient 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.

8.6.4 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.

8.6.5 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.

9.0 STUDY PROCEDURES/ASSESSMENTS

9.1 Clinical Procedures/Assessments

9.1.1 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 Study Flow Chart and more frequently if clinically indicated. Lab values are to be reviewed and documented in the database as adverse events, if applicable (clinically significant). Adverse experiences will be graded and recorded throughout the study up to the Safety Follow Up visit according to NCI CTCAE Version 5.0 (see Appendix B). Toxicities will be characterized in terms described in Table 8.

For patients 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 patients who are hospitalized, due to their disease, the PI will review their records and determine what may be relevant event(s), procedures, and medications that should be documented in the study record.

Please refer to Sections 10 and Appendix B for detailed information regarding the assessment and recording of AEs.

9.1.2 Physical Exam

The investigator or qualified designee will perform a physical exam during the screening period, prior to the administration of each dose of trial treatment and at treatment

discontinuation as specified in the Study Flow Chart (Section 8.1) Clinically significant abnormal findings should be recorded as adverse events.

9.1.3 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 Study Flow Chart (Section 8.1). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

9.1.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

9.2 Laboratory Procedures/Assessments

9.2.1 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 within 4 weeks prior to trial entry (if not done within 4 weeks 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 patient, tumor response will be assessed by CT scan or MRI. Scans performed prior to cycle 1 need to be repeated at subsequent visits as outlined in Section 8.1 (prior to cycles 3 and 5 +/- 7 days, then approximately every three months per standard of care). Lesions detected at baseline need to be followed using same imaging methodology.

9.2.2 Tumor Tissue Availability/Collection & 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.[41]

We will obtain archival tumor, for immunohistochemical staining. Expression of PD-L1 will be correlated with response, OS, and PFS and toxicities.

Peripheral blood mononuclear cells will be obtained from patients at baseline prior to study treatment and after 3 cycles. Circulating CD8 T_{ex} cells pre- and post-treatment will be assessed by flow cytometry looking for established T_{ex} markers: $CD8^{+}$, $PD\text{-}1^{+}$, $CTLA\text{-}4^{+}$, $CD45RA^{lo}$, $CD27^{+}$, $Eomes^{hi}$, $T\text{-}bet^{lo}$. Ki67 is a marker of cell proliferation and T-cell reinvigoration in checkpoint blockade in mouse and humans.[42, 43] We will look at changes in cell proliferation Ki67 in PD-1+ CD8 T cell after treatment with pembrolizumab, as has been seen in melanoma.[25]

T-cells activated by DCs exposed to platinum chemotherapy produce higher levels of IFN-γ and IL-2 compared to untreated DCs.[18] Anti-PD-1 therapy has been shown to increase IFN-γ producing PD-1^{+}CTLA-4^{+} and PD-1^{+}CXCR5^{+} subsets of CD8 cells, consistent with reinvigoration of T_{ex} cells.[25] To test for reinvigoration of T_{ex} cells, we will analyze interferon gamma production by stimulating pre- and post-treatment PBMCs *in vitro* with phorbol myristate acetate and ionomycin then perform intracellular cytokine staining with anti-PD-1 and anti-IFNγ antibodies before flow cytometry.

9.2.3 Laboratory Procedures

Details regarding specific laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 4 below.

Laboratory tests for screening or entry into the Re-Treatment 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.

Table 4. Laboratory Tests

Hematology	Chemistry	Urinalysis[c]	Other
Hematocrit (Hct)	Albumin	Blood	CA-125
Hemoglobin (Hgb)	Alkaline phosphatase	Glucose	ANA
Platelet count (Plt)	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT or PTT
Absolute Neutrophil Count (ANC)	Carbon Dioxide [b] *(CO_2 or bicarbonate)*	Microscopic exam *(If abnormal)*	Thyroid stimulating hormone (TSH)
Red Blood Cell Count (RBC)	Lactate dehydrogenase (LDH)	Urine pregnancy test [a]	Free thyroxine (T4)
Absolute Lymphocyte Count	Blood Urea Nitrogen (BUN)		Total triiodothyronine (T3)
	Direct Bilirubin (if total bili > upper limit of normal)		Serum β-human chorionic gonadotropin[a]
	Total Bilirubin		(β-hCG)[b]
	Chloride		Blood for correlative studies
	Glucose		
	Sodium		
	Uric Acid Potassium		
	Phosphorus Magnesium		
	Total Protein		
	Calcium		

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

[b] If considered standard of care in your region.

[c] Urinalysis, as needed

9.2.4 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.

9.3 Withdrawal/Discontinuation

When a patient 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 Sections 10.1 - Assessing and Recording Adverse Events and Appendix B. Patients 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 9.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 9.4.5) and then proceed to the Follow-Up Period of the study (described in Section 9.4.6).

Participants who withdraw prior to completion of the trial should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 10.1.

9.4 Visit Requirements

Visit requirements are outlined in Section 8.1 – Study Flow Chart. Specific procedure-related details are provided above in Section 8.2 - Study Procedures.

9.4.1 Screening

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

9.4.2 Screening Period

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

9.4.3 Treatment Period

The treatment period is 24 months of uninterrupted treatment with pembrolizumab or 17 administrations of study drug, whichever is later, or until progression of disease. Patients 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. Patients with disease progression may continue study drug per discretion of PI.

9.4.4 Post-Treatment Visits

Once a patient 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 to request tumor imaging reports approximately every six months 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 approximately every six months until death, withdrawal of consent, or the end of the study, whichever occurs first.

9.4.5 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. Patients 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 9.5) may have two or more safety follow-up visits, one after the Treatment Period and then after a Re-Treatment Phase.

9.4.6 Survival Follow-up

Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy, the patient moves into the survival follow-up phase and approximately every six months 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.

9.5 Re-Treatment Phase (9 Cycles)

All participants who stop study intervention without progression by RECIST may be eligible for up to an additional 9 cycles (approximately 1 year) of pembrolizumab treatment, after a dose of carboplatin, if they progress after stopping study treatment from the current treatment phase (either initial or re-treatment). Patients may repeat the Re-Treatment Phase of this study multiple times as long as the study remains open and the participant meets the following conditions:

Either

- Stopped current study intervention phase (either initial or re-treatment phase) after investigator determined no evidence of progression based on RECIST 1.1, and
    - Was treated with at least 4 cycles of study treatment before discontinuing treatment, and
    - Received at least 1 treatment with pembrolizumab beyond the date when the initial absence of RECIST progression was declared

OR

- Had stopped study intervention after completion of 17 administrations (approximately 2 years) of study intervention for reasons other than RECIST disease progression or intolerability
- Had stopped a re-treatment phase of 9 administrations (approximately 1 year) of study intervention for reasons other than RECIST disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping current study treatment phase (either initial or re-treatment phase) or has an increase in CA125 increase to more than twice the upper limit of normal or two times the nadir value after completing current study treatment phase (either initial or re-treatment phase), and
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

Patients with radiographic progression during a re-treatment phase may be permitted a single re-priming dose of carboplatin and continue on study at discretion of PI.

An objective response or disease progression that occurs during the Re-Treatment Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

Visit requirements are outlined in Section 8.1 – Study Flow Chart.

10.0 ADVERSE EVENTS

10.1 Assessing and Recording Adverse Events

Reference Appendix B – Data Safety and Monitoring Plan for more details.

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.

Adverse events will be recorded from the time the consent form is signed through the Safety Follow Up visit. Adverse events will be collected on day 1 of each cycle through patient self-reporting and clinician observation. Events may be clarified from previous medical records. Clinically significant lab values are to be reviewed and documented in the database as adverse events, if applicable.

10.1.1 Definition of an Overdose for This Protocol & Reporting of Overdose to the Sponsor

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."

10.1.2 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.

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

10.2.1 Serious Adverse Events

Reference Appendix B – Data Safety and Monitoring Plan for more details.

10.2.2 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 10.1.1 - 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

3. 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.

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 Ed, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

10.2.2 Evaluating Adverse Events

A qualified physician/physician extender will evaluate adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. 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.

10.3 Expected Adverse Events

Table 5. Pembrolizumab Expected Adverse Events

Likely (≥10% of patients)	Less likely (≥5%)	Rare but serious (≥0.2%)
Anemia	Fatigue	Pneumonitis
Fatigue	Decreased appetite	Nausea
Headache	Hypothyroidism	Diarrhea
Itching	Thyroiditis	Fever
Vomiting	Itching	Colitis
Cough	Diarrhea	Pneumonia
Nausea	Arthralgia	Sarcoidosis
Weakness	Weakness	Encephalitis
Diarrhea	Nausea	Autoimmune hepatitis
Decreased appetite	Myalgia	Hyperthyroidism
Shortness of breath	Vitiligo	Hypoparathyroidism
Arthralgia		Shortness of breath
Rash		Myasthenic syndrome
Constipation		Vasculitis - Inflammation of the blood vessels (Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue)
Back pain		Sclerosing cholangitis
Swelling (limbs)		Low sodium in blood
Rash		Arthritis
Fever		Adrenal insufficiency
		Immune-mediated myocarditis
		Sevens-Johnson Syndrome (SJS)
		Toxic Epidermal Necrolysis (TEN)

Likely (≥10% of patients)	Less likely (≥5%)	Rare but serious (≥0.2%)
		Graft vs. host disease (GVHD) in patients with a history of hematopoietic stem cell transplant (HSCT). This condition can lead to death If you have had a solid organ transplant, you may experience rejection of the transplanted organ Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis). Inflammation of the stomach (gastritis). You may have pain in your belly, feel full, or sick to your stomach. You may also experience nausea, vomiting or loss of appetite. Low number of red blood cells (cells that carry oxygen) due to destruction of red blood cells (hemolytic anemia). You may feel weak, tired, lightheaded, short of breath, or have a fast heartbeat. You may also experience difficulty with physical exercise, pale or yellow skin, dark urine, or fever. Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food (exocrine pancreatic insufficiency). You may have bloating, gas, discomfort in your belly, diarrhea, abnormal stool that is oily, or weight loss. Inflammation of the protective sac surrounding your heart (pericarditis) which can cause sharp chest pain and shortness of breath (especially when lying flat), fever, and a fast or irregular heartbeat. In severe

Likely (≥10% of patients)	Less likely (≥5%)	Rare but serious (≥0.2%)
		cases, your heart may have difficulty pumping blood throughout your body.

Table 6. Carboplatin Expected Adverse Events

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

10.3.4 Potential Overlapping Toxicities

Table 7. Potential Overlapping Toxicities

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

Likely (>10% of patients)	Less likely (>5%)	Rare but serious (>0.2%)
Constipation		

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.

10.4 PI 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.

Table 8. Evaluating Adverse Events

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

V5.0 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	
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.)

V5.0 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:	
	Rechallenge	Was the patient 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.)	

11.0 STATISTICAL CONSIDERATIONS & ANALYSIS

11.1 Statistical Consideration & Analysis

This is a single arm trial testing the effect of carboplatin and pembrolizumab to prevent progression after serological detection of recurrence in ovarian cancer. We will compare the progression free survival based on radiographic imaging at 6 months (primary endpoint) to historical control rates for this population of patients treated by letrozole or tamoxifen. It has been reported that, if treated with letrozole, the rate of progression free survival at 6 month was 26%, and if treated with tamoxifen, the median progression free survival was 4.5 months and the rate of progression free survival at 6 month was 28%.[38, 44] Standard of care for the treatment of serological recurrences still include observation or treatment with tamoxifen and letrozole. Our inclusion criteria for serologically recurrent ovarian cancer, defining CA-125 levels twice the upper limit of normal without radiographically measurable disease, match those from these benchmark studies, so we will have a similar patient population compared to these historical controls.

The sample size is driven by the hypothesis that the investigational treatment will double the rate of progression free survival at 6 months (from 26% to 52%, or from 28% to 56%), and determined to be to 22 or 19 for the two benchmark rates. Therefore, a sample size of 22 patients will be adequate to test doubling of either of the benchmark rates (letrozole or tamoxifen). With this sample size, we will have 90% power to detect doubling of the median progression free survival from 4.5 months (treated by tamoxifen) to 9 months. [38, 44] We note that a 5 month increase in survival is what ovarian cancer patients surveyed report they would consider important for them in a hypothetical new therapy.[45] Therefore we conclude that a sample size 22 will be sufficient to test either primary or secondary end point against the two benchmark treatments.

To more efficiently conduct this trial with interim futility and efficacy stopping rules, we will use a Fleming two-stage design.[46, 47] Existing two-stage designs only account for dichotomized response, therefore we use progression-free rate at 6 months (the primary endpoint) in interim analysis. In the first stage we will enroll 15 patients, if we observe 4 patients or less progression free at 6 months, then stop the trial for futility; if we see 8 or more patients with no progression, then we will stop the trial for efficacy; if we see 5-7 patients with no progression, then we will continue the trial to the second stage, enrolling additional 7 patients.

The comparison of the observed rate of the primary endpoint- progression free survival at 6 months and the secondary endpoint- radiographic recurrence rate to the benchmark rate will be conducted by Fisher's exact test. The Kaplan-Meier survival curve will be plotted and the median progression free survival will be compared to the historical progression free survival with greenwood confidence interval. PD-L1 expression will be scored as positive or negative based on prior literature. The prediction of clinical response by PD-L1 expression status will be evaluated in multiple metrics, including PFS and the rate of PFS at 6 months. Logistic regression or Cox proportional hazard model will be employed to evaluate the prediction of PD-L1
status toward clinical endpoints, using one-sided test with the hypothesis that higher expression or positive status entails improved clinical outcome.

The PD-L1 expression will be evaluated by immunohistochemistry staining in combined tumor and inflammatory cells. Positivity will be defined by >1% staining. The predictive value of PD-L1 positivity toward the rate of PFS at 6 months will be evaluated by odds ratios computed by logistic regression, first individually and then combined as four strata. We will test the association of individual marker, the combined two marker panel, and the interaction between the two markers. We will also evaluate whether adding T-cell response to PD-L1 will be increase the accuracy of predicting clinical response by comparing the fitness between the two models (one with T-cell response and the other one without T-cell response). ROC curve and AUC will be evaluated for different panels of markers and the incremental value of adding a particular marker to AUC performance will be assessed.

As part of the translational research objectives, we will evaluate the potential of the Combined Positive Score (CPS), a measure of PD-L1 expression, as a predictive biomarker for treatment response. CPS will be collected at baseline for all enrolled patients. We plan to explore the association between CPS and clinical outcomes, including PFS at 6 months. Using receiver operating characteristic (ROC) curve analysis and other threshold-finding approaches (e.g., Youden index, maximally selected rank statistics), we will identify potential CPS cutoffs that best discriminate between patients with favorable versus unfavorable outcomes. These analyses are exploratory in nature and intended to inform future validation studies.

We next investigate the power of the biomarker study. Suppose we are recruiting 22 patients, half of them will be progression-free at 6 months (responder). The table below shows the power of detecting a significant difference between a significant association between the biomarker positivity and the rate of progression-free survival at 6 months for a range of marker positive rates in responders and non-responders.

	Proportion of marker positive in a responder = 75%	Proportion of marker positive in a responder = 90%
Proportion of marker positive in a non-responder = 15%	0.82	0.98
Proportion of marker positive in a non-responder = 30%	0.49	0.83
Proportion of marker positive in a non-responder = 45%	0.22	0.54

Clearly, the sample size only allows for adequate power to detect a large difference (highly strong association) between marker positivity and clinical response. However, the same PD-L1 assay we plan to use has been reported in non-small cell lung cancer as a single marker. Patients with a PD-L1 proportion score of less 1% had a 8.1% objective response rate to pembrolizumab, compared to an objective response rate of 45.4% in those with a PD-L1 proportion score of 75% or greater.[48] PD-L1 immunohistochemistry staining by Discovery Life Sciences, LLC on archival tumor from our

pembrolizumab/carboplatin trial also suggests that a large difference based on this marker may be possible in ovarian cancer patients treated with this combination.

12.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

12.1 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 10.

Table 9. Product Descriptions

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

12.1.1 Packaging and Labeling Information

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

12.1.2 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.

12.1.3 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.

12.1.4 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.

13.0 ADMINISTRATIVE AND REGULATORY DETAILS

13.1 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.

13.2 Study Team Roles and Responsibilities

Dr. Liao, the Principal Investigator (PI) will be responsible for the oversight of the study. The PI is responsible for the preparation and implementation of the protocol. The PI also analyzes the results of the study data. 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. Dr. Liao will delegate tasks to qualified research staff for this study as needed.

Research physicians/physician extenders will be responsible for conducting informed consent conferences and eligibility determination at the initial visit. Throughout the duration of the study, they will perform physical exams, and collect, review, and attribute adverse events per protocol. In addition, they will be available to answer patient study related questions. They collaborate attentively with the research staff to ensure the safety and efficacy of the patient.

Research Nurses/Coordinators will be responsible for recruitment, initial screening, baseline event collection, coordination of clinical treatment, study visits and follow up. They may, do medication/adverse event collection review with patients and ensure it 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 be responsible for maintaining regulatory documentation to the various agencies involved with this research and assist with ensuring 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

13.3 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)/physician extender, 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.

13.3.1 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.

https://www.washington.edu/research/policies/gim-10-financial-conflict-of-interest-policy/

13.3.2 Compliance with Law, Audit and Debarment

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

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov.

Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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15.0 APPENDICES

Appendix A. ECOG Performance Scale

Performance status: Patients will be assessed according to the current ECOG performance scale.

ECOG performance scale

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

Appendix B.

Data Safety and Monitoring Plan (DSMP)

A. Purpose

To ensure that the Cancer Vaccine Institute (CVI) follows NIH/NCI/CTEP/FDA guidelines with respect to: (1) accurate assessment and timely reporting of adverse drug reactions associated with investigational drugs, (2) adherence to protocol, and (3) accurate reporting of data. The DSMP will be approved by Fred Hutchinson Cancer Research Center (FHCRC) /University of Washington (UW) – Cancer Consortium IRB (FHCRC/UW – CC IRB) in Seattle, Washington.

The Principal Investigator (PI), for this project, is responsible for the study design, delegating responsibility/authority, study conduct and final analysis of the data. Regulations defining the responsibilities for assessment and reporting of all adverse events (AE), serious AE (SAE), and unexpected AEs are defined by the Code of Federal Regulations: 21 CFR 312.32 and Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 published by the Cancer Therapy Evaluation Program (CTEP), a division of the NCI/NIH.

This clinical study will rely upon the monitoring of the trial by the Principal Investigator (P.I.) in conjunction with Research Nurse(s), Clinical Research Staff, Statistician, Independent Medical Monitor and an Independent Study Monitor assigned by the Clinical Research Support (CRS) of the FHCRC/UW–CC IRB.

The Independent Medical Monitor for this study is Edward Marzbani, MD. The Medical Monitor will be notified when the study is open prior to patients being recruited in order to orient them to the study. The Medical Monitor will then review the study approximately every 6 months throughout the study treatment period. The Medical Monitor will review patient recruitment and retention, adherence to protocol, follow-up, data quality, and participant risk versus benefit.

If a SAE occurs the PI will be notified along with the Food and Drug Administration (FDA), Medical Monitor, FHCRC/UW CC IRB, UW Translational Research Unit (TRU), and U.S. Army Medical Research and Materiel Command Human Subjects Research Review Board (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) and Merck (providing the product).

B. Objectives

1. To ensure that the PI and Clinical Research Staff follow federal and institutional regulatory guidelines with respect to timely reporting of adverse reactions associated with investigational drugs.
2. To define classification of adverse drug reactions as expected or unexpected.
3. To define classification of adverse drug reactions as serious or non-serious.

4. To ensure compliance and accuracy of documentation of SAE reactions reportable to: (1) FDA (2) Medical Monitor, (3) FHCRC/UW CC IRB, (4) UW TRU, (5) USAMRMC ORP HRPO, and (6) Merck.

C. Adverse event reporting policy and procedures

1. Evaluation of adverse events: Patients are monitored for the development of toxicities by assessing adverse events lab values throughout the study. Criteria for Adverse Events will be CTCAE Version 5.0.

2. Definitions of adverse events (AEs):

   a. *AE* - any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or 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.

      An adverse event may include

      - an exacerbation of a pre-existing illness that would stop treatment of a standard chemotherapy treatment.
      - an increase in frequency or intensity of a pre-existing episodic event or condition.
      - a condition detected or diagnosed after study drug administration.
      - continuously symptoms that were present at baseline and worsen following the start of the study.
      - Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

      An adverse event does not include:

      - medical or surgical procedures unrelated to the treatment of the disease (e.g., surgery, endoscopy, tooth extraction, or transfusion); however, the condition that leads to the procedure may be an adverse event.
      - pre-existing diseases, conditions, or laboratory abnormalities present or detected at the start of the study that do not worsen.
      - progression of the cancer unless it is considered to be drug related by the investigator.

- hospitalizations or procedures that are done for elective purposes not related to an untoward medical occurrence (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions).
- the disease being studied or signs/symptoms associated with the disease unless more severe than expected for the patient's condition.
- overdose of study drug without any clinical signs or symptoms.

b. *Expected AE* - an event that may be reasonably anticipated to occur as a result of the study procedure.

c. *Unexpected Adverse Event* - an AE that is not described in the IND and/or consent form and is unanticipated. An event that might have been anticipated but is more serious than expected or occurs more frequently than expected, could be considered an unexpected adverse event.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above could be considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

3. Scale of scoring adverse events
   a. Grade 1 = mild adverse event
   b. Grade 2 = moderate adverse event
   c. Grade 3 = severe adverse event
   d. Grade 4 = life-threatening or disabling adverse event
   e. Grade 5 = death related to adverse event.

4. Attribution of adverse event

   a. 5 (definite): the adverse event is clearly related to the investigational agent.
   b. 4 (probable): the adverse event is likely related to the investigational agent.
   c. 3 (possible): the adverse event may be related to the investigational agent.
   d. 2 (unlikely): the adverse event is doubtfully related to the investigational agent.
   e. 1 (unrelated): the adverse event is clearly NOT related to the investigational agent.

5. SAE event reporting

This timing for reporting is outlined below by regulatory agency (Appendix B - Table 1).

A serious adverse event includes adverse event(s) occurring at any dose or during use of Merck's product that is unexpected and related and results in:

1. Death.
2. Life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization

4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

Hospitalizations that do not meet these criteria are:

- reasons described in the protocol, e.g., drug administration, protocol-required testing.
- social reason in the absence of an AE.

6. Events of Clinical Interest: Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs (see Appendix B for SAE requirements). For more details, reference Section 10.2.2.

FDA (for trials using an Investigational New Drug (IND) – Serious adverse events will be reported per 21 CFR 312.32 by telephone or facsimile transmission (using either the narrative format, the MedWatch Form 3500A Unexpected, related to the investigational product and serious adverse events are reported in writing (using either the narrative format, the MedWatch Form 3500A to the FDA (Center for Biologics) within 15 calendar days after initial receipt of the information concerning the event.

Yearly written progress reports to the FDA will summarize expected or non-serious unexpected adverse events.

Independent Medical Monitor - At a minimum, the medical monitor should comment on the outcomes of serious adverse event(s) unexpected and related to treatment with pembrolizumab or prepare an unbiased written report of the event. They should also indicate whether they agree with the details of the report provided by the study investigator.

Fred Hutchinson Cancer Research Center/UW Cancer Consortium IRB - We will follow the current AE reporting policy of the FHCRC – CC IRB.

University of Washington Translational Research Unit (UW TRU) - The TRU will receive copies of the documents submitted to the FHCRC/UW CC-IRB within 7-10 calendar days.

USAMRMC ORP HRPO - although we will report expected and unexpected serious and unexpected serious/fatal events to the FHCRC/UW CC IRB we will also report these unanticipated events to the USAMRMC ORP HRPO promptly by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), reported by telephone (301-619-2165), or by facsimile (301-619-7803) to the HRPO.

A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Development Command, ATTN: FCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

Merck (providing drug for this trial) **-**

Notify within 2 – business days (but no longer than 3 calendar days of learning of the event) 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.

Expediated reporting also includes overdose, pregnancy/lactation exposure, event of clinical interest (ECI).

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.

Subjects with serious adverse events must be followed up for outcome.

Follow-up reports will need to be completed until resolution/baseline status of the unanticipated event that was not available at the time of initial reporting.

Appendix B - Table 1. Adverse event reporting

	Expected	Expected	Unexpected	Unexpected
	Non-Serious	Serious	Non-Serious	Serious
	Attribution * (Possible, Probable, Definite)	Attribution * (Possible, Probable, Definite)	Attribution * (Possible, Probable, Definite)	Attribution * (Possible, Probable, Definite)
FDA	Annual Progress Report	Annual Progress Report	Annual Progress Report	FDA Form 3500A or Narrative Format – ASAP but within 7-15 days)

	Expected	Expected	Unexpected	Unexpected
	Non-Serious	Serious	Non-Serious	Serious
	Attribution * (Possible, Probable, Definite)	Attribution * (Possible, Probable, Definite)	Attribution * (Possible, Probable, Definite)	Attribution * (Possible, Probable, Definite)
Independent Medical Monitor	Bi-annual Meeting (twice a year)	Bi-annual Meeting (twice a year)	Bi-annual Meeting (twice a year)	FHCRC Adverse Event Expedited Reporting Form – Following the FHCRC/UW CC-IRB policy
FHCRC/UW – Consortium IRB	Continuation Review Report	Continuation Review Report	Continuation Review Report	FHCRC Adverse Event Expedited Reporting Form – Following the FHCRC/UW CC-IRB policy
UW TRU	Copy of Continuation Review Report	Copy of Continuation Review Report	Copy of Continuation Review Report	Copy of FHCRC/UW CC-IRB Adverse Event Expedited Reporting Form
USAMRMC ORP HRPO	Quarterly or Annual Progress Report	Quarterly or Annual Progress Report	Quarterly or Annual Progress Report	Promptly
Merck (SAE and ECI)	NA	NA	NA	2-3 business days of learning of the event

7. <u>Procedure for reporting SAEs:</u>

   a. Identify the classification/attribution of the adverse event as defined above using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0).

   b. After appropriate medical intervention has been instituted, the Principal Investigator or his/her designee will be notified within 24 hours.

   c. File appropriate reports immediately by phone/fax with appropriate agencies, as described in Appendix B -Table 1.

d. Notify the patient's primary physician or referring physician within a medically appropriate timeframe, depending on the classification of the adverse event.

e. Submit written reports to appropriate agencies.

f. Document the adverse event in the patient's research file, using a progress note to describe the event and treatment, if appropriate.

g. File copies of all forms/correspondence relating to the adverse event in the patient's research file.

D. Clinical trials monitoring operational procedures

1. Clinical data documentation

a. *Internal study monitoring*:

Clinical labs are evaluated at each patient visit for the development of toxicity (AEs) related to the vaccine. Clinically significant abnormal lab values may be faxed to the patient's physician.

A Research Physician, physician extender or PI sees each patient at each visit with the following evaluations being completed: toxicity evaluation, physical assessment and AEs summary (these evaluations are part of the source documentation that is filled out at each visit). Grade 1 and 2 non-serious and expected AEs will be reviewed with the PI or designee regularly. All other AEs will be reported to the PI or designee at the time they become known and reported as outlined above in Appendix B - Section C.

Each patient research file is audited for completeness, legibility, and accuracy. Audits may be conducted by a designated clinical research staff member(s) on an ongoing basis.

b. Biannual review with the independent Medical Monitor:

The Medical Monitor 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

c. *Biannual study audit*:

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support 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), Fred Hutch Scientific Review Committee (SRC), and the Fred Hutch/University of Washington 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.

2. Data validity/integrity

Systems to insure data integrity have been put into place to provide multiple checks to data entry. Patient eligibility is initially reviewed by the Research Coordinator/Research Nurse and the PI or designee during the screening portion of the study. The chart is then reviewed by a study physician/physician extender after the consent conference and before study procedures start. It is then ultimately signed off by the PI or designee.

Clinical laboratory monitoring data is reviewed by a qualified clinician (Research MD, physician extender, Research Nurse and/or P.I.) and any abnormalities are assessed. Patient records are kept in the patient's research file and reviewed at biannual monitoring visits. Data is taken from the patient's source documentation, the patient's research file, and entered into a database which links data to patient by a Unique Patient Identifier and is accessible by password code only. Data entry is made by the Research Clinical Research Staff members. A percentage of all data entry is reviewed by a member of the clinical research team and/or the Independent Study Monitor.

Appendix C.

Response Evaluation Criteria in Solid Tumors (RECIST) v. 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):228-4.

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

Appendix D.

Carboplatin insert:
https://labeling.pfizer.com/ShowLabeling.aspx?id=4379

APPENDIX E.

ABBREVIATIONS, ACRONYMS AND SYMBOLS

AUC	Area under the curve
CA-125	Cancer antigen 125
CBC	Complete Blood Count
CD11c	Cluster of differentiation 11c
CD24	Cluster of differentiation 24
CD45	Cluster of differentiationcd8 45
CD8	Cluster of differentiation 8
CMP	Complete Metabolic Panel
CR	Complete response
CT	Computed Tomography
CTLA-4	Cytotoxic T lymphocyte associated protein 4
CVI	Cancer vaccine institute
DNA	Deoxyribonucleic acid
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
ELISPOT	Enzyme linked immunospot assay
FDA	Food and drug administration
FHCRC	Fred Hutchinson Cancer Research Center
FIGO	International federation of gynecology and obstetrics
GOG	Gynecologic oncology group
HLA-DR	Human leukocyte antigen
DR IFN-γ	Interferon gamma
IL-2	Interleukin 2
IL-6	Interleukin 6
IND	Investigational new drug
IRB	Institutional review board
ITHS	Institute of translational health sciences
IV	Intravenous
mg	milligram
MPs	Microparticles

NCT	ClinicalTrials.gov registry number
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein ligand 1
PD-L2	Programmed cell death protein ligand 2
PFS	Progression-free Survival
PHI	Protected Health Information
PI	Principal investigator
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
ROC	Receiver operator curve
SCCA	Seattle cancer care alliance
SD	Stable disease
SGO	Society of gynecologic oncology
STAT6	Signal transducer and activator of transcription 6
Tex	Exhausted T cell
TIL	Tumor infiltrating lymphocytes
TMDD	Target-Mediated Drug Disposition
UW	University of Washington