PROTOCOL 3475-250

TITLE: PHASE II OPEN LABEL NONRANDOMIZED SINGLE ARM TRIAL OF THE ANTI PD 1 THERAPY PEMBROLIZUMAB IN COMBINATION WITH FIRST LINE PLATINUM BASED CHEMOTHERAPY FOLLOWED BY 12 MONTHS MAINTENANCE PEMBROLIZUMAB MONOTHERAPY FOR PATIENTS WITH SUBOPTIMALLY CYTOREDUCED STAGE III/IV EPITHELIAL OVARIAN CANCER.

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This is an investigator-initiated study. Denise Uyar is the principal investigator and may also be referred to as the sponsor-investigator. Dr. Uyar is conducting the study, holds the IND, and is acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.
The sub-Investigators listed above would act on behalf of the Dr. Denise Uyar in her absence.

CONTENTS

LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITION OF TERMS

Abbreviation/Acronym	Definition
Mm	micron
5HT3	receptors in the vomiting center, chemoreceptor trigger zone and small intestine
ADA	anti–drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration - time curve
BCG	Bacillus Calmette-Guerin vaccine against tuberculosis
BID	twice daily
BRAF	protein kinase that is encoded by the BRAF gene
BRAF V600	Specific mutation occurring within activation segment of kinase domain in BRAF gene
°C	degrees Celsius
CA 125	cancer antigen 125
CBC	complete blood count
CD3	cluster of differentiation 3
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CD14	cluster of differentiation 14
CD19	cluster of differentiation 19
CD21	cluster of differentiation 21
CD24	cluster of differentiation 24
CD25	cluster of differentiation 25
CD27	cluster of differentiation 27
CD28	cluster of differentiation 28
CD38	cluster of differentiation 38
CD56	cluster of differentiation 56
CD279	cluster of differentiation 279

CD45RA	protein tyrosine phosphatase regulating src-family kinases, expressed on all hematopoietic cells
cfDNA	cell free DNA
CIRL	Clinical Immunology Research Laboratory
CLIA	Clinical Laboratory Improvement Amendment
CNS	central nervous system
Crcl	creatinine clearance
CRF	case report form
CT	computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DAKO ACIS III	DAKO automated cell imaging system III
DHEP	Diethylhexylphthalate
DNA	deoxyribonucleic acid
DP	drug product
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOC	epithelial ovarian cancer
°F	degrees Fahrenheit
FACT-O	Functional Assessment of Cancer Therapy - Ovary
FFPE	fresh frozen paraffin embedded
FoxP3	forkhead box P3
GCSF	granulocyte stimulating growth factors
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HCl	hydrochloric acid
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA-DR	MHC class II cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6 region 6p21.31
Ig	immunoglobulin

IgD	immunoglobulin D
IgG4	immunoglobulin G subclass 4
IgM	immunoglobulin M
IgV	immunoglobulin V
IHC	immunohistochemistry
IRB	institutional review board
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IV	Intravenous
IVEX-II	IV extension filter infusion set
IVEX-HP	IV extension hydrophilic filter infusion set
LVP	large volume parenteral
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NaOH	sodium hydroxide
NCCN	National Comprehensive Cancer Network
NK cells	natural killer cells
NSCLC	non-small cell lung cancer
OS	overall survival
OTC	over the counter
PDAC	pancreatic adenocarcinoma
PDCD1	PDCD1 gene encodes PD-1 protein
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression free survival
PK	pharmacokinetic
PVC	polyvinyl chloride
Q / q	every
Q3W	Every 3 weeks
QOL	quality of life
RECIST	response evaluation criteria in solid tumors

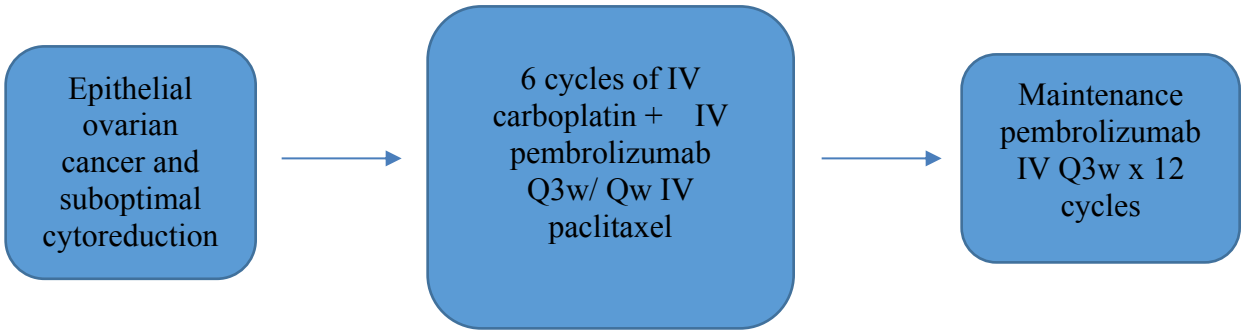
T cells	thymus gland lymphocyte
TILs	tumor-infiltrating lymphocytes
ULN	upper limit of normal
USP	United States Pharmacopeia
WBC	white blood cell
ZAP70	zeta-chain-associated protein kinase **70**

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab/Carboplatin/Taxol in epithelial ovarian cancer followed by maintenance pembrolizumab
Trial Phase	*II*
Clinical Indication	Epithelial Ovarian Cancer
Trial Type	Single Arm, Open label non-randomized
Type of control	Historical Control
Route of administration	IV
Trial Blinding	none
Treatment Groups	Single arm
Number of trial subjects	30
Estimated enrollment period	*18 months*
Estimated duration of trial	*48 months*
Duration of Participation	72 months or closure of trial

2.0 TRIAL DESIGN

2.1 Trial Diagram



Phase II single arm, open label, nonrandomized study. The aim of our study is to assess the Progression Free Survival (PFS) in suboptimally cytoreduced (defined as any gross residual disease) epithelial ovarian/ primary peritoneal/ fallopian tube cancer patients treated with the novel combination of carboplatin Q3w/Qw paclitaxel IV with pembrolizumab IV Q3w followed by maintenance pembrolizumab IV Q3w OR carboplatin and paclitaxel IV Q3w with pembrolizumab IV weekly followed by maintenance pembrolizumab IV Q3w. (Choice of IV chemotherapy regimen may be determined by anticipated tolerance per treating physician discretion.) The choice between the chemotherapy treatment regimens will be agreed upon by the study patient and their enrolling physician prior to entry.

NOTE: Patients who have not attained a normalized CA-125, have stable disease or partial response to therapy on CT imaging at the completion of cycle 6 may continue to receive paclitaxel and carboplatin (with pembrolizumab) for up to 9 cycles (if deemed necessary by the treating physician). Patients who continue with cycles 7-9 will continue with all study assessments as described in the study flow chart. A CT scan should be obtained at the completion of combination therapy and prior to the start of maintenance therapy.

In the case of a hypersensitivity reaction to paclitaxel or baseline neuropathy > grade 2, paclitaxel may be substituted with Q3w docetaxel per treating physician discretion after discussion with the sponsor (See table 5.4).

Stage III/IV epithelial ovarian cancer with suboptimal cytoreduction and/or
CT with measurable residual disease

DAY 1
Carboplatin AUC 6 IV
and
Paclitaxel 80 mg/m^2
+
Pembrolizumab 200 mg IV

DAY 8
Paclitaxel 80 mg/m^2 IV

DAY 15
Paclitaxel 80 mg/m^2 IV

Repeat every 3 weeks for 6 cycles

Followed by maintenance Pembrolizumab IV
DAY 1 every (Q) 21 days x 12 cycles

*The choice between the chemotherapy treatment regimens will be agreed upon by the study patient and their enrolling physician prior to entry.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** Assess Progression Free Survival (PFS) of combination platinum-based therapy with anti-Programmed Death (PD)-1 therapy followed by maintenance anti-PD-1 therapy in patient with suboptimally/ residual disease following cytoreduction of epithelial ovarian/ primary peritoneal/ fallopian tube cancer, which for the purposes of the protocol will be referred to as epithelial ovarian cancer (EOC).

Hypothesis: Our hypothesis is that anti-PD therapy combined with standard chemotherapy will improve the PFS in this population and have a tolerable safety profile.

3.2 Secondary Objectives & Hypotheses

(1) **Objective:** Assess Overall Survival (OS) of combination platinum-based therapy with anti-PD-1 therapy followed by maintenance anti-PD-1 therapy in patient with suboptimally/ residual disease following cytoreduction of EOC.

Hypothesis: Our hypothesis is that anti-PD therapy combined with standard chemotherapy will improve the OS in this population and have a tolerable safety profile.

(2) **Objective**: Monitor quality of life during combination therapy and single agent maintenance therapy with anti-PD-1 therapy with the Functional Assessment of Cancer Therapy (FACT) surveys at intervals during therapy.

Hypothesis: We hypothesize that combination chemotherapy and anti-PD-1 therapy will not adversely affect quality of life during combined and maintenance therapy duration.

3.3 Exploratory Objectives:

The overall objectives pertain to the development of biomarkers for prediction and monitoring of disease status.

(1) **Objective**: Assess the PD-1 and PD-L1 expression in preserved tissue obtained at the time of initial diagnosis for patients with suboptimally/ residual disease following cytoreduction of ovarian cancer using immunohistochemistry (IHC) and correlate with clinical outcomes.

(2) **Objective:** Assess serial immune profiles from blood samples obtained post-surgery, prior to initiation of chemotherapy, after completion of combination therapy, during anti-PD-1 maintenance therapy and at time of recurrence with the intention of identifying potential correlations with clinical outcomes.

Hypothesis: We hypothesize that analysis of the tumor microenvironment using IHC staining for PD-1 and PD-L1 may correlate with response to therapy. Furthermore, we hypothesize that peripheral blood monitoring of immune cell profiles may provide biomarkers that correlate with response to therapy. We hypothesize that tumor immune monitoring during this study will be able to be utilized for improvement of the rational design of future trials with better understanding of timing, dosing and scheduling of combination therapy.

3.4 Biomarker Studies:

(3) **Objective:** Collection of serial blood samples for analysis of cell free DNA (cfDNA) in ovarian cancer patients over a series of time points and explore the potential role of cfDNA as a tool for identifying serum biomarkers.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

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

4.1.1.1 PD-1/PD-L1 pathway plays a critical role in tumor immune evasion

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/ CD279) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regulatory cells and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic

tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.1.2 Pembrolizumab designed to directly block the interaction between PD-1 and its ligands PD-L1 and PD-L2.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

In the 1-month and 6- month toxicology study in Cynomolgus monkeys, pembrolizumab administered once a week and once every other week respectively, intravenously up to 200 mg/ kg resulted in no adverse treatment related effects. The clinical summary of results thus far as of 2014 for pembrolizumab monotherapy and combination therapy include a total of 6,294 subjects with both hematologic and solid tumors in a total of 18 phase I, II, III clinical trials sponsored by Merck.

Specifically, KEYNOTE-021 (NCT02039674) is a multicohort phase I/II trial of pembrolizumab (2mg/kg vs 10 mg/kg) plus platinum- doublet chemotherapy (carboplatin / paclitaxel or carboplatin/ pemetrexed) in advanced treatment naïve patients with non-small cell lung cancer. A total of 65 patient were enrolled for study. The overall incidence of adverse events was 95% (62 of 65 subjects). The most commonly reported AEs experienced in this population across all dose regimens were fatigue (49.2%), constipation and nausea (26.2% each), decreased appetite (23.1%), diarrhea (18.5%) and anemia and alopecia (15.4% each). The incidence of drug related AEs was 86.2% (56 of 65 subjects). The most commonly reported drug related AEs in this population were fatigue (35.4%), nausea, decreased appetite and alopecia (13.8% each), diarrhea (12.3%), and constipation and aspartate aminotransferase elevation (10.8% each). Grade 3-5 drug related AEs were reported 23.1% of subjects (15 of 65 subjects). The most common grade 3-5 drug related AEs in this population across all groups were aspartate aminotransferase elevation (6.2%) and anemia and alanine aminotransferase elevation (4.6% each). Adverse events resulting in discontinuation of study were reported in 3.1% (2 of 65 subjects). Interstitial lung disease, dermatitis allergic and drug eruption were the only AEs resulting in discontinuation and were reported 1 subject each (1.5%). A total of 8 subjects' experienced serious drug related AEs as follows: anemia, febrile

neutropenia, atrial fibrillation, colitis, pyrexia, hypersensitivity, alanine aminotransferase elevation, aspartate aminotransferase elevation, drug eruption, rash and urticarial. Preliminary efficacy results indicate no difference across all groups suggesting a flat dose-exposure relationship. The overall response rate observed for pembrolizumab in combination with chemotherapy was promising and warranted further examination; continuing phase II trials are underway in non-small cell lung cancer.

4.2 Rationale

4.2.1 Rationale for this Trial and Selected Subject Population

4.2.1.1 Epithelial Ovarian Cancer (EOC)

Epithelial ovarian cancer (EOC), inclusive of peritoneal and fallopian tube cancers, is one of the most common gynecologic malignancies and the fifth most common cause of cancer death in women. Approximately 22,000 cases of epithelial ovarian cancer are diagnosed annually in the United States. This results in nearly 15,000 deaths annually in the United States (http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-2013). Initial treatment for ovarian cancer is usually surgical cytoreduction followed by adjuvant platinum and taxane chemotherapy [1-4]. At the time of diagnosis over 75% of patients present with stage III or IV disease meaning that disease has spread into the peritoneal cavity or distally[5]. Despite several new developments and new chemotherapeutic regimens survival has improved only modestly over the last two decades. While overall 5-year survival has improved from 30% to 50%, 5-year survival remains only 25% for women with advanced stage disease.

4.2.1.2 Surgical Cytoreduction and Adjuvant Therapy

One of the most important prognostic factor for advanced epithelial ovarian cancer is the amount of residual tumor at the completion of initial surgical cytoreduction. Virtually all retrospective reports have shown an inverse correlation between the largest diameter of the residual tumor and survival [6-8]. Patients who undergo optimal cytoreduction (defined as no gross residual tumor after surgical cytoreduction) have been found to have the most favorable prognosis as compared to patients with any gross residual disease. The reported rates of optimal cytoreduction, however, vary widely in the literature and have been reported to range from 20-80%. A recent meta-analysis reported an average rate of optimal cytoreduction of only 42% [6]. The ability to achieve an optimal disease status is dependent on the skill of the operating surgeon, patient co- morbidities and individual tumor biology. Those patients who undergo aggressive cytoreductive procedures but do not achieve an optimal cytoreduction have demonstrated decreased overall survival placing them in a particularly poor prognostic group. In one review the median overall survival in patients with optimal versus suboptimal cytoreduction was 39 versus 17 months [8]. Defining optimal in this population is increasingly more difficult and most agree that any residual disease is a negative prognostic indicator.

All patients with advanced EOC will receive chemotherapy as well as surgery. Modern chemotherapy for EOC has incorporated many different methods of the administration of platinum based regimens. Intraperitoneal therapy with combination platinum and taxane agents has demonstrated improved progression free survival and overall survival but has not been widely

accepted due to its significant toxicity. This regimen is reserved for patient who have undergone optimal cytoreduction; patients who are not optimally cytoreduced are not candidates for this therapy. Conventional regimens are typically recommended in the setting of suboptimal cytoreduction and utilize intravenous carboplatin and paclitaxel combination therapy administered every 21 days (triweekly). Alternatively, carboplatin has been administered every 21 days or triweekly, while the paclitaxel is given weekly over the 21 day cycle (dose dense regimen). This dose dense regimen has been actively studied in EOC recently due the demonstrated benefit in breast cancer patients receiving weekly paclitaxel [9]. Weekly paclitaxel in combination with carboplatin every 3 weeks has yielded improved PFS in phase III studies comparing this regimen to conventional triweekly carboplatin and paclitaxel (median overall survival of 100 months versus 62 months) and has had a more manageable toxicity profile making it an attractive option for primary therapy [10]. Recent prospective data, however, indicates that the progression free survival between Q3w carboplatin and Qw paclitaxel versus Q3w paclitaxel is not significantly different [52]. Specifically, recent studies utilizing carboplatin with weekly paclitaxel in suboptimally cytoreduced (>1 cm residual disease) compared with conventional triweekly carboplatin and paclitaxel patients resulted in a favorable median PFS of 17.6 months versus 12.1 months [11]. Dose dense therapy has since been adopted as one of the standard of care options for advanced ovarian cancer National Comprehensive Cancer Network (NCCN) guidelines.

Given these limitations for suboptimally cytoreduced patients, it is clear that improved strategies for the delivery of cytotoxic therapy, novel strategies or novel combinations should be actively pursued for this population.

4.2.1.3 Rationale for Ovarian Cancer as a Target for Immune Therapy

Evidence is accumulating to support the significant role the immune system plays in all types of malignancies. Recent evidence has concluded that ovarian cancer is an immunogenic tumor similar to melanoma and a valid immunotherapy target [12, 13]. Over the past decade multiple studies have greatly increased our understanding of the immune responses in ovarian cancer patients. Studies have demonstrated that those patients with ovarian cancer whose tumors were noted to have greater CD3+ tumor infiltrating lymphocytes (TILs) experienced longer progression free and overall survival [14-16]. Several investigators have correlated immune escape mechanisms, such as increased CD4+CD25+FoxP3+T regulatory cells and programmed death 1 ligand, in ovarian cancer populations with a poor survival [14, 17-19]. In addition, several studies have found that higher ratios of CD8+ cells / CD4+CD25+FoxP3+ T regulatory cells to be favorable prognostically [20, 21]. Together these findings indicate that ovarian cancer is a valid target for immunotherapy.

4.2.1.4 Combining Chemotherapy and Immunotherapy

Increasing evidence indicates that several agents in the standard EOC chemotherapy, such as carboplatin and paclitaxel, initially thought to have immunosuppressive effects actually have important immunostimulatory effects. Hato et al[22] demonstrated that platinum based therapy augments the capacity of dendritic cells to induce antigen-specific T cell proliferation, induces down regulation of PD L-1 and PD L-2 and effectively decreases the immunosuppressive capacity of tumor cells via the STAT6 pathway. Paclitaxel has been found to be immunostimulatory with upregulation of the cytotoxic T-cell function [23] and decrease of T regulatory cell populations [24]. Specifically, dose dense chemotherapy's clinical advantage may in fact be linked to its potential

immune advantages over conventional therapy. In a study by Chang et al [25] dose dense combination therapy with weekly platinum and paclitaxel was utilized in an ovarian tumor model and was found to be less toxic to the immune system, reduced immunosuppression by the tumor microenvironment and triggered recruitment of macrophages and tumor-specific CD8+ T cell responses to tumors. These results were then validated in 14 patients with recurrent ovarian cancer. As a result of these findings, combining chemotherapy and immunotherapy, once thought to be incompatible, is now thought to be a rational therapeutic option.

The ideal window (dose and scheduling) for combining immunotherapy and chemotherapy is currently under investigation, however, preclinical studies by Diaz et al [24] have found that the combination of vaccine therapy when combined concomitantly with cytotoxic doses of carboplatin and paclitaxel in mice produced an enhanced anti-tumor effect compared with therapy with the vaccine alone. This lends support to the concept that the concomitant combination of immunomodulation with standard chemotherapy has potential to be an effective strategy. In addition, in a phase 2 study by Braly et al [26] evaluating the immune adjuvant properties of front-line carboplatin-paclitaxel with alternative schedules of intravenous oregovomab chemo-immunotherapy in advanced ovarian cancer, found that treatment emergent CA125-specific cellular immunity was measured more commonly with simultaneous (cycle day 1) administration of oregovomab therapy with chemotherapy versus one week delayed infusion of oregovomab after chemotherapy ($p=0.04$) and that additional clinical parameters favored this schedule. Timing of immunotherapy with chemotherapy is an active area of research.

Combination chemotherapy and immunotherapy strategies are emerging, and safety data is becoming available. The Merck-sponsored protocol P011 is a combination therapy trial in which pembrolizumab monotherapy was compared with pembrolizumab in combination with cisplatin/pemetrexed and carboplatin/paclitaxel. Adverse events were generally manageable and infrequently required discontinuation of pembrolizumab treatment. Thus, the feasibility of the combined strategy as well as the safety of the combination has been demonstrated.

4.2.1.5 Maintenance Therapy in Ovarian Cancer

The mechanism by which ovarian cancer evades chemotherapy is not fully understood. The concept of 'ovarian cancer repopulation' as reviewed by Telleria et al[27] elaborates on the phenomenon that a population of cancer cells may have an intrinsic ability to escape cytotoxic therapy and have the ability to repopulate into solid tumors. He emphasizes that the period of time in remission is an ideal opportunity to introduce consolidative maintenance therapy as a means of blocking tumor repopulation. Several clinical studies have looked closely at the addition of maintenance therapy for prolongation of tumor remission in ovarian cancer patients. The strongest studies to date have incorporated maintenance therapy with additional cycles of cytotoxic chemotherapy (paclitaxel) or antiangiogenic agents (bevacizumab). Both have demonstrated an effect on progression free survival but have yet to demonstrate an impact on overall survival. They are hampered as well by their prolongation of toxicity and expense, respectively [3, 28]. Despite this, the concept of maintenance therapy remains a rational strategy that requires further evaluation in ovarian cancer.

Our study therefore proposes a strategy to integrate immune therapy with the current standard chemotherapy for ovarian cancer via a phase II open label nonrandomized single arm study of

intravenous (IV) combination carboplatin /paclitaxel chemotherapy in suboptimally cytoreduced patients with stage III/IV epithelial ovarian cancer with concomitant IV administration of anti-PD-1 antibody Pembrolizumab (200 mg IV) day 1 of each 3 week cycle concomitantly with carboplatin every 21 days and paclitaxel administered weekly every 21 days followed by 12 cycles of IV Pembrolizumab maintenance monotherapy therapy (200 mg IV q 3 weeks). Our primary objectives will be to determine if this subset of ovarian cancer patients observes an improved progression free survival. In addition, we will assess the safety and overall survival from this regimen compared to historical controls. Our secondary objectives will include documentation of patient quality of life (QOL) at intervals throughout the study and evaluation of potential biomarkers with assessment of the tumor microenvironment at the time of diagnosis. We will also accumulate data on the immune cell subsets during the study to inform future designs of clinical trials employing immune therapy in combination with chemotherapy and/or maintenance therapy.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight-based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on

exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

4.2.3 Rationale for Endpoints

We have selected Progression Free Survival as defined by Response Evaluation Criteria in solid Tumors (RECIST) 1.1 criteria as the primary endpoint [29]. Response based endpoints are standard in phase II trials [30].

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary Efficacy Variables

The primary efficacy variable is progression free survival for suboptimally cytoreduced (patients having any measurable residual disease post-surgical debulking) Stage III/IV ovarian cancer with combination platinum based chemotherapy and anti-PD-1 therapy followed by maintenance anti-PD-1 therapy compared to historical controls [10].

Progression of disease or recurrence is defined as increasing clinical, radiological or histological evidence of disease as defined in 7.1.2.6. Patients with progression of disease based on clinical or histological basis must also have a CT scan performed for further confirmation. CT scan will be scheduled at specific intervals (Trial Flow Chart 6.0) but may also be performed at discretion of investigator if recurrent or progression of disease or symptoms warrant evaluation.

Progression free survival (PFS) will be defined as date of completion of primary therapy to the date of first clinical, biochemical, or radiological evidence of progression or death due to any cause. PFS will be censored at the last assessment of disease progression for living patients.

PFS is considered the best outcome for a phase II trial and the most informative [31].

4.2.3.1.2 Secondary Efficacy Variables

4.2.3.1.2.1 *Overall survival for suboptimally cytoreduced Stage III/IV ovarian cancer with combination platinum based chemotherapy and anti-PD-1 therapy followed by maintenance anti-PD-1 therapy compared to historical controls.*

4.2.3.1.2.2 *Fact-O: Quality of life on maintenance anti-PD-1 therapy as measured with QOL (FACT-O) surveys at intervals during therapy.*

The Functional Assessment of Cancer Therapy questionnaire for ovarian cancer (FACT-O) is a short questionnaire grouped by logical categories that can be completed by most patients without assistance within 5 minutes. The FACT-O allows patients to weight each category of questions based on the categories' perceived importance to the quality of the patients' lives. Internal consistency as measured by Cronbach's alpha is 0.92 and test retest reliability is .81[32].

4.2.3.2 Biomarker Research

4.2.3.2.1.1.1 *Tumor micro environment: The relationship of survival to the tumor microenvironment at the time of diagnosis for patients with suboptimally cytoreduced ovarian cancer using immunohistochemistry (IHC) staining for antibodies of PD-1 and PD-L1 in paraffin embedded tissue of tumor obtained at the time of their initial surgery.*

Pembrolizumab is an anti-PD-1 antibody that was FDA approved via the accelerated process for patients with ipilimumab-refractory melanoma. PD-L1 expression is a possible biomarker to identify patients for PD-1 directed therapy [33-36]. Several PD-L1 expression assays have been described [37-39]; studies addressing assay comparison, standardization, or validation are not yet published. PD-L1 expression is also unlikely to be the only candidate biomarker for predicting response to PD-1 directed therapy.

PD-L1 and PD-1 IHC will be performed on FFPE tissue samples using standard IHC procedures. Commercially available, IHC-validated PD-L1 clones have been identified. The PD-L1 monoclonal antibodies utilized in this study will be SP142, E1L3N. Several other validated PD-L1 monoclonal antibodies, e.g., E1J2J, 5H1 and 28.8 are not commercially available; if these clones become available then they will be used as well. The commercially available, IHC- validated PD-1 clone NAT will be used for analysis of PD-1 expression.

IHC will be optimized by adjusting heat induced epitope retrieval conditions (ie, low pH and high pH), PD-L1 and PD-1 titers, and the inclusion or exclusion of a signal-boosting linker. Specificity can be determined if necessary by pre-incubating the antibody with blocking peptides, which should compete with the tissue for the PD-L1 epitope binding site. Tumor-associated lymphocytes will be characterized using IHC for CD1, CD3, CD4, CD8, FoxP3, and CD19. Tonsil and placenta will serve as positive controls. Additional control tissues are non-small cell lung cancer (NSCLC),

cervical cancer, Hodgkin lymphoma, pancreatic adenocarcinoma (PDAC), prostate cancer, and skin squamous cell cancer (SCC).

IHC stained slides will be analyzed as follows: PD-L1 and PD-1 expression on tumor membranes will be measured by a pathologist. The percent of tumor cells that stain positive will be determined either manually or with an automated cell imaging system (DAKO ACIS III). Samples will be scored as either PD-L1 or PD-1 positive if PD-L1 or PD-1 is detected on $\geq$ 5% of tumor cells [33, 36-39]. Tumor-associated lymphocytes will be assessed for PD-L1 and PD-1 expression as well.

4.2.3.2.1.1 *The relationship of pembrolizumab treatment and patient survival with immune signatures from blood and serum samples.*

The clinical reality of immune checkpoint blockade as a cancer immunotherapy has prompted an unprecedented need to monitor patient immunity. This need has resulted in an international effort to develop peripheral biomarkers that cluster into immune profiles. As part of this initiative, we will determine the longitudinal progression of patient peripheral immune signatures when treated post-surgically with combination chemotherapy and pembrolizumab (C/P). We will thus have longitudinal intra-patient immune monitoring over the course of the study. An immune profile will be determined by combining peripheral immune cell subset and serum cytokine signatures pre and post C/P treatment. Blood and serum samples will be obtained following surgery, upon completion of the initial phase of C/P treatment (~18 weeks), at the midway time point of the maintenance phase of therapy and at completion of maintenance therapy. An additional blood and serum sample will be obtained at the time of disease relapse. It is our goal to identify a peripheral immune profile that reflects an immunogenic response to pembrolizumab immunotherapy and correlates with an increase in survival.

Immune Cell Subsets

As a measure of systemic immunity, the relative percentage of circulating immune cells will be assessed by multiparametric flow cytometry. Multiparametric flow cytometry will allow for identification of immune cell subsets by recording the simultaneous expression of biomarkers unique to that cell subset. Flow cytometry will be performed on a LSR II cytometer (BD Biosciences) located in the Clinical Immunology Research Laboratory, a CLIA certified lab that performs clinical flow cytometry at the Medical College of Wisconsin. We will use flow cytometry of antibody stained peripheral blood mononuclear cells (PBMCs) to evaluate the relative percentage of cell types including T, B, NK and myeloid cells. As an indirect indicator of T cell function, the expression of T cell inhibitory receptors, activation markers, as well as the presence of regulatory T cells will be determined. Correlating changes in immune cell subsets with pembrolizumab treatment and survival will facilitate the identification of a peripheral immune signature that correlates with increased anti-tumor immunity. The antibody panels designed to identify the percentage of immune cell subsets present in PBMCs are shown in **Table 4.2.**

Serum Cytokines

Serum cytokine concentration is readily accessible and an efficient means to assess peripheral immunity. Changes in serum cytokines have been reported in cancer patients. However, currently,

there are no defined cytokine signatures that are cancer specific or predictive of disease outcome. For this study, serum cytokines will be analyzed longitudinally before and after pembrolizumab therapy. Serum cytokines will be quantified using the human cytokine/chemokine 65-plex array (Eve Technologies). This array performs analysis of the following cyto/chemokines: CXCL1, CCL1, IFNalpha2, IFNgamma, IL-1alpha, IL-1beta, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-16, IL-17A, IL-18, IL-20, IL-21, IL-23, IL-28a, IL-33, IP-10, LIF, MCP-1, MCP-2, MCP-3, MCP-4, MDC, MIP-1alpha, MIP-1beta, MIP-1d, PDGF-AA, PDGF-AB/BB, RANTES, SDF-1 a+b, sCD40L, SCF, TARC, TGFalpha, TNFalpha, TNFbeta, TPO, TRAIL, TSLP, and VEGF. We envision that subsequent to pembrolizumab treatment changes in the cytokine signature combined with changes in the immune cell subset signature will define an immune profile that correlates with enhanced anti-tumor immunity and prolonged survival.

Table 4.2 Antibody Panels.

T, B, NK and myeloid cells	Immune suppressive myeloid cells	Checkpoint receptors T cells (1)	Checkpoint receptors T cells (2)	T regulatory cells	Activation markers T cells
CD11b	CD11b	CD223	CTLA-4	CD127	CD45RA
CD3	CD3	CD3	CD3	CD3	CD3
CD68	CD274	CD279	CD279	FoxP3	CD8
CD33	CD33	CD8	CD8	CD25	CD25
CD19	CD273	LAG 3	CD39	CD39	CD69
CD56	CD14	CD4	CD4	CD4	CD4

Clinical Immunology Research Laboratory.

The Clinical Immunology Research Laboratory (CIRL) is a Clinical Laboratory Improvement Amendments (CLIA) certified clinical laboratory specializing in immunodiagnostics. The CIRL currently offers over 30 flow cytometric based assays to evaluate the human immune system, and over 2000 samples are processed in the CIRL yearly. As a clinical reference lab, consistent, reproducible, and well-controlled results are not only essential but required by the Centers for Medicare and Medicaid Services, the agency that regulates all laboratories testing in the United States.

4.2.3.2.1.2 *We will collect serum samples for future exploration of cell free DNA in this population as a potential serum biomarker.*

Ovarian cancer is typically diagnosed in advanced stages due to its lack of effective screening and limited ability to diagnose the disease in its early stages. Genomic variations are frequently found in tumor tissue but determination via tissue is a very costly measure and does not allow for the potential benefits of early diagnosis in the setting of ovarian cancer. It is well known that tumor-released DNAs are detectable as cell free DNAs (cfDNAs) in bodily fluids [40-42]. Whole genome sequencing has revealed significant DNA copy number variations in tumor tissues as well as in cell free DNA plasma of cancer patients. The collection and analysis of cfDNA from circulating blood in patients with cancer diagnoses may provide a means of determining the genomic variations present in a patient without direct tumor biopsy. As a result, there has been a growing interest in trying to use tumor-derived cfDNA as a non-invasive biomarker to detect the presence of malignancy, follow treatment response, gauge prognosis, or monitor for recurrence [43, 44]. The genetic analysis of cfDNA in circulating bodily fluids is often referred to as "liquid biopsy" [45-47]. Unlike tissue biopsy, the liquid biopsy is able to capture whole landscape of genomic abnormalities derived from both primary and metastatic tumors, therefore effectively eliminates heterogeneity issue facing traditional biopsy. In the planned future study, we will take advantage of collected plasma from these patients in the trials. Dr. Liang Wang, Professor of Pathology, Microbiology and Molecular Genetics at Medical College of Wisconsin will analyze the cfDNAs collected from patient plasma samples for copy number variations and gene mutations using next generation sequencing technology on plasma samples at serial time points during the study. We will correlate the genomic and genetic variations discovered in cfDNA with patients' response to the treatment and clinical outcomes for advanced stage ovarian cancer. This study will facilitate the new biomarker discovery for monitoring treatment effect and disease progression.

5.0 STUDY DESIGN

5.1 Overview of the study

This is a multi-institutional Phase II single arm, open label, nonrandomized study of 30 patients with suboptimal epithelial ovary cancer where the combination of carboplatin/ paclitaxel/ pembrolizumab is followed by maintenance pembrolizumab.

5.1.1 Rationale for single arm

The potential pool of patients is limited and with the potential for improving patient outcome it is important to complete the study as early as possible. There is good recent data with historical controls.

5.2 Diagnosis/condition for Entry into the Trial

5.2.1 Subject Inclusion Criteria

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

- Have advanced stage III/ IV epithelial ovarian, fallopian tube or primary peritoneal cancer
- Be willing and able to provide written informed consent/assent for the trial.
- Be ≥ 18 years of age on day of signing informed consent.
- Suboptimal cytoreductive surgery defined as any residual disease noted per operative report and/ or have measurable/ macroscopic disease (defined as target and /or non-target lesions) based on RECIST 1.1.
- Be willing to provide tissue from a newly obtained excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.*
- Have a performance status of 0, 1 or 2 on the ECOG Performance Scale (see Appendix).
- Demonstrate adequate organ function as defined in Table 5.1
- All screening labs should be performed within 28 days of treatment initiation. Screening labs performed within 10 days of treatment initiation can be used for C1D1. If screening labs are used for C1D1, serum creatinine must be done within 5 days of C1D1. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- **Table 5.1 Adequate Organ Function Laboratory Values**

System	Laboratory Value
Endocrine	
Thyroid function testing (TSH)	0.350 – 5.500 ulU/mL
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR**	≤1.5 X upper limit of normal (ULN) **OR**

Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤ 5 X ULN for subjects with liver metastases**
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

5.2.1.1 Subject Exclusion Criteria

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

- Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Has a known history of active TB (Bacillus Tuberculosis)
- Hypersensitivity to pembrolizumab or any of its excipients.
- 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.
    - Note: Subjects with < Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Has a known additional malignancy within the last 3 years, or 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.

- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

- 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.

- Has an active infection requiring systemic therapy. (Patients with active urinary tract infections (UTI) at screening should be treated and a repeat urinalysis should be obtained prior to study treatment.)

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

- Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study. The investigator should consult the Study Chair.

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

- 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.

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

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

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

- Patients with borderline ovarian tumors, recurrent epithelial ovarian/ primary peritoneal cancer/fallopian tube cancer or non-epithelial ovarian cancer are not eligible.

- Has received a live vaccine within 30 days of planned start of study therapy.

  Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.3 Trial Treatments

The treatment to be used in this trial is outlined below in Table 5.2.

Table 5.2. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q21 days	IV infusion	Day 1 of each 3-week cycle followed by maintenance therapy*	Experimental
Carboplatin	AUC 6	Q21 days	IV infusion	Day 1 of each 3-week cycle	Standard
Paclitaxel	80 mg/m^2	Q7 days	IV infusion	Day 1, 8, 15 of each 3-week cycle	Standard
Paclitaxel	175mg/m^2	Q21 days	IV infusion	Day 1 of each 3-week cycle	Standard
Docetaxel	75mg/m^2	Q21days	IV Infusion	Day 1 of each 3-week cycle	Standard
*Maintenance single agent pembrolizumab will be continued day 1 of each 3-week cycle x 12 cycles after completion of combination pembrolizumab + standard chemotherapy. *If Paclitaxel is discontinued due to toxicity as defined in Section 5.3.1.2.1, upon initiation of docetaxel, the carboplatin dose should be reduced by one dose level per institutional standard.					

5.3.1 Dose Selection/Modification

5.3.1.1 Dose Selection

The rationale for selection of doses 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.

5.3.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related Grade 3-4 hematologic toxicities or Grade 3 non-hematologic toxicities and severe or life-threatening AEs until resolved to grade 0-1 or as per pembrolizumab guidelines and guidelines for carboplatin and paclitaxel. If drug related toxicity for pembrolizumab or carboplatin or paclitaxel is identified, treatment must be held until toxicity resolves to grade 0-1. See pembrolizumab specific guidelines and Section 5.3.1.2.1 for guidelines for carboplatin and paclitaxel. See Section 5.3.9.1.2 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. Treatment delays are to be kept to a minimum and every effort should be made to maintain the intended schedule. No treatment delays are permitted for other than documented toxicity. If delays of greater than three weeks occur, patients must be taken off study.

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

Table 5.3 Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

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

Table 5.3 Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Hematologic	3	Toxicity resolves to grade 0-1	Permanently discontinue if inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

5.3.1.2.1 Dose Modification Guidelines for Carboplatin, Paclitaxel and Docetaxel.

Hematologic Toxicity:

- Initial treatment modification will consist of cycle delay and/or up to 1 dose level reduction of either carboplatin or paclitaxel or both per anticipated tolerance as determined by treating physician discretion.
- Erythropoietin use is permitted based on standard clinical guidelines (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126481.htm). Erythropoietin should not be used in patients with underlying venous thromboembolic disease.
- Patients will not receive prophylactic growth factors (filgrastim, pegfilgrastim) unless they experience recurrent neutropenic complications after specified treatment modifications per treating physician discretion.
- Patients may NOT receive amifostine or other protective reagents.
- Treatment decisions will be based on the absolute neutrophil count (ANC) rather than total white cell count (WBC).
- Subsequent cycles of therapy will not begin until the ANC is > 1500 cells/mm3 and the platelet count is >100,000 cells/mm3 for patients on the Q3W therapy. For patients on dose-dense (weekly) paclitaxel, subsequent cycles of therapy will not begin until ANC is >1000 cells/mm3 and the platelet count is >75,000 cells/mm3. Therapy will be delayed for a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate counts within a 4-week delay may be removed from study per discussion with the study sponsor.

- The day 8 and day 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is at least 50,000/ mcl. If not given those doses are omitted and not made up. If after omission of a dose the subsequent labs again do not meet criteria and a second dose requires omission, then chemotherapy should be reduced by one dose level.

- For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia (ANC < 500) persisting > 7 days, reduce chemotherapy by one dose level (Table 5.4) on subsequent cycles.

- For subsequent occurrences of febrile neutropenia, and/or grade 4 neutropenia (ANC < 500) persisting > 7 days, chemotherapy may be reduced by second dose level and/ or growth factors may be initiated at the discretion of the treating provider.

- Patients with grade 3 thrombocytopenia (< 50,000 cells/mm3) at any time will have a one dose level reduction of carboplatin.

- If dose modified patients experience recurrent delays of > 2 weeks or develop febrile neutropenia during subsequent cycles, then G-CSF (Neupogen or Neulasta) should be added if the patient is not already receiving G-CSF.

- If patients on the Q3w pembrolizumab, carboplatin and Qw taxol regimen experience continued treatment delays due to treatment related toxicity then consideration to changing regimen to Q3w carboplatin/ paclitaxel (or docetaxel) with pembrolizumab should be discussed with the sponsor. Dosing of Q3w carboplatin/docetaxel with pembrolizumab will be per institutional standard.

Neuropathy:

Paclitaxel weekly (Qw) regimen.

Grade 2 or greater peripheral neuropathy requires reduction of one dose level of paclitaxel and delay in therapy for a maximum of 2 weeks until recovered to grade 1. If ≥ grade 2 neuropathy does not resolve to ≤ grade 1 within 2 weeks, discontinue weekly paclitaxel and initiate paclitaxel 135 mg/m2 q 3 weekly with carboplatin and pembrolizumab according to their next planned administration. Sponsor should be notified if patients require change of regimen. If ≥ grade 2 neuropathy does not resolve to a grade 1 or less within 2 weeks for a subject on the q 3 week paclitaxel at 135 mg/ m^2 regimen, discontinue paclitaxel and start subject on q 3 week docetaxel 75mg/m^2 (or per anticipated tolerance per treating physician) starting on day 1 of the next cycle. See dose modifications as noted in table 5.4.

Paclitaxel q 3 weekly (Q3w) regimen.

Grade 2 or greater peripheral neuropathy requires reduction of one dose level of paclitaxel and delay in therapy for a maximum of 2 weeks until recovered to grade 1. If ≥ grade 2 neuropathy does not resolve to ≤ grade 1 within 2 weeks, discontinue paclitaxel and start subject on q 3 weekly docetaxel 75mg/m^2 (or per anticipated tolerance per treating physician) starting on day 1 of the next cycle. See dose modifications as noted in table 5.4.

Docetaxel q 3 weekly (Q3w) regimen.

If while on docetaxel ≥ grade 3 peripheral neuropathy occurs, then delay docetaxel for a maximum of 3 weeks until recovery to ≤ grade 1. If peripheral neuropathy fails to recover to ≤ grade 1 within 3 weeks, contact study sponsor before discontinuation of docetaxel.
Hepatic Toxicity: Grade 3 (or greater) elevations in AST, ALT, alkaline phosphatase or bilirubin require reduction of one dose level for paclitaxel and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

Renal toxicity:

Grade ≥ 2 renal toxicity requires dose reduction of one dose level of carboplatin and delay in therapy until recovered to grade 1 for a maximum of 3 weeks. If delay greater than 3 weeks occurs, the Sponsor must be notified and patient will be removed from study. Serum creatinine should be drawn with each cycle per flow chart table 6.0 for calculation of creatinine clearance.

Alopecia: No dose modification will be made for alopecia.

Fatigue: No dose modification will be made for fatigue grade ≤ 2.

Gastrointestinal Toxicity: Bowel obstruction: Patients may continue with study treatment for grade 1 partial obstructions that do NOT require medical intervention.

≥ grade 2 GI toxicity requires dose reduction of one dose level of docetaxel.

Hypersensitivity Reactions: Hypersensitivity reactions should be managed per institutional standards. In the event of a hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel according to institutional guidelines (See table 5.4).

Management Guidelines for unrelated adverse events:

For unrelated adverse events, you can hold treatment week by week to evaluate for up to 3 weeks. If after 3 weeks, the adverse event is still unresolved, contact the study sponsor for either discontinuation from the study or continuation of treatment. If the treatment delays fall on days 8 or 15 of a treatment cycle, these days will be eliminated for that treatment cycle only.

Table 5.4. Chemotherapy Dosing Modifications

Study Drug	**Initial Dose Level**	**Dose Level -1**	**Dose Level -2**
Paclitaxel	80 mg/m^2	60 mg/m^2	40 mg/m^2
Paclitaxel	175mg/m^2	150mg/m^2	135mg/m^2
Carboplatin	AUC 6	AUC 5	AUC 4
Docetaxel*	75mg/m^2	60 mg/m^2	50 mg/m^2
*Upon initiation of docetaxel, carboplatin dose should be reduced by one dose level.			

5.3.2 Timing of Dose Administration

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

Patients may be treated up to 8 weeks from cytoreductive surgery but no sooner than 3 weeks from surgery.

All trial treatments will be administered on an outpatient basis.

5.3.2.1 Pembrolizumab

Administration

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion Day 1 every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Supplier

Pembrolizumab will be supplied by Merck.

Formulation

Two Drug Product (DP) dosage forms are available for pembrolizumab: a white to off-white lyophilized powder, 50 mg/vial, and a liquid, DP 100 mg/vial, both in Type I glass vials intended for single use only.

Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. Pembrolizumab is formulated with L-histidine as a buffering agent, polysorbate 80 as surfactant, sucrose as a stabilizer/tonicity modifier, and hydrocholoric acid (HCl) and /or sodium hydroxide (NaOH) for pH adjustment if necessary.

Pembrolizumab Solution for Infusion 100mg/vial is a liquid DP, and has the identical formulation as that of the reconstituted lyophilized vial.

Preparation

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Storage

Both drug product dosage forms are stored under refrigerated conditions (2°C - 8°C).
The product after reconstitution with sterile water for injection and the liquid drug product are a clear to opalescent solution which may contain proteinaceous and extraneous particulates. The reconstituted lyophilized product and the liquid product are intended for IV administration. The

reconstituted DP solution or the liquid DP can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted or liquid DP solution in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

5.3.2.2 Carboplatin

Administration

Carboplatin will be administered at an AUC of 6 over 30-60 minutes Day 1 every 3 weeks.

Every effort should be made to keep the schedule of chemotherapy administration to every 3 weeks, however, occasionally chemotherapy administration may need to be given off schedule due to logistical reasons.

Supplier
Carboplatin is commercially available

Formulation
Carboplatin is supplied as a sterile lypophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Preparation
Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial strength	Diluent volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for eight hours at room temperature, since no antibacterial preservative is contained in the formulation it is recommended that carboplatin solutions be discarded eight hours after dilution.

NOTE: aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Storage
Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

5.3.2.3 Paclitaxel

Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*.

Administration
Paclitaxel at a dose of 80 mg/ m^2 will be administered Day 1, Day 8, and Day 15. Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral Nitroglycerin. Nothing else other than 0.9% sodium chloride is to be infused through the line where paclitaxel is being administered.
*If the provider's choice is paclitaxel q 3 weekly, paclitaxel will be administered IV over 3 hours on day 1 of every 21 day cycle.

Supplier
Paclitaxel is commercially available.

Formulation
Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml, in 5 ml vials (30 mg/vial) or 17 ml vials (100 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% in dehydrated alcohol, USP, 50%. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. The contents of the vial must be diluted just prior to clinical use.

Preparation
Paclitaxel, at the appropriate dose, will be diluted in 500-1000 cc of 0.9% sodium chloride injection, USP or 5% dextrose injection, USP (D5W) (500 cc's is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexylphthalate (DHEP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Storage
The intact vials should be stored between 2-25ºC (36-77ºF).

Stability
Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

5.3.2.4 Docetaxel

Docetaxel is a microtubule inhibitor.

Administration
The final docetaxel dilution for infusion should be administered as a 1 hour intravenous infusion.

All patients should be pre-medicated with oral corticosteroids (such as dexamethasone 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions

Supplier
Docetaxel is commercially available.

Formulation
Docetaxel is supplied in a single dose vial as a sterile, non-pyrogenic, non-aqueous viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in water) vial. It is supplied in two vial formulations; 20mg/0.5ml or 80mg/2ml of docetaxel. Docetaxel is also supplied as a pre-diluted 10mg/ml concentration in 80mg and 20mg vials.

Preparation
Using the pre-diluted 10mg/ml formulation: Aseptically withdraw the required amount of docetaxel (10mg/ml) with a calibrated syringe and inject into a 250ml infusion bag of 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Thoroughly mix the infusion by manual rotation. Inspect the final product for particulate matter or discoloration prior to administration, if it is not clear or appears to have precipitation, the product should be discarded.

NOTE: Contact of docetaxel with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Storage
Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Stability
Docetaxel final dilution for infusion is stable for 4 hours (including the 1hour intravenous administration time) if stored at room temperature, between 2°C and 25°C (36°F and 77°F).

Adverse Effects: Consult the package insert for the most current and complete information.

5.3.2.5 Biometric Considerations

Actual body weight will be used for paclitaxel/docetaxel dose calculations and adjusted body weight will be used for carboplatin dose calculations. However, if the Actual Body weight is < Ideal Body weight, then use Actual Body weight to calculate the creatinine clearance.

- The patient's initial weight will be used to determine the dosing of all agents for the duration of the study. If a patient's weight changes by > 10% during the course of the study, the dose for all agents will be recalculated with the new weight per institutional standard.

Dose Calculation
The patient's height and weight will be determined at the screening visit. Weight should be obtained prior to treatment on day 1 of every treatment cycle. If the patient's weight changes by greater than 10% prior to the start of the cycle, then the drug doses will be recalculated.

- The dose of carboplatin will be calculated using the Calvert Formula using a glomerular filtration rate (GFR) from the modified Cockcroft-Gault formula.
  Carboplatin dose (mg) = target AUC x (GFR + 25)
- For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance. The creatinine clearance is calculated by the modified Cockcroft-Gault formula.
  CrCl = [((140 - age in years)) x (adjusted body weight in kg)) / (72 x serum creatinine in mg/dl))] x 0.85
- In patients with an abnormally low serum creatinine (less than or equal to 0.6 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.6 mg/dl.
- The maximum absolute dose of carboplatin (AUC 6) given to each patient will be limited to 900mg.

5.3.3 Sequence

- On cycle day 1, pembrolizumab should be administered first over 30 minutes followed by paclitaxel administration over 1-hour infusion followed by carboplatin as a 30-60 min minute infusion last. The regimen can be administered in an outpatient setting.
- On cycle Day 8 and 15 paclitaxel will be administered over 1 hour in an outpatient setting.
- During maintenance therapy cycles, single agent pembrolizumab will be administered over 30 minutes.

*Patients who experience a hypersensitivity reaction to paclitaxel or toxicity (see section 5.3.1.2.1) may be switched to docetaxel per investigator's discretion.

*Paclitaxel and Carboplatin reactions will be managed according to each individual institution's approved Standard of Care guidelines.

*Please discuss prevention of hypersensitivity reactions to Carboplatin in patients receiving more than 6 cycles of carboplatin, with the study sponsor.

Table 5.5 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

5.3.4 Paclitaxel Ancillary Medications

Dexamethasone (20 mg po or 12 mg IV or equivalent) administered 30 minutes prior to paclitaxel. Steroids administered for paclitaxel premedication are allowed per protocol with pembrolizumab administration.

- Diphenhydramine (25 mg IV) (or equivalent) 30 minutes prior to paclitaxel.
- Famotidine (or equivalent) (20 mg IV) 30 minutes prior to paclitaxel.
- An antiemetic regimen containing a 5HT-3 antagonist (ondansetron, granisetron, or palonosetron) is recommended.

***Docetaxel Pre-medications:** It is recommended that patients be pre-medicated with dexamethasone 8mg orally taken the night before, morning of and evening after each treatment.

5.3.5 Trial Blinding/Masking

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

5.3.6 Randomization or Treatment Allocation

This is a single arm open label trial.

5.3.7 Stratification

There is no stratification.

5.3.8 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.3.8.1 Acceptable Concomitant Medications

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

during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment (Medication received by the subject for surgery related to study indication may be excluded) and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.8.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- 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 chemotherapy premedications or to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.3.9 Rescue Medications & Supportive Care

5.3.9.1 Adverse Events and 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 in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which

might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.3 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document in section 5.3.9.1.2.

Table 5.5 Potential expected adverse reactions with pembrolizumab therapy.

System Organ Class	Adverse Event Term
- Endocrine disorders	- Adrenal insufficiency
- Endocrine disorders	- Hyperthyroidism
- Endocrine disorders	- Hypophysitis
- Endocrine disorders	- Hypopituitarism
- Endocrine disorders	- Hypothyroidism
- Endocrine disorders	- Secondary adrenal insufficiency
- Endocrine disorders	- Thyroid disorder
- Eye disorders	- Uveitis
- Gastrointestinal disorders	- Abdominal pain
- Gastrointestinal disorders	- Colitis
- Gastrointestinal disorders	- Diarrhea
- Gastrointestinal disorders	- Pancreatitis
- General disorders and administration site conditions	- Asthenia
- General disorders and administration site conditions	- Pyrexia
- Hepatobiliary disorders	- Autoimmune hepatitis
- Hepatobiliary disorders	- Hepatitis
- Injury, poisoning and procedural complications	- Infusion related reaction
- Metabolism and nutrition disorders	- Diabetic ketoacidosis
- Metabolism and nutrition disorders	- Hyponatremia
- Metabolism and nutrition disorders	- Type 1 diabetes mellitus
- Musculoskeletal and connective tissue disorders	- Arthralgia
- Musculoskeletal and connective tissue disorders	- Back pain
- Musculoskeletal and connective tissue disorders	- Myositis
- Nervous system disorders	- Guillain-Barré syndrome
- Renal and urinary disorders	- Nephritis
- Respiratory, thoracic and mediastinal disorders	- Cough
- Respiratory, thoracic and mediastinal disorders	- Pneumonitis
- Skin and subcutaneous tissue disorders	- Pruritus
- Skin and subcutaneous tissue disorders	- Rash
- Skin and subcutaneous tissue disorders	- Severe skin reaction
- Skin and subcutaneous tissue disorders	- Vitiligo

5.3.9.1.2 Events of Clinical Interest (ECI) Reporting and ECI Treatment Guidelines

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothyroidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, and nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information below. The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy. Further details around frequency, reporting, and management of immune-related adverse events (irAEs) are specifically described below. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are further described below.

Immune-related adverse reactions.

An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. The most commonly reported immune-related adverse events across the dose schedules are hypothyroidism (7.2%), pneumonitis (2.9%), hyperthyroidism (2.2%), colitis (1.3%) and skin
AEOSI (1.3% including all terms).

Table 5.6 Frequency of immune-related adverse reactions

	Pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2117				
Adverse Reaction	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Hypothyroidism	7.8	5.9	0.1	0	0
Hyperthyroidism	2.9	0.6	0.1	0	0
Pneumonitis	2.4	0.9	0.6	0.1	<0.1
Colitis	1.7	0.4	1.7	0.1	0
Hepatitis	0.8	0.1	0.5	0.1	0
Hypophysitis	0.7	0.2	0.3	<0.1	0
Nephritis	0.3	0.1	0.1	<0.1	0
Diabetes Mellitus	0.1	<0.1	<0	<0.1	0

Table 5.7: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.

General Instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
Diarrhea/Colitis	Grade 2 or 3	Withold	• Administer corticosteroids (initial dose 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e peritoneal signs andileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST/ALT elevation or Increased bilirubin	Grade 2	Withold	• Administer corticosteroids (initial dose of 0.5-1mg/kg prednisone or	• Monitor with liver function tests (consider weekly or more frequently until liver

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

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

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune hemolytic anemia
– Aplastic anemia
– Disseminated Intravascular Coagulation (DIC)
– Hemolytic Uremic Syndrome (HUS)
– Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
– Thrombotic Thrombocytopenic Purpura (TTP)
– Any Grade 4 anemia regardless of underlying mechanism
All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However, the AE should be reported regardless of etiology.

***Infusion Reactions**:*

Table 5.7 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs.	**Stop Infusion and monitor symptoms.** **Report as ECI** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

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

Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

– Clinical course of the event

– Course of treatment

– Evidence supporting recovery

– Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

5.3.10 Diet/Activity/Other Considerations

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

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

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

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

Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

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

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

5.3.11.1 Use in Nursing Women

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

5.3.12 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
  Note: For unconfirmed radiographic disease progression, please see Section 7.1.2.7.
  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.
- Unacceptable adverse experiences as described in Section 5.3
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed planned study protocol.
- Administrative reasons.

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

5.4 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and completed 12 cycles (36 weeks) of IV pembrolizumab maintenance therapy.

5.5 Subject Replacement Strategy. None

5.6 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles**								**Additional Cycles (per treating physician's discretion)**			**Maintenance Therapy** **Begins 3 weeks after completion of combination chemotherapy**		**Post-Treatment**		
Treatment Cycle/Title:	**Main Study Screening (Visit 1)**	**1**			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**12 Cycles** **(every 3 weeks = 1 cycle)**		**Safety Follow-up**	**Follow Up Visits [n]**	**Survival Follow-Up [o]**
Scheduling Window (Days):	-28		Day 8 [i]	Day 15[i]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	+ 3	± 7 days		30 days (± 7 days) post discontinue	Every 12 weeks (±14 days) post discontinue	Every 4-6 months
Administrative Procedures																	
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Demographics and Medical History	X	X			X	X	X	X	X	X	X	X					
Prior and Concomitant Medication Review	X	X			X	X	X	X	X	X	X	X	X				
Trial Treatment Administration		X			X	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status [k]															X	X	X
Survival Status [k]															X	X	X
Clinical Procedures/Assessments																	

Trial Period:	**Screening Phase**	**Treatment Cycles**								**Additional Cycles (per treating physician's discretion)**			**Maintenance Therapy** **Begins 3 weeks after completion of combination chemotherapy**	**Post-Treatment**		
Treatment Cycle/Title:	**Main Study Screening (Visit 1)**	**1**			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**12 Cycles (every 3 weeks = 1 cycle)**	**Safety Follow-up**	**Follow Up Visits [n]**	**Survival Follow-Up [o]**
Scheduling Window (Days):	-28		Day 8 [i]	Day 15[i]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	+ 3	± 7 days	30 days (± 7 days) post discontinue	Every 12 weeks (±14 days) post discontinue	Every 4-6 months
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X	X [p]			X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status		X [p]			X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																
Pregnancy Test – Urine or Serum β-HCG	X[a]															
PT/INR and PTT	X															
CBC with Differential	X	X [m]	X	X	X	X	X	X	X	X	X	X	X	X		
CA125	X	X [m]			X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X [m]			X	X	X	X	X	X	X	X	X	X		
Urinalysis	X															
T3, FT4 and TSH	X				X		X		X		X		X[b]	X		
Efficacy Measurements																

Trial Period:	**Screening Phase**	**Treatment Cycles**								**Additional Cycles (per treating physician's discretion)**			**Maintenance Therapy** **Begins 3 weeks after completion of combination chemotherapy**		**Post-Treatment**		
Treatment Cycle/Title:	**Main Study Screening (Visit 1)**	**1**			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**12 Cycles (every 3 weeks = 1 cycle)**		**Safety Follow-up**	**Follow Up Visits [n]**	**Survival Follow-Up [o]**
Scheduling Window (Days):	-28		Day 8 [i]	Day 15[i]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	+ 3	± 7 days		30 days (± 7 days) post discontinue	Every 12 weeks (±14 days) post discontinue	Every 4-6 months
Tumor Imaging[c]	X												X[d]				
Tumor Biopsies/Archival Tissue Collection																	
Archival or Newly Obtained Tissue Collection	X												X[e]				
Correlative Studies Blood Collection																	
Immune studies blood collection	X												X[f]		X [q]	X[j]	X[j]
Biomarker blood collection	X												X[f]		X [q]	X[j]	X[j]
Quality of Life Survey	X					X			X				X[g]		X	X[h]	

Key:

a: Obtain for women of childbearing potential.
b. Thyroid function tests to be obtained every 2nd cycle while on pembrolizumab

c: CT scan of abdomen/ pelvis with contrast (if contrast clinically feasible) to be performed. CT of the chest if clinically applicable.
d: CT chest/abdomen/ pelvis with contrast (if contrast clinically feasible) should be done at the completion of combination therapy (prior to start of maintenance therapy), at the end of maintenance therapy (prior to safety follow-up) and if clinically indicated.

*NOTE: If a patient has not attained a normalized CA-125 value and /or a patient has stable disease or partial response on CT imaging at the completion of 6 cycles of combination therapy, the patient may continue to receive combination therapy for up to 9 cycles (per treating physician's discretion). A CT scan should be obtained prior to the start of maintenance therapy.

e: If new tissue available from histologic confirmation of recurrent disease through tissue block.
f: Immune panel and biomarker blood will be collected after completion of combination therapy before onset of maintenance therapy (i.e. Prior to treatment maintenance Cycle 1), after 6 cycles of maintenance therapy and at the completion of maintenance therapy
g: Quality of life survey to be done Cycle 7 Day 1 of maintenance therapy and at the safety follow-up visit.
h: QOL survey will be obtained at one final point at approximately 6 months after completion of maintenance therapy (i.e. at follow-up visit 2).
i: Day 8 and Day 15 flow chart specifications apply to **all cycles with weekly paclitaxel.**
j: At every follow-up and Survival follow-up visit and at the time of recurrence or suspected recurrence.
k: Subjects should be followed for survival and post study anticancer therapy until new anticancer drug therapy begins.
l: Weight will only be collected on Day 1 of each Treatment Cycle. Both Height and Weight should be collected at screening.
m: Cycle 1 Day 1 safety labs do not need to be repeated if screening labs were done within 10 days of treatment initiation. Serum creatinine should be obtained no more than 5 days prior to the start of treatment.
n: Follow Up: Every 12 weeks (±14 days) post discontinuation for up to 24 months.
o: Survival Follow-Up: Every 4-6 months for up to 36 months. Note: Patients who do not progress during the survival follow-up will continue to be followed for overall survival via phone calls and/or chart until disease progression, death, withdrawal of consent or lost to follow-up.
p: Screening physical examinations and ECOG performance status do not need to be repeated if done within 10days of treatment initiation.
q: Immune studies blood collection and Biomarker blood collection should be collected at the safety follow-up visit if patient discontinues for any reason other than disease progression or recurrence.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Site Activation and Subject Enrollment

7.1.1.2.1 Once the IRB approval is received at the coordinating site (MCW), Sponsor Investigator will inform Merck and the participating site. Participating site must submit the most current protocol, informed consent forms and other documents as prepared and submitted by the MCW site to their respective IRB. Informed consent language may vary based on the requirements of the local IRB of each site. A site initiation visit (SIV) will be conducted via teleconference to train the study staff at both sites and to discuss important milestones. An initial in person visit may also be necessary for initial training.

7.1.1.2.2 Screening will be performed for potential study patients after they have consented to trial participation. If a patient is screened - regardless of whether or not they are registered to the study – their details should be entered into the MCW Oncore CTMS. The Participating Institution will receive Oncore CTMS training from the MCW Oncore CTMS Administrator. The Coordinating Site will conduct monthly conference calls to discuss any ongoing questions or concerns regarding the conduct of the study. Patients will receive a screening ID that will be used to identify the patient throughout the study. At this time patients will be considered registered on the study.

7.1.1.2.3 Documentation of both the informed consent process and that the process occurred prior to a subject's entry into this study is recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the investigator's study files at each participating institution.

7.1.1.2.4 Participating Sites will upload all de-identified source documents with patient study IDs confirming patient eligibility into Oncore CTMS. The coordinating center will review all documents and confirm eligibility.

7.1.1.2.5 **Enrollment.** Patients will be considered enrolled in the study once the coordinating site has confirmed that all screening eligibility criteria have been met.

7.1.1.3 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.

7.1.1.4 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.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.7 Assignment of Screening Number

Unique number will be generated at each site corresponding to site designation assignment and then numerically according to the order in which patient was screened.

7.1.1.8 Assignment of Randomization Number: None.

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

Assessment will be made prior to each cycle as noted in Trial Flow Chart Section 6.0.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

Each participating site will be responsible for adverse event assessing and reporting to the respective site IRBs. Each serious unexpected event must be reported to the Sponsor-Investigator within 24 hours as specified in the protocol. The Sponsor-investigator will further evaluate the event and report to regulatory agencies.

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs). The principle investigator may report any event considered as potentially immune related as an event of clinical interest regardless of the listed events of clinical interest listed in the ECI guidelines.

A member of the study staff from each site should complete the SAE eCRF within 24 hours of learning of the event and email (uyarIITMerck3475-250@mcw.edu) or fax (414-805-6622) the completed form signed by the site investigator to the Medical College of Wisconsin.

The initial SAE should be followed until resolution and updated in the SAE eCRF. Follow-up SAE information is sent to the same contacts listed above. Each site is responsible for reporting SAEs to their local Institutional Review Board per institutional guidelines.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs. Please refer to section 5.3.9.1 for information regarding identification and management of irAEs and ECIs.

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart (Section 6.0), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Weight will be collected on Day 1 of each Treatment Cycle. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Functional assessment of Cancer Therapy –Ovary Trial of Outcome Index (FACT-O TOI)

This 26 item summary score captures the FACT- General (FACT-G) QOL dimensions of Physical Well-Being (7 items), Functional Well-Being (7 items), and the Ovarian Cancer subscale (12 items). By combining these three subscales, we are assured of including the full range of physical aspects of QOL in advanced EOC [32].

7.1.2.7 Tumor Imaging and Assessment of Disease

Completion of combined carboplatin, paclitaxel and pembrolizumab therapy
Patients must have in the opinion of the investigator, clinical complete response or partial response and have no evidence of disease progression on the post-treatment scan or a rising CA 125 level following completion of this initial regimen to proceed to maintenance therapy.

Parameters of Response-RECIST 1.1 Criteria [29]
Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be 20 mm when measured by conventional techniques, including plain x-ray, CT, and MRI, or 10 mm when measured by spiral CT.

Baseline assessment
Baseline documentation of '*Target'* and '*Non-Target*' lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. *Target* lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *Non-Target* lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present" or "absent". All baseline evaluations of disease status should be performed as close as **possible to the start of treatment and never more than 4 weeks before the beginning of treatment**.

Best Response
Measurement of the longest dimension of each lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline. Reporting of these changes in an individual case should be in terms of the *best response* achieved by cases since entering the study.

Complete Response (CR) is disappearance of all *target* and *non-target* lesions and no evidence of new lesions documented by two disease assessments at least 4 weeks apart. Normalization of CA125, if elevated at baseline, is required for ovarian carcinoma studies.

Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non- target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.

Increasing disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions within 8 weeks of study entry. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.

Stable Disease is any condition not meeting the above criteria. Patients with a stable disease response or better (CR, PR) will be eligible to continue onto maintenance therapy with pembrolizumab.

Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease*.

Progression (measurable disease studies) is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry.
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry.
    - The appearance of one or more new lesions.

- Death due to disease without prior objective documentation of progression.
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided).

Recurrence (non-measurable disease studies) is defined as increasing clinical, radiological or histological evidence of disease since study entry.

7.1.2.7.1 Survival Times

Survival time is the observed length of life from entry into the study (first dose of therapy) to death or the date of last contact.

Progression-Free Survival (measurable disease studies) time is the period from study entry (first dose of therapy) until disease progression, death or date of last contact. PFS will be censored at the last assessment of disease progression for living patients.
Recurrence-Free Survival (non-measurable disease studies) time is the period from study entry (first dose of therapy) until disease recurrence, death or date of last contact.

Overall Survival (OS) time will be defined as observed length of life from entry into the protocol (first dose of therapy) to death, or for living patients, date of last contact (regardless of whether or not this contact is on a subsequent protocol). Patients who do not progress during the survival follow-up will continue to be followed for overall survival via phone calls and/or chart until disease progression, death, withdrawal of consent or lost to follow-up.
Progression-Free Interval (PFI) time will be defined as date from entry onto the protocol (first dose of therapy) to the date of clinical or radiologic evidence of progressive disease.

7.1.2.7.2 Subjective measurements

Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTC.

7.1.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling

Archival tissue will be utilized, and correlative blood sampling will be performed according to Section 4.2.3.2 and will be collected according to Trial Flow Chart Section 6.0.

7.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.1.

Table 7.1 Laboratory Tests

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

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

‡ If considered standard of care in your region.

Laboratory tests for screening should be done within 28days of treatment initiation. Screening laboratory tests done within 10 days of treatment initiation can be used for C1D1. Laboratory tests done within 10 days prior to entry into the Second Course Phase (maintenance phase) can be used for D1 of the maintenance phase. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations. None

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

7.1.4.2 Blinding/Unblinding. Not applicable.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period: Estimated period for screening and enrollment is 18 months.

7.1.5.2 Treatment Period: Treatment period is estimated to be 48 months.

7.1.5.3 Post-Treatment Visits: The initial post treatment visit will occur at 4 weeks ($\pm$ 7 days) post completion of all therapy and may coincide with Safety Follow-Up Visit detailed below.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur

within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be clinically assessed every 12 weeks (± 14 days) to monitor disease status. For the first 2 years the clinical assessment time point will occur every 12 weeks (± 14 days). After 2 years the clinical assessment time point will change to every 4-6 months. Every effort should be made to collect information regarding disease status until the start of a new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.4.1 Survival Follow-up

Progression of disease or recurrence is defined as increasing clinical, radiological or histological evidence of disease. Patients with progression of disease based on clinical or histological basis must also have a CT scan performed for further confirmation. CT scan may be performed at discretion of investigator if recurrent or progression of disease or symptoms warrant evaluation. Progression will not be defined as rising CA 125 alone.

Progression free survival (PFS) will be defined as of study entry (first dose of therapy) to the date of first clinical or radiological evidence of progression or death due to any cause. PFS will be censored at the last assessment of disease progression for living patients.

Overall survival (OS) will be defined as observed length of life from entry into the protocol (first dose of therapy) to death due to any cause, or for living patients, date of last contact or completion of study. Patients who do not progress during the survival follow-up will continue to be followed for overall survival via phone calls and/or chart until disease progression, death, withdrawal of consent or lost to follow-up.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart 6.1.

7.2 Assessing and Recording Adverse Events

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

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

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

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

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose > 20% of the recommended 200 mg dose for pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

Definition of overdose of carboplatin:

The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. Maximum carboplatin dose (mg) should not exceed target AUC (mg x min/mL) x 150 mL/min. In trials with AUC of 6 this would result in a maximum dose of 900 mg.

Definition of overdose for paclitaxel:

There is no established threshold identified as an overdose for paclitaxel.

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

7.2.3.1 Serious Adverse Events

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

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

Refer to Table 7.2 for additional details regarding each of the above criteria.

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Additional adverse events:

ECIs (both non-serious and serious adverse events) identified in Section 5.3.9.1 from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 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.

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

Table 7.2 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	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation	

	with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	

Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.4.1 Sponsor Responsibility for Reporting Adverse Events

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

Serious adverse events experienced after signing consent should be reported according to the institution's IRB and regulatory authorities as well as the Medical College of Wisconsin if the investigator suspects a causal relationship to study treatment.

7.2.5 Trial Monitoring/ Quality Assurance

7.2.5.1 Study Monitoring will be conducted by the CTSI's Clinical Trial office, which will be responsible for ongoing oversight, monitoring, source documentation confirmation, protocol compliance, adverse events, etc. The MCW Principal Investigator will have access to the study data for all of the patients entered onto this study. Data storage is carried out according to MCW Institutional Policy. The MCW Principal Investigator will oversee the conduct of the study.

7.2.5.2 Quality Assurance

•The study will be reviewed annually by MCW.

• 10% of subject files will be selected randomly for review (max 10 subjects at each monitoring timepoint).

• Consent/eligibility and objective based data will be reviewed for those files selected

• 1 file will be selected randomly for a comprehensive review at each monitoring time point.

After each QA review, a letter/report will be provided to the study staff and the DSMC. Necessary corrective action or training will be provided to the staff as needed throughout and following each QA review. Directed audits may be requested at any time by the CCCTO QA Staff, DSMC, Research Manager, study staff member, or administrative staff.

8.0 STATISTICAL CONSIDERATIONS

8.1 Planned Efficacy Evaluations

8.1.1 Primary Efficacy Variables

The primary efficacy variable is progression free survival for suboptimally cytoreduced Stage III/IV ovarian cancer with combination platinum based chemotherapy and anti-PD-1 therapy followed by maintenance anti-PD-1 therapy compared to historical controls.

Progression of disease or recurrence is defined as increasing clinical, radiological or histological evidence of disease as defined in 7.1.2.7. Patients with progression of disease

based on clinical or histological basis must also have a CT scan performed for further confirmation. CT scan may be performed at discretion of investigator if recurrent or progression of disease or symptoms warrant evaluation.

Time to progression free survival (PFS) will be defined as date of completion of primary therapy to the date of first clinical, biochemical, or radiological evidence of progression or death due to any cause or to data of last assessment. PFS will be censored at the last assessment of disease progression for living patients.

8.1.2 Secondary Efficacy Variables

- Overall survival for suboptimally cytoreduced Stage III/IV ovarian cancer with combination platinum based chemotherapy and anti-PD-1 therapy followed by maintenance anti-PD-1 therapy compared to historical controls.
- Quality of life on maintenance anti-PD-1 therapy as measured with QOL (FACT-O) surveys at intervals during therapy as noted in Trial Flow Chart (Section 6.0).

8.1.3 Biomarker variables

- The relationship of survival to the tumor microenvironment at the time of diagnosis for patients with suboptimally cytoreduced ovarian cancer using immunohistochemistry (IHC) staining for antibodies of PD-1 and PD-L1 in paraffin embedded tissue of tumor obtained at the time of their initial surgery
- The relationship of survival and serial immune profiles from blood samples obtained post-surgery, prior to initiation of chemotherapy and during anti-PD-1 maintenance therapy.

8.2 Planned populations for study

8.2.1 Safety population

The safety population will consist of all patients who have received at least one dose of study medication, whether withdrawn prematurely or not.

8.2.2 Analysis Population

8.2.2.1 The observed cases (OC)

This will include all patients must have undergone tumor assessment at baseline, received at least the first cycle of pembrolizumab in combination with first line platinum based chemotherapy, and must have had at least one post-dose tumor assessment.

This population (OC) will be the primary population for all analyses of primary and secondary efficacy variables of the observed cases (i.e. the actual assessments at each visit).

8.2.2.2 The completers population (CS)

This will include the subset of OC who completed all treatments.

8.2.2.3 Per-protocol population

The per-protocol population will be defined as the subset of the OC who completed all treatments and who did not have any major protocol violations (such as lack of compliance to the study medication schedule). The definitions of these protocol violations will be finalized before the database closure and will be documented in the analysis plan.

8.3 Statistical Analysis

8.3.1 Patient Demographics and Characteristics Data

To evaluate comparability between study patients and historical controls regarding patient characteristics at baseline, demographic and disease characteristics will be summarized using descriptive statistics. In addition, previous and concomitant diseases and medications will be summarized by treatment group to assess comparability between the groups.

All information will be listed by group (study or historical) and patient, and will be summarized. Frequencies will be presented for the categorical variables (e.g. race) and descriptive statistics will be presented for continuous variables (e.g. weight, age).

8.3.2 Efficacy Variables

8.3.2.1 Statistical Method

All efficacy data will be analyzed including CS patients. Per-protocol analysis will be done only if more than 10% of the CS patients do not qualify for the per-protocol analysis. For all efficacy variables, the baseline value will be defined as the last value taken prior to the start of the first study medication.

8.3.2.2 Continuous Variables

8.3.2.2.1 *Survival*

The efficacy parameters of survival will be analyzed using Kaplan Meier curves stratified by group where the groups are compared using a log rank sum test.

8.3.2.2.1.1 *Additional Analysis*

In addition to the above described primary analysis, the following analysis will be done.

1. As a supportive model a Cox proportional hazard model with clinical covariates such as interruption or not and age if the model is appropriate. If it is not appropriate, other models which do not assume proportionality will be investigated.

8.3.2.2.2 QOL

QOL will be analyzed using a mixed effects covariance pattern model to utilize all the data collected over time with consideration of the variance-covariance matrix of the repeated measures. This method allows a general unstructured variance-covariance matrix and allows patients to have incomplete data across scheduled time points. The method applied is also known as mixed-effects repeated measures analyses (MMRM).

The primary model will include independent variables of the fixed, categorical effects of assessment visit, along with the continuous effects of baseline and baseline-by-assessment interaction up to week 4. An unstructured variance-covariance structure will be used to model the within-patient errors and different variance-covariance structures will be tried for goodness-of-fit exploration. The 95% confidence intervals (CI) of change from baseline will be reported.

8.3.2.2.3 Tumor microenvironment at the time of diagnosis

We will examine the relationship of PFS the for patients with suboptimally cytoreduced ovarian cancer with immunohistochemistry (IHC) staining for antibodies of PD-1 and PD-L1 in paraffin embedded tissue of tumor obtained at the time of their initial surgery by stratifying by those with a "positive stain" in a Kaplan Meier analysis.

8.3.2.2.4 Serial immune profiles from blood samples

The relationship of survival and obtained post-surgery, prior to initiation of chemotherapy and during anti-PD-1 maintenance.

We will examine the trajectory of serum levels over time with plots. We will examine PFS using a generalized linear mixed model with survival as a repeated outcome and cytokine levels as a time varying covariates.

We will look for a "signature" of cytokine levels that predicts PFS of 18 months or better using principal component analysis, un-supervised (using a factor approach) and supervised clustering. Further we will examine changes in the signature over time.

8.3.3 Missing Data Handling

The dropout pattern will be plotted and summarized. To assess effects of dropouts, the dropout cohort analysis will be performed by summarizing the change of primary and secondary efficacy variables by using different dropout cohorts. Dropout cohorts will be formed by patients that had their last primary efficacy measurement in the same assessment interval Patients who drop out or removed from the study due to an adverse symptom profile will be reported as a safety outcome.

To allow for bias due to varying assessment times, symptomatic/non-radiologic events and missing data due to lack of follow-up, sensitivity analyses as per Bhattacharya[48] will be

performed. Briefly simulation studies with varying hypothetical progression times simulated by a uniform distribution within the assessment times will be used and also times backdated to the last progression free assessment. In another analysis we will restrict the definition of lack of PFS to only include those who have radiologic evidence. Finally we will make conservative assumptions for the treatment arm and not for the historical controls in a comparison.

8.3.4 Safety Data

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE) version 5.0. Any adverse event which changes the CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report worksheet. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.
The regimen would be considered unfeasible for further study if a definite drug related grade 3 or higher SAE occurs in at least 33% of patients. This study design reflects the desire to terminate accrual early if sufficient evidence accumulates to consider the regimen unfeasible. The total accrual will be 30 patients. The study will use a 2-group sequential design to assess feasibility of delivering the study regimen. Fifteen (15) patients will be entered into each stage of the trial, unless excessive toxicity is observed in a previous stage. The decision rules for whether or not to advance to the next stage of the study are summarized in the following table 8.1:

Table 8.1 Safety requirement

Stage	Cumulative accrual	Minimum cumulative number of events to stop and consider regimen unfeasible
1	15	5 in 15 patients
2	30	10 in 30 patients

In the case of a safety event suspending the study, a prompt cumulative examination of all data and circumstances of these events will be conducted by the Medical College of Wisconsin DSMC to determine whether the study should be resumed, whether the protocol will be revised, or whether the study will be discontinued permanently.

Each participating site's IRB will be notified of any event that triggers postponement of enrollment in this study. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant IRBs will be obtained prior to resuming the study at each participating institution.
Decisions regarding ongoing study participation of patients on study will be made on a case by case basis after discussion with the participating site's Principal Investigator and Study Principal Investigator.

8.4 *Determination of Sample Size*

The primary outcome is progression free survival. The primary comparison is the PFS of the treatment sample compared to controls. The comparison is a log rank sum test at an alpha of 0.05. It will only be feasible in a five year period to recruit 30 patients. Using the study by Katsumata [11] the median survival time was~18 months for a dose dense regime for those with ≥1cm remaining post-surgery. We plan to accrue patients over 18 months with a follow-up of at least 18 months. Realistically an increase of median PFS by 6 months would indicate efficacy but with a treatment sample of 30 and the control sample from Karsumata of 168, we would have at least 80% power to detect at least an increase from 18 months to 39 months, an optimistic outcome. We expect that the PFS is likely to be 24 months rather than 18 months and that would certainly be clinically significant and would consider this encouragement to pursue a larger study as this is a pilot study. The sample size calculation was done using PASS 11, with the sample size base on the work of Lakatos [49, 50]. It was assumed that the percentage of dropouts in each group was 1% and the rate of accrual was uniform.

8.5 Study Data Collection, Monitoring, and Record Retention

8.5.1 Data Management

This study will report clinical data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms (eCRFs). Key study personnel are trained on the use of OnCore™ and will comply with protocol specific instructions embedded within the OnCore™ forms. Patient demographics, patient specific study treatment calendars, adverse events, reporting of deaths, and other information required for annual reporting will be placed in OnCore™ and other research databases maintained by MCW IT.

8.5.1.1 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore™ based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the biostatistical team prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore™ at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until the end of required study participation.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 9.1.

Table 9.1. Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.2 Compliance with Financial Disclosure Requirements

All financial disclosure requirements will be complied with for this study.

10.3 Compliance with Law, Audit and Debarment

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (MCW CC DSMC). A summary of the MCW CC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.) Review all DSM reports.
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCW CC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

10.6 Data Management

The OnCore data management system will be utilized for this study.

11.0 APPENDICES

11.1 ECOG Performance Status

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

11.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

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

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

* As published in the European Journal of Cancer:

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

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

11.4 Translational Research Specimen Instructions

Required Specimen Code	Collection Time Point	Instructions	Shipping Specification
All patients			
FFPE Primary or Metastatic Tumor (T01) Block	Prior to all treatment.	Pathology report must accompany all specimens. Please see Laboratory Manual	MCW Department of OB/GYN *Department of Obstetrics & Gynecology* *FMCLB* *Medical College of Wisconsin* *9200 W Wisconsin Ave., Milwaukee, WI 53226*
Post Op Serum (SB01) 7-10 ml of blood drawn into red top tube	Prior to all treatment.	See Laboratory Manual	MCW Department of OB/GYN
Post Op Plasma (PB01) 7-10 ml blood drawn into purple top EDTA tube	Prior to all treatment.	See Laboratory Manual	MCW Department of OB/GYN
Post op Whole blood (WB01) 7-10 cc collected in sodium heparin tube dark green top tube	Prior to all treatment.	See Laboratory Manual	Clinical Immunodiagnostic & Research Laboratory (CIRL)
Serum (SB02)	After completion of combined therapy before maintenance.	See Laboratory Manual	MCW Department of OB/GYN
Plasma (PB02)			MCW Department of OB/GYN
Whole Blood (WB02)			CIRL
Serum (SB03)	After 6 cycles of maintenance therapy completed.	See Laboratory Manual	MCW Department of OB/GYN
Plasma (PB03)			MCW Department of OB/GYN
Whole Blood (WB03)			CIRL
Serum (SB04)	At completion of maintenance therapy.	See Laboratory Manual	MCW Department of OB/GYN
Plasma (PB04)			MCW Department of OB/GYN

Whole Blood (WB04)			CIRL
Serum (SB05)	Follow up Visit 1	See Laboratory Manual	MCW Department of OB/GYN
Plasma (PB05)			MCW Department of OB/GYN
Whole Blood (WB05)			CIRL
Serum (SB06)	Follow up Visit 2	See Instructions above	MCW Department of OB/GYN
Plasma (PB06)			MCW Department of OB/GYN
Whole Blood (WB06)			CIRL
Serum (SB07)	Follow –up Visit 3	See Instructions above	MCW Department of OB/GYN
Plasma (PB07)			MCW Department of OB/GYN
Whole Blood (WB07)			CIRL
Serum (SB08)	Follow-up Visit 4	See Instructions above	MCW Department of OB/GYN
Plasma (PB08)			MCW Department of OB/GYN
Whole Blood (WB08)			CIRL
Serum (SB9)	Follow-up Visit 5	See Instructions above	MCW Department of OB/GYN
Plasma (PB9)			MCW Department of OB/GYN
Whole Blood (WB9)			CIRL
Serum (SB10)	Follow-up Visit 6	See Instructions above	MCW Department of OB/GYN
Plasma (PB10)			MCW Department of OB/GYN
Whole Blood (WB10)			CIRL
Serum (SB11)	Follow-up Visit 7	See Instructions above	MCW Department of OB/GYN
Plasma (PB11)			MCW Department of OB/GYN
Whole Blood (WB11)			CIRL

Serum (SB12)	Follow-up Visit 8	See instructions above	MCW Department of OB/GYN
Plasma (PB12)			MCW Department of OB/GYN
Whole Blood (WB12)			CIRL
Serum (SB13)	At time of Disease Progression/Recurrence	See instructions above	MCW Department of OB/GYN
Plasma (PB13)			MCW Department of OB/GYN
Whole Blood (WB13)			CIRL

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