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Matched Paired Pharmacodynamics and Feasibility Study of Pembrolizumab in Combination with Chemotherapy in Frontline Ovarian Cancer

Sponsor: UT MD Anderson Cancer Center
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1.0 STUDY SUMMARY

Abbreviated Title	Pembrolizumab with Chemotherapy in Frontline Ovarian Cancer
Study Phase	II
Clinical Indication	Primary Ovarian, Peritoneal, or Fallopian Tube Cancer
Study Type	Feasibility Study
Type of control	NACT patient population
Route of administration	IV
Treatment Groups	Pembrolizumab + paclitaxel/carboplatin; Pembrolizumab maintenance
Number of Study subjects	30
Estimated duration of Study	36 months
Duration of Participation	14 months

2.0 OBJECTIVE(S) & HYPOTHESIS (ES)

2.1 Primary Objective(s) & Hypothesis (es)

(1) **Objective:** To evaluate progression-free survival of paclitaxel/carboplatin and pembrolizumab in patients with advanced stage, metastatic ovarian cancer undergoing NACT.

Hypothesis: The treatment program will be associated with prolonged PFS relative to contemporary controls treated with standard care chemotherapy

2.2 Secondary Objective(s) & Hypothesis (es)

(1) **Objectives**:

a. To describe the feasibility of combination therapy and maintenance pembrolizumab in this population

b. To evaluate the safety of combination and maintenance pembrolizumab

c. To report overall survival

2.3 Exploratory Objective

(1) **Objectives:**

i. To describe the sequential effects of chemotherapy on immune response and PD-1 expression and receptor occupancy

ii. To evaluate circulating lymphoid populations (subsets)

iii. To determine tissue PD-L1 expression and T-cell infiltration

3.0 BACKGROUND & RATIONALE

3.1 Background

Ovarian Cancer: Primary epithelial ovarian cancer is an orphan disease for which little substantive progress has been made over the last 30 years. Nevertheless prevalence is increasing (currently nearing 200,000 affected women), due to several intrinsic and extrinsic factors such as better and more aggressive surgical and supportive medical care, as well as, an increasing cache of active agents, used alone, in combination, and sequentially in these patients over a long duration of time. Median survival for the collective is approaching 5 years despite there being no measurable increase in cure rates.[1] **Ovarian Cancer Moonshot:** Both of these elements in care are the focus of the M. D. Anderson Ovarian Cancer Moonshot. This ambitious program, the goal of which is to reduce mortality in these diseases, combines high grade serous ovarian cancer with triple negative breast cancer due to high fidelity genomic homology and opportunity to share surgical and medical strategy to accomplish its mission.[2] As part of the ovarian cancer Flagship surgical project most patients with suspected primary ovarian cancer undergo a preoperative laparoscopic assessment to accomplish the following: diagnosis, metastatic disease burden score (modified Fagotti score), tissue acquisition.[3] Confirming a primary in the ovary, fallopian tube and peritoneum, the disease burden score is used to triage primary cytoreduction or use of neoadjuvant chemotherapy followed by interval cytoreduction. The tissue sampling (along with blood and urine) is integral to the program and is directed in nature. That is, all patients have tissue collection from the primary (ovary or fallopian tube), the omentum, and at least 2 metastatic peritoneal sites. Additional reservoirs in the pelvic peritoneum (in the absence of adnexa or adnexal disease) and intestinal mesentery may be taken. Triage to surgical approach is made based on the likelihood of leaving residual disease (non-R0 resection). Our laparoscopic triage is accomplished by scoring made by two independent and blinded surgeons; those patients scored <10 undergo primary cytoreduction (with up to a 2 week interval). Those with scores ≥10 undergo neoadjuvant chemotherapy (NACT, 3 cycles) followed by interval surgery followed by 3 cycles of chemotherapy (± maintenance therapy). Prior to April 1, 2018, patients with scores <8 underwent primary cytoreduction (with up to a 2 week interval), and patients with scores ≥8 underwent neoadjuvant chemotherapy (3 cycles) followed by interval surgery followed by 3 cycles of chemotherapy (± maintenance therapy).

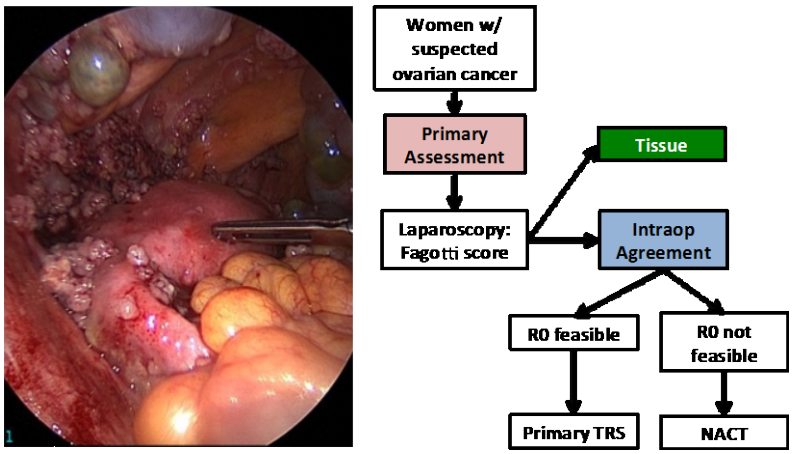


Figure 1 describes the general algorithm of laparoscopic triage in MS.

Our previous laparoscopic scoring algorithm used from April 1, 2013 until March 31, 2018 was based on initial laparoscopic scoring algorithm published by Fagotti et al. which identified a predictive index value (PIV) cutoff of 8 to avoid a suboptimal primary tumor reductive surgery and these patients being

dispositioned to neoadjuvant chemotherapy. This laparoscopic model has been revised based on additional data presented by the Fagotti group in 2015, which revealed when excluding those patients that had mesenteric retraction and miliary carcinomatosis on the small bowel by laparoscopic assessment, a predictive index value cutoff of 10 could be used to avoid a suboptimal primary tumor cytoreduction and these patients being dispositioned to neoadjuvant chemotherapy. Thus, at our institution we implemented a change to our laparoscopic scoring algorithm on April 1, 2018, in which patients scoring PIV <10 without mesenteric retraction or small bowel miliary carcinomatosis will be dispositioned to primary tumor reductive surgery, and patients scoring PIV ≥ 10 will receive neoadjuvant chemotherapy.

At surgery, repeated tissue, blood and urine are collected. All tissue is fresh frozen and stored, and annotated. This strategy has been accomplished in nearly 80 consecutive patients (~10/month) with compliance over 95%. Tissue pairing is available in nearly 50 patients treated with standard paclitaxel/carboplatin (predominately dose dense paclitaxel). Optimal (R0) resection has improved to greater than 90% in both surgical strata, which represents a substantial improvement over historical rates.

Novel Therapeutics: Often quoted survival data from clinical study experience suggests primary ovarian cancer is a chemo-sensitive disease with measurable responses occurring in up to 70% of patients with 50% of these being complete responses. However, pathological complete response after induction NACT is rare (4-6%) and recurrence after clinical CR (after 6-8 cycles) is observed in nearly 75% of patients at a median of 10 months (suboptimal) to 28 months (R0).[4-7] This highlights the need for better frontline therapy, since recurrent disease is seldom curable. Several novel biological agents have been, or are being, investigated in front-line phase III studies including bevacizumab (GOG-218, ICON-7), nintedanib (LUME-1), trebananib (TRINOVA-3), and veliparib. Of the three anti-angiogenesis studies completed, none has improved overall survival, and impact on PFS has been modest. It is largely appreciated that immune evasion and suppression is a central feature of the ovarian cancer microenvironment. Immune abrogation has also been linked to primary and adaptive chemoresistance and angiogenesis.[8] Thus, prolonged immunocompetence represents the most promising intervention to achieve lasting tumor suppression promoting survival. Despite its promise and significant attention over the last 35 years, little progress has been made with various immunotherapeutic approaches, including peptide-based vaccination, poxviral vectors, carbohydrate based vaccines, dendritic cell-based vaccination, lymphocyte-based vaccination, and most recently immunotherapy.[9] Governance of T-cell activation in the tumor microenvironment occurs via an intricate network of regulatory pathways. Negative regulatory pathways are controlled through CTLA4, B7-H1, and B7-H4 (among others), and positive regulatory pathways are controlled through CD28, B7 family members, tumor necrosis factor and tumor necrosis factor receptor family members (e.g., CD40), and inducible T-cell costimulator. Undesired autoimmunity against cancer in the microenvironment is promoted under conditions of chronic T-cell exposure to tumor-associated antigens. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1 function normally to counteract T-cell activation to self-antigens. However, they serve as one of several mechanisms leveraged by tumors to promote immune escape to normal surveillance. CTLA-4 and PD-1 signaling contribute to CD4+ CD25+ regulatory T cell (Treg) activation with decreases antigen presenting cell function and effector T-cell proliferation.[10] Further, PD-1 contributes to T-cell exhaustion in peripheral tissues. Clinical experience with agents targeting PD-1/PD-L1 and CTLA-4 are limited but responses to both classes of agents have been observed among ovarian cancer patients enrolled in phase I studies of solid tumors.

Strategy: To better inform primary therapy strategies with sequential and combined chemotherapy and Pembrolizumab. Safety of paclitaxel/carboplatin/Pembrolizumab has been shown in NSCLC.

3.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. 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 CD3□, PKC□ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. 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 [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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 [18; 19; 20; 13]. 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 [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

3.1.2 Preclinical and Clinical Study Data

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

3.2 Rationale

3.2.1 Rationale for the Study and Selected Subject Population

Often quoted survival data from clinical study experience suggests primary ovarian cancer is a chemo-sensitive disease with measurable responses occurring in up to 70% of patients with 50% of these being complete responses. However, pathological complete response after induction NACT is rare (4-6%) and recurrence after clinical CR (after 6-8 cycles) is observed in nearly 75% of patients at a median of 10 months (suboptimal) to 28 months (R0).[4-7] This highlights the need for better frontline therapy, since recurrent disease is seldom curable. Several novel biological agents have been, or are being, investigated in front-line phase III studies including bevacizumab (GOG-218, ICON-7), nintedanib (LUME-1), Trebananib (TRINOVA-3), and veliparib. Of the three anti-angiogenesis studies completed, none has improved overall survival, and impact on PFS has been modest. It is largely appreciated that immune evasion and suppression is a central feature of the ovarian cancer microenvironment. Immune abrogation has also been linked to primary and adaptive chemoresistance and angiogenesis.[8] Thus, prolonged immunocompetence represents the most promising intervention to achieve lasting tumor suppression promoting survival. Despite its promise and significant attention over the last 35 years, little progress has been made with various immunotherapeutic approaches, including peptide-based vaccination, poxviral vectors, carbohydrate based vaccines, dendritic cell-based vaccination, lymphocyte-based vaccination, and most recently immunotherapy.[9] Governance of T-cell activation in the tumor microenvironment occurs via an intricate network of regulatory pathways. Negative regulatory pathways are controlled through CTLA4, B7-H1, and B7-H4 (among others), and positive regulatory pathways are controlled through CD28, B7 family members, tumor necrosis factor and tumor necrosis factor receptor family members (e.g., CD40), and inducible T-cell costimulator. Undesired autoimmunity against cancer in the microenvironment is promoted under conditions of chronic T-cell exposure to tumor-associated antigens. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1 function normally to counteract T-cell activation to self-antigens. However, they serve as one of several mechanisms leveraged by tumors to promote immune escape to normal surveillance. CTLA-4 and PD-1 signaling contribute to CD4+ CD25+ regulatory T cell (Treg) activation with decreases antigen presenting cell function and effector T-cell proliferation.[10] Further, PD-1 contributes to T-cell exhaustion in peripheral tissues. Clinical experience with agents targeting PD-1/PD-L1 and CTLA-4 are limited but responses to both classes of agents have been observed among ovarian cancer patients enrolled in phase I studies of solid tumors. To better inform primary therapy strategies with sequential and combined chemotherapy and Pembrolizumab. Safety of paclitaxel/carboplatin/Pembrolizumab has been shown in NSCLC.

The selected subject population are women with advanced stage, metastatic ovarian cancer. Although our goal is to triage patients with suspected ovarian cancer by following the Ovarian Cancer Moon Shot algorithm described above, patients may still be considered eligible to participate on this trial even if they do not undergo a preoperative laparoscopic evaluation at MD Anderson as long as they have already received no more than four cycles of prior neoadjuvant chemotherapy or have a disposition to neoadjuvant chemotherapy with planned interval tumor reductive surgery. For instance, some patients may have undergone a laparoscopic evaluation at another hospital, they may be found to have extensive disease via other imaging, or they may have been diagnosed with primary ovarian cancer at another hospital. In each of these instances the preoperative laparoscopy would not be necessary. In cases where a preoperative

laparoscopy will not be performed, adequate tissue from a diagnostic or research biopsy will be required to meet the primary objective of this study.

3.2.2 Rationale for Dose Selection/Regimen/Modification

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects 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 (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and indication settings.

3.2.3 Rationale for Endpoints

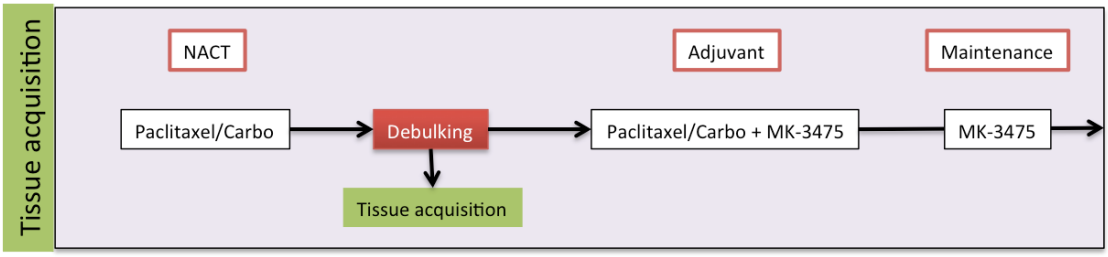
3.2.3.1 Efficacy Endpoints: The primary endpoint for this trial is progression-free survival with secondary endpoints of safety, tolerability, overall survival, and translational endpoints of immune response elements in blood and tumor tissue. The trial is powered for efficacy against a contemporarily evaluated cohort defined by primary inoperability (discussed above). Our provision of the estimated PFS in this population is based on historical data of NACT trials and our own patient population similarly defined. This is outlined in detail in the Statistical Analysis Plan, Section 10.0)

3.2.3.2 Biomarker Research: There is the potential that certain immune markers may predict response to immunotherapy agents including pembrolizumab. PD-L1 overexpression correlates with malignancy and immune regulation in ovarian cancer.[11] PD-L1 has been suggested to predict anti-PD-1 responses (Antonia S, 2013 abst). In a phase 1 trial of pembrolizumab, pretreatment tumor PD-L1 expression by immunohistochemistry (IHC) was a statistically significant predictor of response (Garon E, 2013 abst.). We will also examine these geographically paired tissues for cellular DNA, RNA, proteins and PD-1 expression, and tumor tissue expression of PD-L1 (+/- other markers i.e. IDO, LAG-3, TIM-3, ICOS, etc.). See Section 7.3 for details

4.0 STUDY DESIGN

This is a non-randomized, phase II study to assess progression-free survival of paclitaxel/carboplatin and Pembrolizumab for women with advanced stage, metastatic ovarian cancer undergoing neoadjuvant chemotherapy.

4.1 Study Diagram



4.2 Eligibility Criteria

Newly diagnosed advanced stage, ovarian, fallopian tube, or primary peritoneal cancer.

4.2.1 Inclusion Criteria

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

1. Signed, written Informed Consent

2. Women 18 years of age or older

3. Histology showing high-grade epithelial non-mucinous ovarian, primary peritoneal, or fallopian tube cancer

4. No more than 4 prior cycles of chemotherapy treatment for primary advanced (Stage III or IV) epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.

5. No prior treatment involving irradiation, hormonal therapy, immunotherapy, investigational therapy, and/or other concurrent agents or therapies for ovarian cancer.

6. A disposition to neoadjuvant chemotherapy with planned interval tumor reductive surgery after 4 complete cycles of treatment

7. Planned dose-dense chemotherapy with combination carboplatin and paclitaxel given intravenously

8. Have measurable disease based on RECIST 1.1.

    a. Measurable disease is defined at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each "target" lesion must be ≥20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥10 mm when measured by spiral CT.

    b. Patients with non-measurable but evaluable solid tumors may be deemed eligible contingent upon PI review.

9. Peripheral neuropathy Grade 0 or 1 by NCI CTCAE version 4.0

10. Tissue from an archival tissue sample or fresh tissue obtained from a core or excisional biopsy of a tumor lesion.

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

12. Adequate organ function as determined by the following laboratory values:

    a. ANC ≥1,500 /mcL
    b. Platelets ≥100,000 / mcL
    c. Hgb ≥9 g/dL or ≥5.6 mmol/L
    d. Creatinine Clearance ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
    e. Total Bilirubin ≤ 1.5 X ULN
        OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
    f. AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN
        OR ≤ 5 X ULN for subjects with liver metastases
    g. INR/PT ≤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)

h. PTT ≤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

13. Women of child-bearing potential (intact uterus) should have a negative urine or serum pregnancy within 72 hours prior to receiving the first 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. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. 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 (Reference Section 6.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

15. Pre-treatment fresh frozen tissue if available for research purposes. This tissue can be collected from preoperative laparoscopy, other diagnostic biopsy, or a research-specific biopsy.

16. Signed informed consent on protocol LAB02-188.

4.2.2 Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Histology showing mucinous or low grade epithelial carcinoma

3. History of another primary malignancy except for:

    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and or low potential risk for recurrence

    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

    - Adequately treated carcinoma in situ without evidence of disease e.g., cervical cancer in situ

    - Concomitant Stage 1A/B, Grade 1-2 endometrioid endometrial cancer as allowable contemporary tumor

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

5. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

6. Patients with ovarian cancer not medically fit for diagnostic laparoscopy prior to initiation of therapy

7. Patients with any evidence of severe or uncontrolled systemic disease (e.g. severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease], uncontrolled chronic renal disease [glomerulonephritis, nephritic syndrome, Fanconi Syndrome or Renal tubular acidosis]), or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension blood pressure $\geq$140/90, active bleeding diatheses or active infection.

8. 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 study treatment.

9. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., $\leq$ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

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

    - Note: Subjects with $\leq$ 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.

11. No active autoimmune disease that has required systemic treatment in past two 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.

12. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

13. Has an active infection requiring systemic therapy.

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

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

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

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

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

19. Has received a live vaccine within 30 days prior to the first dose of study treatment.

20. Patients with tuberculosis.

21. Patients with known hypersensitivity to pembrolizumab or any of its excipients

22. Patients receiving concurrent additional biologic therapy

23. History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin, paclitaxel not responsive to traditional desensitization procedures.

24. Patient that is not able to understand or to comply with the study instructions and requirements or has a history of non-compliance to the medical regimen.

4.3 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the Study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the MDACC if enrollment into the Study is inappropriate, the Study plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.7.

A subject must be discontinued from the Study 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 8.1.1

  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 8.1.1
- Unacceptable adverse experiences as described in Section 9.1.3
- 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 Study treatment or procedure requirements
- The subject is lost to follow-up
- Completed 23 total cycles of treatment with Pembrolizumab

  Note: 23 cycles of study medication is calculated from the date of first dose. Subjects who stop Pembrolizumab after 23 cycles may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 6.3.2.1.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7.1 Schedule of Assessments. 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 9.1.3. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.4 Clinical Criteria for Early Study Termination

Early Study 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.

5.0 INVESTIGATIONAL PRODUCTS

5.1 Pembrolizumab

Pembrolizumab will be supplied to the investigator as a powder to be reconstituted for infusion by Merck and Co pharmaceutical company.

5.1.1 Formulation/packaging/storage

Two Drug Product (DP) dosage forms are available for MK-3475: 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.

5.1.2 Doses and treatment regimen

Pembrolizumab will be administered in the out-patient setting with paclitaxel and carboplatin. Pembrolizumab infusion solution will be administered at a fixed dose of 200 mg IV infusion on day 1 of a cycle, every 21 days for 3 cycles (cycle length = 3 weeks) and during maintenance therapy.

Maintenance therapy will be administered until progression (approximately 10 months) with Pembrolizumab 200 mg IV on Day 1 every 21 days.

Pembrolizumab will be infused prior to paclitaxel and carboplatin.

5.1.3 Study drug preparation

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.

- MK-3475 Powder for Solution for Infusion, 50 mg/vial (manufactured using the partially formulated DS), is reconstituted with sterile water for injection prior to use. MK-3475 DP is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary).

- MK-3475 Solution for Infusion 100 mg/vial is a liquid DP (manufactured using the fully formulated DS), and has the identical formulation as that of the reconstituted lyophilized vial.

5.1.4 Dose administration

Study treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the Schedule of Assessments (Section 7.1). Study treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All Study treatments will be administered on an outpatient basis. Pembrolizumab will be administered first and as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.3.2.1). 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).

Appendix I contains specific instructions for Pembrolizumab dose reconstitution, preparation of the infusion fluid, and administration.

5.1.5 Monitoring of dose administration

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessments (see Section 7.1)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. The adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 2 in Section 6.3.2.1.

5.1.6 Accountability and dispensation

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF). See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage or to obtain a copy of the DARF.

5.1.7 Disposal of unused investigational study drug

Standard institutional pharmacy procedures will be followed.

5.2 Paclitaxel

Paclitaxel will be obtained from the institutional pharmacy through standard mechanisms.

5.2.1 Formulation/packaging/storage

Per manufacturer's guidelines.

5.2.2 Doses and treatment regimen

Subjects will be administered paclitaxel in line with normal clinical practice, with a dose and schedule of 80mg/m2 intravenously every week. It is expected that subjects will receive between 3 and 6 cycles of paclitaxel.

5.2.3 Product preparation

Per manufacturer's guidelines.

5.2.4 Dose administration

Paclitaxel will be dosed at 80 mg/m^2 infused according to institutional standards on day 1, 8 and 15 every 21 days followed by carboplatin.

Paclitaxel doses should be calculated prior to each course of therapy. Dosing of paclitaxel will be based on the subject's BSA in m2. Paclitaxel dose will be capped at a body surface area (BSA) of 2.0.the manufacturer's guidelines.

Details of dose preparation and administration is in section 6.4, Timing of Dose Administration, of the protocol.

5.2.5 Monitoring of dose administration

Per manufacturer's guidelines.

5.2.6 Disposal of unused product

Standard institutional pharmacy procedures will be followed.

5.3 Carboplatin

Carboplatin will be obtained from the institutional pharmacy through standard mechanisms.

5.3.1 Formulation/packaging/storage

Per manufacturer's guidelines.

5.3.2 Doses and treatment regimen

Subjects will be administered carboplatin in line with normal clinical practice, with a dose and schedule of AUC 6 given intravenously. It is expected that subjects will receive between 3 and 6 cycles of carboplatin.

5.3.3 Product preparation

Per manufacturer's guidelines.

5.3.4 Dose administration

Carboplatin will be administered based on the subject's creatinine clearance and target AUC of 6.

Carboplatin doses should be calculated prior to each course of therapy.

Details of dose preparation and administration is in section 6.4., Timing of Dose Administration, of the protocol.

5.3.5 Monitoring of dose administration

Per manufacturer's guidelines.

5.3.6 Disposal of unused product

Standard institutional pharmacy procedures will be followed.

6.0 TREATMENT PLAN

Patients will undergo tissue acquisition followed by neoadjuvant chemotherapy (NACT) during the induction phase. Initial clinical measurement of disease will include the following: physical exam, CA125 and CT imaging. All patients felt to be appropriate surgical candidates will proceed with diagnostic laparoscopy for peritoneal disease assessment with issuance of a score by 2 independent blinded surgeons. Those patients who score $\geq$ 8 will be offered NACT per protocol. All patients will undergo repeat clinical assessment after 3 cycles of NACT. As part of standard of care this includes physical exam, CA125 and CT imaging. It will not include laparoscopy as the scoring system is not validated for use after initiation of chemotherapy. Progression after NACT will be defined by RECIST criteria.

NACT consisting of paclitaxel/carboplatin will be administered at 80mg/ m^2 and AUC 6 respectively for a total of three cycles followed by interval debulking surgery. A cycle will consist of 21 days. The chemotherapy regimen may be administered in an outpatient setting. Patients will be assigned to receive treatment every 3 weeks as follows:

Day 1: Carboplatin at AUC=6 followed by Paclitaxel 80 mg/m^2

Day 8: Paclitaxel 80 mg/m^2

Day 15: Paclitaxel 80 mg/m^2

Day 22: Repeat the cycle- this is Day 1 of the next cycle

The carboplatin dose is calculated as follows (using a modified Calvert formula): Total dose (mg) =Target AUC x (Creatinine clearance + 25)

Paclitaxel dose will be capped at a body surface area (BSA) of 2.0

The experimental treatment to be used in this study is outlined below in Table 1 and will be administered in combination with carboplatin and paclitaxel following interval cytoreductive surgery.

TABLE 1 STUDY TREATMENT

REGIMEN DESCRIPTION					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pembrolizumab*		200 mg	IV	Day 1 q 21 days	

Carboplatin	1. Pre-medicate with Zofran 8 mg in 50cc NS IVPB 30 min. prior to Carboplatin infusion. 2. Needles or IV sets containing aluminum that may contact the drug must not be used.	AUC 6 reconstituted in 250cc.	IV short infusion after completion of Paclitaxel through separate IV line	Day 1 q 21 days	3 weeks (21 days)
Paclitaxel	Pre-medicate with Dexamethasone, Diphenhydramine and Famotidine 30 minutes prior to Paclitaxel.	80 mg/m^2 in 500 cc in D5W	IV according to institutional standards **before** Carboplatin	Day 1, 8 and 15 q 21 days	
*Pembrolizumab will be administered prior to paclitaxel and carboplatin. During this phase there will be 3 infusions before re-imaging at completion The Pembrolizumab dosing interval may be increased due to toxicity as described in Section 6.3.2.1.					

Maintenance therapy will be administered for up to 20 cycles or until progression with Pembrolizumab 200 mg IV D1 q 21 days.

Study treatment should begin as close as possible to the date on which treatment is allocated/assigned.

6.1 Study description

This is a non-randomized, phase II study to assess progression-free survival of paclitaxel/carboplatin and Pembrolizumab for women with advanced stage, metastatic ovarian cancer undergoing neoadjuvant chemotherapy (NACT).

6.2 Subject recruitment and enrollment

Patients will be recruited from the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center. All new patients with the potential diagnosis of advanced stage high grade serous ovarian, primary peritoneal, or fallopian tube cancers will be screened by the designated research nurse and/or study investigators for eligibility. Upon referral, they will undergo assessment to determine if they are a surgical candidate by their primary physician. Potential surgical candidates will be approached for study participation and informed consent about participating on this trial.

6.2.1 Subjects who qualify for preoperative laparoscopic assessment

Laparoscopic surgery is part of standard of care practices. At our center, most patients presenting with presumed advanced-stage high-grade serous ovarian, fallopian tube, or primary peritoneal cancer are considered for laparoscopic tumor evaluation and sample collection prior to a primary tumor reductive surgery. A validated scoring system is utilized to determine ability to resect to no gross residual disease (R0) (Fagotti et al, 2006). Patients that are scored as < 10 proceed to a primary tumor reductive surgery at a later date. Patients that are scored as ≥ 10 will receive neoadjuvant chemotherapy with subsequent interval tumor reductive surgery. As part of our standard practice, tissue is obtained at the time of laparoscopy from 4 sites for diagnosis (described below) and tumor banking for research. Potential subjects that are to undergo neoadjuvant chemotherapy based on Fagotti score ≥ 10 will then be informed further about this study, and informed consent documents will be reviewed and signed. Patients may elect to leave the study at any time. Upon confirmed eligibility, subjects will proceed to treatment as described below. Patients that are to undergo upfront tumor reductive surgery based on Fagotti score will not proceed on this trial.

6.2.2 Subjects who do not undergo preoperative laparoscopic assessment

In addition to patients described in the section above, others will not qualify for the preoperative laparoscopy but can still participate on this trial. Patients with suspected but un-diagnosed disease with evidence of not being resectable via scans (e.g. visible lung or abdominal metastases) or who elect not to receive a laparoscopy can be enrolled. Fresh tissue from their standard-of-care diagnostic biopsy will be used for protocol-specific analyses. Additionally, patients who have a tissue histologic diagnosis may still be eligible; however, these subjects may require a biopsy to provide adequate tissue for the primary endpoint of this protocol.

6.2.3 Subjects who have had previous NACT treatment

Neoadjuvant chemotherapy treatment with carboplatin and paclitaxel is part of standard of care practices. At our center, most patients presenting with presumed advanced-stage high-grade serous ovarian, fallopian tube, or primary peritoneal cancer are considered for carboplatin and paclitaxel in the neoadjuvant setting. Patients that have had no more than four previous induction cycles of carboplatin and paclitaxel as standard of care treatment and have fresh frozen tissue will be considered for this trial. Patients must sign consent and enroll on study at or prior to the tumor reduction surgery pre-operative visit. Patients who have had previous NACT treatment, must have available fresh tissue from their standard-of-care diagnostic biopsy to be used for protocol-specific analysis

6.2.4 Subjects who have had interval debulking surgery.

Patients who have undergone interval debulking surgery will be considered for this trial. Patients must sign consent and enroll on study at or prior to treatment with adjuvant therapy to include carboplatin and paclitaxel plus investigational agent, pembrolizumab. Patients may participate provided fresh tissue is available from the interval debulking surgery and have not received post-surgical chemotherapy.

6.3 Dose Selection/Modification

6.3.1 Dose Selection

Pembrolizumab infusion solution will be administered at a fixed dose of 200 mg IV on Day 1 q 21 days. Details on the dose preparation and administration are provided in the Study Drug Preparation and

Administration document located in Appendix I. Paclitaxel will be administered based on the subject's BSA in m^2 according to the manufacturer's guidelines. Carboplatin will be administered based on the subject's creatinine clearance and target AUC of 6. Details of dose preparation and administration will be as per manufacturer's guidelines. Carboplatin and paclitaxel will be administered according to department guidelines.

6.3.2 Dose Modification

6.3.2.1 Dose Modification of Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. The adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 2 below. See Section 9.1.3.2 and Events of Clinical Interest Guidance Document for supportive care guidelines, including the use of corticosteroids.

TABLE 2: DOSE MODIFICATION GUIDELINES FOR DRUG-RELATED ADVERSE EVENTS.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
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	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	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.
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.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

Dosing interruptions of pembrolizumab are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

In case toxicity does not resolve to Grade 0-1 within 3 weeks after last infusion, Study treatment should be discontinued after consultation with the MDACC. With investigator and MDACC agreement, subjects with

a laboratory adverse event still at Grade 2 after 3 weeks may continue treatment in the Study only if asymptomatic and controlled. For information on the management of adverse events, see Section 6.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of Pembrolizumab should be discontinued from study treatment.

Under certain conditions, a dose interruption of carboplatin or paclitaxel may be required. Should the dose interruption last for >21 days, the patient should be discontinued from study treatment. Further, if a patient does not tolerate the lowest possible dose, treatment with Pembrolizumab must be discontinued. Treatment modifications regarding chemotherapy will be employed in a sequential manner using cycle delay and dose reduction. Patients who experience grade 4 thrombocytopenia (<25,000 platelets/mcl) or bleeding associated with grade 3 thrombocytopenia (25,000 to <50,000/mcl), will have a dose reduction of carboplatin one level, without change in paclitaxel dosage. Study treatment modification that results in interruption of study treatment for more than 21 days will require premature study treatment discontinuation.

TABLE 3: CRITERIA FOR TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITIES

Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications & Management of Toxicities**
NONE	
No toxicity	**Maintain dose level**
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	On Day 1 of each cycle: Hold all treatment if ANC < 1.0 x 10^9/L On Days 8 & 15 of each cycle: Hold treatment (paclitaxel only) if ANC < 0.5 x 10^9/L First occurrence: Hold all treatment (chemotherapy and Pembrolizumab) until ANC ≥ 1.0 x 10^9/L then (may give G-CSF): • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level (all treatment) Second occurrence: Hold all treatment (may give G-CSF) until ANC,≥ 1.0 x 10^9/L ,then ↓ 1 dose level (all treatment)
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C) or Grade 3/4 neutropenia with documented infection	First occurrence: Hold all treatment until resolved to ≤ Grade 2 (may give G-CSF):, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level (all treatment) Second occurrence: Hold all treatment until resolved to ≤ Grade 2 (may give G-CSF), then ↓ 1 dose level (all treatment) or discontinue patient from study treatment at the investigator's discretion
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level unless Day 1 of each cycle: Hold all treatment if PLT < 100 x 10^9/L On all other study days; maintain dose level.

Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications & Management of Toxicities**
Grade 3 (PLT < 50-25 x 10^9/L)	On days 8 & 15 of each cycle: Hold treatment (paclitaxel only) if PLT < 50 x 10^9/L First occurrence: Hold all treatment until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level (all treatment) Second occurrence: Hold all treatment until resolved to ≤ Grade 1, then ↓ 1 dose level (all treatment)
Grade 4 (PLT < 25 x 10^9/L)	First occurrence: Hold all treatment until resolved to ≤ Grade 1, then ↓ 1 dose level (all treatment) Second occurrence: Hold all treatment until resolved to ≤ Grade 1, then ↓ 1 dose level (all treatment) or discontinue patient from study treatment at the investigator's discretion
HEPATIC	
Bilirubin** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN), with ALT or AST ≤ 3.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level (all treatment)
Grade 3 (> 3.0 - 10.0 x ULN), with ALT or AST ≤ 3.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level (all treatment) • If resolved in > 7 days discontinue patient from study treatment** Continue to monitor LFTs* every other week or more frequently if clinically indicated until the end of treatment with study medication.
Grade 4 (> 10.0 x ULN)	Hold all treatment and discontinue patient from Pembrolizumab therapy**

Worst toxicity (CTCAE Grade)**	Recommended Dose Modifications & Management of Toxicities
AST or ALT**	
Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN) if not increased from baseline and without bilirubin elevation to > 2.0 x ULN	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN) if increased from baseline and without bilirubin elevation to > 2.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ grade 1, then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level (all treatment)
Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ Grade 1 (or ≤ Grade 2 in case of liver metastasis), then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level (all treatment) Continue to monitor LFTs* every other week or more frequently if clinically indicated until the end of treatment with study medication.
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Hold all treatment until resolved to ≤ grade 1, then ↓ 1 dose level (all treatment)

Worst toxicity (CTCAE Grade)**	Recommended Dose Modifications & Management of Toxicities
Drug induced liver injury (Hy's Law)	
Patients with AST/ALT > 3 x ULN and total bilirubin > 2 x ULN with no evidence of obstruction (such as elevated ALP, malignancy, impaired glucuronidation (Gilbert syndrome) or pharmacologic factors), with no other explanation (e.g. viral, alcoholic or autoimmune hepatitis, hepatobiliary disorders, cardiovascular causes, concomitant medications) may have drug-induced liver injury. In such cases, • discontinue** the patient from Pembrolizumab (remove from study but may continue chemotherapy at discretion of study chair) and report as SAE. In any case, • monitor patient, including LFTs*, weekly or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization.	

* LFTs include: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), AP (fractionated if AP is grade 2 or higher) and GGT). For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only. ** Patients who discontinue study treatment should be monitored weekly, including LFTs or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Hold all treatment until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ 1 dose level (all treatment)
Grade 4	Hold all treatment and discontinue patient from Pembrolizumab (may continue chemotherapy at discretion of study chair).
Peripheral neuropathy	
Grade 1 or 2	Maintain dose level
Grade 3	Hold all treatment until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ 1 dose level (paclitaxel only)
Grade 4	Hold all treatment and discontinue patient from Pembrolizumab (may continue chemotherapy at discretion of study chair).
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.	

6.3.2.2 Dose Modification of Paclitaxel

6.3.2.2.1 Docetaxel (Taxotere) Substitution

Chemotherapy induced neuropathy is a known hematologic toxicity associated with paclitaxel. Studies that compared docetaxel-carboplatin versus paclitaxel-carboplatin as first line chemotherapy for ovarian cancer indicated docetaxel-carboplatin appears to be similar in treatment response and progression-free survival to paclitaxel-carboplatin. For the purposes of this trial, docetaxel may be substituted according to standard of care practices for patients with a contraindication to IV paclitaxel.

All patients should be pre-medicated with oral corticosteroids 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. Please refer to Table 3 in section 6.3.2.1 for guidelines on

treatment modifications and management of toxicities. Refer to paclitaxel language for guidance with docetaxel substitution.

If treatment is delayed more than 21 days for reasons of toxicity, then protocol-directed therapy is ended.

6.4 Timing of Dose Administration

Study treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Assessments (Section 7.1). Study treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All Study treatments will be administered on an outpatient basis.

Post-operative adjuvant therapy will commence once the patient's treating physician deems the patient's medical condition appropriate for adjuvant therapy. Therapy will start no sooner than 3 weeks postoperatively and no longer than 6 weeks postoperatively.

6.4.1 Dosing of Pembrolizumab

Pembrolizumab will be administered first and as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.3.2.1). 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).

Appendix I contains specific instructions for Pembrolizumab dose reconstitution, preparation of the infusion fluid, and administration.

6.4.2 Dosing of Paclitaxel

Paclitaxel will be dosed at 80 mg/m^2 infused according to institutional standards on day 1, 8 and 15 every 21 days followed by carboplatin for 3 cycles.

Paclitaxel dose will be capped at a body surface are (BSA) of 2.0.

Preparative regimen for paclitaxel: for all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or p.o.), anti-histamine H1 (such as diphenhydramine) or anti-histamine H2 (such as cimetidine, rantidine, or famotidine).

Recommendations for premedication are for dexamethasome 20 mg IV, diphenhydramine 50 mg IV and famotidine 20 mg IV 30 minutes prior to administration of paclitaxel.

Suggested method of chemotherapy administration: paclitaxel (infusion according to institutional standards) plus carboplatin (1 hour infusion): Premedications dexamethasone 20 mg IV, diphenhydramine 50 mg IV and famotidine 20 mg IV 30 minutes prior to administration. Paclitaxel administered (if ondansetron 8 mg IV needs to be given during paclitaxel infusion, it should be 30 minutes prior to carboplatin infusion) followed by carboplatin 1 hour infusion. The regimen can be administered in an outpatient setting.

The cycle length is three weeks (21 days). Treatment with protocol therapy will continue until one or more of the criteria listed in the discontinuation section are met.

6.4.3 Dosing of Carboplatin

Carboplatin will be dosed on AUC of 6 on Day 1 every 21 days following administration of paclitaxel.

The dose will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated calculated creatinine clearance to present the glomerular filtration rate (GFR).

Preparative regimen for carboplatin: An antiemetic regimen is recommended. The antiemetic regimen used should be based on peer-reviewed consensus guidelines. Suggested regimen is ondansetron 8 mg IV given 30 minutes prior to administration of carboplatin.

Carboplatin solutions will be infused IV over 60 minutes on Day 1 of each cycle. Dosing of carboplatin will be based on the Calvert formula: carboplatin dose (mg) = (Target AUC) x (GFR + 25). For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance (calculated by the method of Cockcroft and Gault, 1976). Maximum GFR is not to exceed 125 ml/minute.

Creatinine clearance (CrCl) from IDMS reported serum creatinine (using current [actual] weight):

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{ABW}^*) \times (0.85) \text{ [female]}}{(72 \times \text{serum creatinine})}$$

Where: CrCl = estimated creatinine clearance in ml/min

Age = patient's age in years

SCr = IDMS serum creatinine in mg/dL

In patients with an abnormally low serum creatinine ($\leq$ 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 0.7 mg/dL.

6.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

6.5.1 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 Study 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 Study treatment and 30 days after the last dose of Study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of Study treatment should be recorded for SAEs and ECIs as defined in Section 9.1.3.

Permitted concomitant therapy: In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited.

6.5.1.1 Antiemetics: Use of anti-emetics is allowed. Prophylactic anti-emetics may be used.

6.5.1.2 Permitted concomitant therapy requiring caution and/or action

6.5.1.2.1 Hematopoietic growth factors: Hematopoietic growth factors (e.g. erythropoietins, G-CSF, and GM-CSF) are not to be administered prophylactically. Routine prophylactic use of G-CSF (Neupogen or Neulasta) is not permitted. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents or as dictated by local practice (see also the guidelines by the American Society of Clinical Oncology (ASCO) available under http://jco.ascopubs.org/cgi/content/full/24/19/3187). However, therapeutic use in patients with serious neutropenic complications such as grade 3 toxicity or higher, cases of febrile neutropenia or sepsis may be considered at the investigator's discretion**.**

6.5.1.2.2 Corticosteriods: Prolonged systemic corticosteroid treatment should not be given during the study except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airway diseases), eye drops or local infections (e.g. intra-articular). Systemic corticosteroid use for chemotherapy pre-medication or for de-sensitization is allowed. A short duration (< 2 weeks) of systemic corticosteroids is allowed (e.g. for chronic obstructive pulmonary disease, or as an anti-emetic).

6.5.1.2.3 Anticoagulation: Anticoagulants other than warfarin/Coumadin derivatives or anti-aggregation agents may be administered under the discretion of the investigator provided they are discontinued in an appropriate time frame prior to surgical intervention

6.5.1.2.4 Contraceptives: For contraception, adequate barrier methods of contraception include diaphragm, condom, intrauterine device (copper), sponge or spermicide. Reliable contraception should be maintained throughout the study and for 120 days after study drug discontinuation.

6.5.2 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 Study:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with MDACC.
- Live vaccines within 30 days prior to the first dose of Study treatment and while participating in the Study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than as premedication for chemotherapy 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 MDACC.

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

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

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

6.6 Rescue Medications & Supportive Care

6.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail 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 6.3.2 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.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

TABLE 4 INFUSION REACTION TREATMENT GUIDELINES

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
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.,	Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

renal impairment, pulmonary infiltrates) Life-threatening; pressor or ventilatory support indicated	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	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.6.2 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. IrAEs may be predicted based on the nature of the Pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify, evaluate, and report irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document located in the Administrative Binder. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the MDACC.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 5.

TABLE 5 GENERAL APPROACH TO HANDLING IRAES

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold Pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold Pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day.

	within 12 weeks of toxicity	Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

6.7 Diet/Activity/Other Considerations

6.7.1 Diet

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

6.7.2 Contraception

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

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a 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 9.1.2 -Reporting of Pregnancy and Lactation to the MDACC 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.

6.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with Pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the MDACC and to Merck without delay and within 24 hours 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 MDACC. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the MDACC and to Merck and followed as described above and in Section 9.1.2.

6.7.4 Use in Nursing Women

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

7.0 STUDY PROCEDURES

The Schedule of Assessments found in section 7.1 summarizes the study procedures to be performed at each visit. Due to scheduling, these visits may occur +/- 3 days from the required time point. Additionally, 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 MDACC 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 Schedule of Assessments and Segments

7.1.1 Schedule of Assessments

Study Assessments	Screening Phase		Neoadjuvant Treatment									Pre-op visit (-14 days)	Tumor Reduction	Post-op visit[s]	Adjuvant Treatment									Maintenance (up to 20 cycles)	Post-Tx Discont.[y]	Survival Follow Up
	Pre-screening	Main Study Screening	Cycle 1			Cycle 2			Cycle 3+[z]						Cycle 4			Cycle 5			Cycle 6[t]					
	Day -28 to -1	Day -21 to -1	Day (± 3 days)												Day (± 3 days)										At time of Discont.	
			1[a]	8	15	1	8	15	1	8	15				1	8	15	1	8	15	1	8	15			
Administrative Procedures																										
Informed Consent[a]	X																									
Inclusion/Exclusion Criteria[b]	X																									
Demographics and Medical History[c]	X		X			X			X			X		X	X			X			X				X	
Prior and Concomitant[d] Medication Review	X		X			X			X			X		X	X			X			X			X	X	
Post-study Anticancer therapy status[e]	X		X			X			X			X		X	X			X			X				X	
Survival Status	X																									X
Clinical Procedures/Assessments																										
Review Adverse Events	X		as clinically indicated												as clinically indicated											
Full Physical Examination[f]	X		X			X			X			X		X	X			X			X				X	
Directed Physical[g] Examination	X		X			X			X			X		X	X			X			X			X	X	
Vital Signs and Weight[h]	X		as clinically indicated												as clinically indicated											
ECOG Performance Status[i]	X		X			X			X						X			X			X			X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																										
Pregnancy Test – Urine or Serum Beta-HCG[m]	X		X			X			X						X			X			X					
PT/INR and aPTT	X											X													X[aa]	
CBC with Differential[j]	X[l]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel[k]	X[l]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	

Urinalysis[m]	X													X			X			X			X		
Amylase	X													X			X			X			X[w]		
Lipase	X													X			X			X			X[w]		
T3, T4, TSH	X													X			X			X			X[x]		
Efficacy Assessments																									
Tumor Imaging[n]	X										X											X	X[w]	X[n]	
CA-125[v]	X		X			X			X		X			X			X			X		X	X	X[w]	
RECIST Measurements	X										X											X		X[w]	
Correlatives																									
Tissue Collection	X	X[o]										X[p]													
Blood Collection[q]			X								X[r]			X[q]			X[q]			X[q]				X	
Study Drugs																									
Pembrolizumab[s]														X			X			X			X		
Paclitaxel[t]			X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X			
Carboplatin[u]			X			X			X					X			X			X					

[a] No study activity may be performed until signed informed consent is on file.

[b] Subject must meet all inclusion and exclusion criteria in order to go on study. Any exceptions to eligibility criteria must be reviewed by the Principal Investigator and IRB approved prior to beginning any study procedures.

[c] A medical history will be obtained by the investigator or qualified designee. Medical history will include 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.

[d] 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 Study. The investigator or qualified designee will record medication, if any, taken by the subject during the Study. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 9.1.3.

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

[f] To include review of: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems. Height will be measured at screening only.

[g] To include review of: upper and lower extremities, eye exam, and blood pressure

[h] Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

[i] The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each new cycle of Study treatment and discontinuation of Study treatment as specified in the Schedule of Assessments. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

[j] To include: Hematocrit; Hemoglobin; Platelet count; WBC (total and differential); Red Blood Cell Count; Absolute Neutrophil Count. Maintenance phase blood work is to occur on Day 1 of each subsequent treatment cycle. Enrolled patients are required to have platelets $\geq$ 75,000/mcL on Day 1 of each cycle and platelets $\geq$ 50,000/mcL on day 8 and 15 of each cycle.

[k] To include: Albumin; Alkaline phosphatase; ALT (SGPT); AST (SGOT); LDH; Uric Acid; Amylase, Lipase, Calcium; Chloride; Glucose; Phosphorus; Potassium; Sodium; Magnesium; Total Bilirubin; Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*; Total protein; BUN;CO_2 (if considered standard of care in your region).

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

[m] To include: Blood; Glucose; Protein; Specific gravity; microscopic exam (if abnormal); Urine Pregnancy test (perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

[n] Tumor assessment may be performed on non-measurable but evaluable disease. CT or MRI to be performed at baseline post cycle 3, post cycle 6, every 12 weeks (+/- 7 days) during the maintenance phase, and at the end of the maintenance phase. For maintenance scans only: A chest CT is indicated as part of the radiographical assessment if used at baseline to assess target or non-target, evaluable disease. Imaging will also take place if patient discontinues at any time other than the scheduled imaging in maintenance phase. If a patient discontinues treatment for any reason other than progression, imaging will take place every 12 weeks (+/- 7 days) until time of progression or start of a new anti-cancer therapy.

o To be obtained prior to neoadjuvant therapy initiation.

p To be obtained during second-look laparoscopy if undertaken.

q This blood work is to occur on Day 1 of the treatment cycle.

r This blood test must occur prior to debulking surgery as part of the standard of care procedures. Patients who are prescribed a fourth cycle of neoadjuvant treatment at the pre-op visit must repeat pre-op bloodwork at the re-scheduled pre-op visit.

s Pembrolizumab (MK-3475) administration will begin on Day 1 of each treatment cycle beginning in Cycle 4.

t Paclitaxel will be administered on Days 1, 8 & 15 of treatment cycles 1-6.

u Carboplatin will be administered on Day 1 of treatment cycles 1-6.

v CA125 test will take place on a monthly basis per standard of care. If Cycle 1 Day 1 is within 28 days of the Screening blood draw, it is unnecessary to repeat the blood draw.

w Urinalysis and tumor imaging should take place every 12 weeks (+/- 7 days) in the Maintenance Phase.

x TSH will be measured at every cycle during maintenance therapy; free T3 and T4 will be measured if TSH is abnormal

y Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 3 months to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

z If clinically indicated, subjects may receive more than three cycles of neoadjuvant chemotherapy per physician's discretion.

aa Not to be performed if patient is removed from study due to disease progression.

7.1.2 Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

Pre-treatment evaluation and testing:

The tests and procedures that are standard of care will only be reviewed for the purposes of this protocol. Pre-treatment testing may be completed on the day of the patient's initial visit to their primary physician or they may be scheduled for a return appointment within 14 days prior to initiation of drug therapy. All testing will be completed prior to initiation of drug therapy. Please see the study calendars for detailed explanations of the procedures and assessments.

7.1.3 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments.

Toxicity will be monitored at the pre-operative and post-operative visits for the tumor reductive surgery and graded using CTCAE v4.03. Treatment will be discontinued if patients are unable to tolerate it due to adverse events.

Interval Tumor Reductive Surgery Evaluation and Testing

Standard of care tests for the planned surgery may be completed on the day of the patient's pre-operative visits for their tumor reductive surgery. Attention to toxicities during the tumor reductive surgery is critical, due to the unknown risk profile of the PD-L1 inhibitor prior to surgery. At this time, the impact of PD-L1 inhibitors on surgical parameters and post-operative complications is unknown. Thus, the anesthesia team will be notified prior to surgery that the patient was on a PD-L1 inhibitor treatment pre-surgery.

Blood will be collected at the pre-operative and post-operative visits for the tumor reductive surgery. This study allows patients to receive either 3 or 4 cycles of neoadjuvant therapy consisting of carboplatin, paclitaxel, and pembrolizumab at the investigator's discretion. The decision to include a fourth cycle of treatment is usually made at the pre-operative visit after blood collection. In the event a patient's treatment plan is revised to have an additional cycle of therapy, the pre-operative blood work must be repeated. Consequently, it is possible patients will potentially have two pre-operative blood work collections. Tumor tissue will also be collected during the interval tumor reductive surgery.

Details for blood collection and processing are located in Section 7.3. All blood and tissue samples will be processed and stored at MDACC by the Gynecologic Oncology Tumor Bank.

7.1.4 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of Study 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 Follow-up Visits

Subjects who discontinue Study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with Pembrolizumab as detailed in Section 6.3.2.1. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with Pembrolizumab according to the criteria in Section 6.0 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.3.2.1.

7.1.6 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 3 months to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.7 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to Study completion, all applicable activities scheduled for the final Study 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 9.1 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 6.3.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.4) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5).

7.2 Description of study procedures

7.2.1 Medical history and physical exam

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

Vital signs (temperature, blood pressure, pulse rate, weight, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On pembrolizumab treatment days, vital signs will be measured within an hour prior to start of pembrolizumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses (at dose levels of 750mg or less), the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

7.2.2 Laboratory Procedures/Assessments

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the Schedule of Assessments. The total amount of blood/tissue to be drawn/collected over the course of the Study (from pre-Study to post-Study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Blood and Tissue Collection Manual.

7.3 Pharmacodynamics Sampling

7.3.1 Collection, Storage, and Handling of Specimen (s)

Adequate tissue will be acquired at the time points noted in the schedule of assessments in Section 7.1.1 (prior to first dose of study drug and at tumor reduction surgery). The pre-treatment tissue may be obtained from one of three possible options.

- Option 1 (for subjects who have undergone a standard-of-care diagnostic laparoscopy): Tissue acquisition will occur under LAB02-188.

- Option 2 (for subjects who do not yet have a tissue histological diagnosis of ovarian, primary peritoneal, or fallopian tube cancer): Tissue acquisition will occur at the time of a standard-of-care diagnostic biopsy.
- Option 3 (for subjects who did not have a standard-of-care laparoscopy and have previously undergone a tissue histologic confirmation procedure but adequate tissue is not available for analysis): Tissue acquisition will occur at the time of a research-only biopsy.

Up to 40 ml of blood will be collected (7- 10 mL in four lavender top [EDTA] collection tubes) at each time point specified in the schedule of assessments in Section 7.1.1. Blood samples will be processed to separate blood fractions (e.g., plasma, white blood cells or PBMCs). Plasma will be frozen into cryotubes and PMBCs will be cryopreserved. Each sample will be labelled as per the "Blood and Tissue Collection Manual." The blood fractions will then be stored in the freezer at -80℃ in the Gynecologic Oncology Tumor Bank at the University of Texas MD Anderson.

7.3.2 Pharmacodynamics Procedures (PD)

The tissue samples and blood fractions will be utilized for the characterization of biological molecules, DNA, RNA, protein including circulating nucleic acids and exosome as well as activation status of hematopoietic and immune cells. Where sufficient material of appropriate quality is available, we will assess DNA mutations and copy number with targeted or whole exome sequencing (WES), RNA levels by RNA-sequencing, and protein levels by reverse phase protein array (RPPA) or immunohistochemistry. Assays will be selected based on the amount of tissue, the tumor content, blood (plasma, white blood cells or PBMC), and whether frozen or paraffin samples are available from each patient. The approaches to perform these research assays are rapidly evolving both in the Gynecologic Oncology Tumor Bank at the MD Anderson Cancer Center and across the world. We will thus perform these assays with the current state of the art assays such as NanoString technology that are available at the time of analysis.

Additionally, immune analyses, including but not limited to evaluation of CD4 and CD8 T cells, will be performed in peripheral blood and tumor samples, as previously published (Liakou CI, et al 2008; Carthon BC, et al 2010; Tang DN, et al 2013; Chen H, et al; 2014).

7.3.3 Analyses and Processes for Ovarian Cancer Moon Shot Program

In addition to IHC assays, DNA/RNA next generation sequencing may be performed for genotype-protein expression. Internal/External Sequencing may be done here at MD Anderson, in one of the Core labs such as the Cancer Genomics Lab, but in some cases samples may be sent to outside collaborators for sequencing and/or analysis such as the Broad Institute. Any sharing or sequencing of samples performed by Broad or any other external collaborator will be conducted under specific contract or Material Transfer Agreement (MTA). We will protect participant’s privacy by coding samples and

keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

7.3.4 Analyses and Process for QualTek Molecular Laboratories

In addition to IHC assays performed under the Ovarian Cancer Moon Shot at MD Anderson Cancer Center, non-STAT PD-L1 IHC testing will be performed with QualTek Molecular Laboratories in a non-CLIA laboratory. QualTek will provide PD-L1 IHC staining and pathology scoring for up to approximately 60 samples from those patients that have enrolled onto study. Samples will be shipped to QualTek as sectioned slides to be used to perform the PD-L1 IHC assay using Merck mouse monoclonal antibody clone 22C3. Samples will be scored only by board-certified pathologists(s) with documented training/pathologist concordance for scoring PD-L1 IHC for the tumor indications for this study.

An H&E stain will be reviewed for confirmation of tumor presence. If a sample does not contain sufficient tumor for evaluation, QualTek will document and inform MD Anderson Cancer Center who will request a new sample for the GYN Tumor Bank if available. If QualTek is unable to evaluate due to unusual histology or staining patterns, the sample will be scored as not-interpretable.

Data will be reported to MD Anderson Cancer Center in a spreadsheet format deemed acceptable and appropriate by both MD Anderson and QualTek. The final dataset encompassing all samples will be provided at the end of the study. Investigator should notify QualTek of any Interim Analysis (IA) required prior to end of study.

A final Clinical Sample Analysis Summary Report will be provided within 2 weeks after the final sample is analyzed. Necessary information includes (a) Report Summary (b) Assay Objective and Overview (c) Sample Reconciliation, i.e. received, assayed, failed, lost, lab locations, contact person), (d) table of all results generated during the course of the study, (e) reviewed and approved by appropriate QualTek personnel (i.e. Medical Director, Lab Director, Study Director and Quality Director).

7.4 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

• Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

• Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

• Ensures that the subject is informed about the sample disposal.

8.0 DISEASE EVALUATION AND METHODS

8.1 Tumor Imaging and Assessment of Disease (RECIST v1.1)

8.1.1 Physical examination

• Lesions detected by physical examination will only be considered measurable if superficial, e.g., skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

8.1.2 Radiological Imaging Guidelines/Procedures

• Study assessments will be performed based on calendar start dates and not by course of therapy to reduce ascertainment bias.

8.1.2.1 CT scan with contrast of the chest, abdomen, and pelvis

• CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

8.1.2.2 MRI scans

• MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

8.2 Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

• Measurable Lesions - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).

- 10 mm caliper measurement by clinical exam (when superficial).

- Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

- Nonmeasurable Lesions - Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- Target Lesions - All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- Non-target Lesions - It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

8.3 Response Criteria

8.3.1 Evaluation of Target Lesions

- Complete Response - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).

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

- Progressive Disease - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

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

8.3.2 Evaluation of Non-target Lesions

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

- Non-complete response/Non-progressive disease - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- Progressive Disease - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from ‘trace’ to ‘large,’ an increase in lymphangitic disease from localized to widespread.

8.3.3 Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive pembrolizumab if investigators consider that subjects continue to benefit from treatment.

8.3.4 Evaluation of Overall Response with Modifications

Confirmation of CR, PR, as well as PD is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. Treatment with pembrolizumab will continue between the initial assessment of PD and confirmation for PD.

Tables 6 and 7 provide overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

TABLE 6. EVALUATION OF OVERALL RESPONSE

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non- target lesion)	No	Complete response
No target lesion at baseline	Complete response	No	Complete response
Complete response	Not evaluable	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion)	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion)	No	Stable disease

TABLE 7. EVALUATION OF OVERALL RESPONSE

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion	Not all evaluated	No	Not evaluable

No target lesion	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion	Any	Yes	Progressive disease

8.4 MRI Scans

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the non-enhancing component, should be performed. The product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

Minimum sequences required:

- Pre-contrast T1, T2/ fluid attenuated inversion recovery (FLAIR)
- Post-contrast T1, with two orthogonal planes (or a volume acquisition) recommended
- Recommended slice thickness ≤ 5 mm with no gap

8.4.1 Measurability of Tumor Lesions

8.4.2 Tumor lesions are categorized as follows:

- Measurable disease is defined as bi-dimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip.
- Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with

margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm. Subjects without measurable disease, such as those who undergo a gross total resection, cannot respond and can only achieve SD as their best radiographic outcome.

- There are two types of non-target lesions
  - Enhancing (T1 with contrast)
  - Non-enhancing (T2/FLAIR)
- These are assessed subjectively. Some rules are recommended for objective assessment of progression e.g., if a nonmeasurable enhancing lesion becomes measurable, AND either has absolute increase of > 5 mm OR > 25% in sum of products of diameter

8.4.3 Response Criteria

8.4.3.1 Evaluation of Target Lesions

- Complete response - Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Subjects with nonmeasurable disease only, cannot have a CR; the best response possible is SD.

- Partial response - Requires all of the following: 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Subjects with nonmeasurable disease only, cannot have a PR; the best response possible is SD.

- Stable disease - Requires all of the following: does not qualify for CR, PR, or progression; stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

- Progression - Defined by any of the following: 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse events, complications of therapy, cerebrovascular events, infection) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

8.4.3.2 Evaluation of Enhancing Non-target Lesions

- Complete response - All enhancing non-target lesions have disappeared completely
- Incomplete response/SD - Enhancing lesions present; stable or decreased in size
- Progressive disease - Unequivocal progression
- Unable to assess - Unable to evaluate enhancing lesions because of technical factors

8.4.3.3 Evaluation of T2/FLAIR Lesion Response

- Improved - Signal abnormality decreased
- Unchanged - Unchanged compared to prior imaging
- Worse - Unequivocal worsening/progression of signal abnormality
- Unable to assess - Unable to evaluate non-enhancing lesions because of technical factors

9.0 SAFETY ASSESSMENTS

9.1 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 study agents, is also an adverse event.

Adverse events may occur during the course of the study 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, or a procedure.

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 9.1.3.

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

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Assessments and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 9.1). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to Study treatment. All toxicity information will be collected in the institutional Data Management Initiative (DMI) database.

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 (irAE). See Section 9.1.3.2 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to section 9.1 for detailed information regarding the assessment and recording of AEs.

9.1.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the MDACC and to Merck

For purposes of this Study, an overdose will be defined as any dose exceeding the prescribed dose for Pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of Pembrolizumab. In the event of overdose, Pembrolizumab does not need to be discontinued, however, 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, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Principal Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220 or 215-661-6229 or 267-305-0809 or aer_mailbox@merck.com)

9.1.2 Reporting of Pregnancy and Lactation to the MDACC 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 Study or within 120 days of completing the Study completing the Study, 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 Principal Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220 or 215-661-6229 or 267-305-0809 or aer_mailbox@merck.com)

9.1.3 Immediate Reporting of Adverse Events to the MDACC and to Merck

9.1.3.1 Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Merck Pharmaceutical:

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 MDACC 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 MDACC 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 or +1-215-661-6229 or +1-267-305-0809 **or the Merck AER mailbox: aer_mailbox@merck.com**

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 or 215-661-6229 or 267-305-0809 or at the Merck AER mailbox: aer_mailbox@merck.com) at the time of submission to FDA.

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

9.1.3.2 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 MDACC and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220 or 215-661-6229 or 267-305-0809 or at the Merck AER mailbox: aer_mailbox@merck.com)

Events of clinical interest for this Study include:

1. an overdose, as defined in Section 9.1.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the MDACC, 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 Study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the MDACC within 24 hours and to Merck Global Safety within 2 working days of the event:

a. Grade ≥ 3 diarrhea
b. Grade ≥ 3 colitis
c. Grade ≥ 2 pneumonitis
d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled “event of Clinical Interest and Immune-Related Adverse Event Guidance Document.” This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Principal Investigator within 24 hours and to Merck Global Safety within 2 working days of the event.

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.

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

9.1.4 Evaluating Adverse Events

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

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

Adverse events can be "expected" or "unexpected."

9.1.5 Attribution of Adverse Events

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

1. Definite – The AE is clearly related to the study treatment
2. Probable – The AE is likely related to the study treatment
3. Possibly – The AE may be related to the study treatment
4. Unlikely – The AE is doubtfully related to the study treatment
5. Unrelated – The AE is clearly NOT related to the study treatment

9.1.6 MDACC 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. Adverse event information will be captured in the DMI database.

All adverse events experienced by participants will be collected from the time of consent until the final study visit. Participants continuing to experience toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For patients that have received no more than 4 previous induction cycles prior to starting study, retrospective adverse event collection should occur as reasonably possible based on first reported data received from outside scanned medical notes in the patient's electronic medical record. The capturing of AE's must follow protocol requirements from the time of consent and going forward.

10.0 STATISTICAL ANALYSIS PLAN

10.1 Statistical Analysis Plan Summary

Futility Monitoring

We will enroll at least 10 patients and at most 30 patients at a rate of 1 patient per month. We will follow all patients for at least 12 months, and we will monitor futility and feasibility as described below. We will use the methods described by Thall et al.[41] to monitor progression-free survival (PFS), and we will stop enrolling patients early if, based on the available data, we have reason to believe that the median PFS is less than that observed with conventional therapy (i.e., 12 months). Formally, we will stop enrolling patients early if

$$\Pr(\text{median PFS}_{\text{experimental}} \geq \text{median PFS}_{\text{conventional}} \mid \text{data from the trial}) < 0.05$$

That is, if there is less than a 5% chance that the median PFS is more than that observed with conventional therapy (i.e., 12 months), then we will stop enrolling patients. Details of how this monitoring rule was constructed are explained in the "*Technical Details*" section below. The operating characteristics of this monitoring rule are shown in the table below and are based on 10,000 simulations of the monitoring rule performed with the "OneArmTTE Version 4.11" program developed in the MD Anderson Cancer Center Department of Biostatistics.

Operating Characteristics for Futility Monitoring Rule

Median PFS (months)	12-month PFS	Pr(Stop Early)	Sample Size			Average Trial Duration (months)
			P_{25}	Mean	P_{75}	
6	0.250	0.9815	10	15.7	19	16.4
9	0.397	0.5337	17	24.2	30	30.8

12	0.500	0.1514	30	28.1	30	38.4
15	0.574	0.0443	30	29.3	30	40.8
18	0.630	0.0170	30	29.7	30	41.5
21	0.673	0.0072	30	29.9	30	41.8
24	0.707	0.0037	30	29.3	30	41.9

We will use the Clinical Trial Conduct (CTC) website, which is housed on a secure server at MD Anderson and maintained by the Department of Biostatistics, to implement the futility monitoring rule. The CTC website is found at https://biostatistics.mdanderson.org/ClinicalTrialConduct. Access to the CTC website will be gained through usernames and passwords provided by the MD Anderson Department of Biostatistics to study personnel responsible for enrolling patients and updating, reviewing, and analyzing patient data. Training on the use of the CTC website will be provided by the study statistician, which particular attention to the importance of timely updating of follow-up dates and recording of events.

Technical Details

At any point in the trial the PFS can be calculated for each patient, with the time interval regarded as censored at the date of last follow-up if the patient is still alive without progressive disease. At each interim analysis, we will apply a Bayesian method for updating prior information with PFS observed to that time. We assume that the PFS for each patient is exponentially distributed with a median of λ_C months for the conventional treatment and a median of λ_E for the experimental treatment. Given the historical data (Greer et al. 2005) and a median PFS of 16 months, we assume λ_C follows an inverse gamma distribution with mean 12 months and standard deviation of 1 month. The middle 95% of this distribution is between 10.20 and 14.11 months. We assume λ_E follows an inverse gamma distribution with a mean of 12 months and a standard deviation of 12 months. The middle 95% of this distribution is between 3.32 and 38.79 months.

The goal of the futility monitoring rule is to guard against a median PFS rate less than that observed with conventional therapy (i.e., 12 months). Patient enrollment will be stopped early if, based on the available data, Pr ($\lambda_E \geq \lambda_C$ | data from the trial) < 0.05. This futility rule was chosen to achieve a relatively high early stopping probability if the true median PFS is less than 12 months for the experimental treatment, while maintaining a relatively low early stopping probability if the median PFS is greater than 12 months for the experimental treatment.

Feasibility Monitoring

We will monitor feasibility, defined as the ability to complete all planned cycles of adjuvant therapy, using the methods of Thall et al.[42]. Adjusted doses where the patient completes the treatment cycle will count as a completed cycle. Study drug may be discontinued at any time at the discretion of the treating physician. We will stop enrolling patients early if P (% of patients unable to complete all planned cycles

of therapy > 10% | data from the trial) > 0.95. That is, given the outcomes from the patients who have been evaluated, if we determine that there is more than a 95% chance that more than 10% of patients are unable to complete all planned cycles of therapy we will stop enrolling patients. This decision rule gives the following monitoring rule. We assume a uniform prior distribution for the percent of patients unable to complete all planned cycles of therapy. Stop enrolling patients if

[# patients unable to complete all planned cycles of therapy / # patients evaluated]

≥ 3/10, 4/15, 5/20, 5/25, 6/30

The operating characteristics of this monitoring rule are shown in the table below and are based on 10,000 simulations of the monitoring rule. The feasibility monitoring rule and operating characteristics were calculated using the Stata command developed by Fellman[43].

Operating Characteristics of Feasibility Monitoring Rule

% of Pts. Unable to Complete Therapy	Pr(Stop Early)	Sample Size			Mean # Unable to Complete Therapy
		P_{25}	Mean	P_{75}	
5%	0.0173	30	30	30	1.5
10%	0.1390	30	30	30	2.8
15%	0.3686	20	30	30	3.7
20%	0.6196	10	25	30	4.1
25%	0.8161	10	15	25	4.3
30%	0.9216	10	10	20	4.4

Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients. We will tabulate tumor response and estimate the rates of residual disease (complete resection, <1 cm residual disease, and ≥1cm residual disease), interval response (pCR) and overall response (CR) with 90% confidence intervals, and we will compare response rates with a contemporary control group using Fisher's exact test.

We will estimate the median PFS with a 90% credible interval, and we will report the posterior probability that the median PFS is greater than 12 months. We will also report the posterior probability that the median PFS is greater than 16 months.

We will also estimate PFS with the product-limit estimator of Kaplan and Meier[44], and we will model PFS as a function of potential prognostic factors (e.g., biomarkers) using Cox[45] proportional hazards regression.

We will estimate the percent of patients unable to complete all planned cycles of therapy with a 90% credible interval. If we enroll 30 patients and find 0 patients unable to complete all planned cycles of therapy, then our 90% credible interval will be 0.2% to 9.2%. We will also report the posterior probability that the percent of patients unable to complete all planned cycles of therapy is more than 10%. If we enroll 30 patients and find 0 patients unable to complete all planned cycles of therapy, then the posterior probability that the percent of patients unable to complete all planned cycles of therapy is more than 10% is 0.038. We will tabulate adverse events by grade and relationship to study drug.

Biomarkers

We assume that a particular biomarker will increase (or decrease) with probability 0.50 if there is no effect of chemotherapy. With 30 patients we will have 80% power with a 1-sided significance level of 0.05 to detect a probability of a particular biomarker's expression increasing (or decreasing) of 0.72 using an exact binomial test. In other words, if chemotherapy has the effect of increasing (or decreasing) expression of a particular biomarker in 72% of patients, we will have 80% power to detect that effect. This same sample size will also give us 80% power with a 1-sided significance level of 0.05 using Fisher's exact test to detect a difference in increasing (or decreasing) expression rates of 0.83 and 0.50 between patients treated with chemotherapy and a corresponding control group of 30 untreated patients, respectively. A sample of 30 patients will also give us 80% power with a 2-sided significance level of 0.05 and a paired t-test to detect an effect size of 0.53 standard deviations for the change in biomarker expression from pre-treatment to post-treatment with chemotherapy. Thirty patients treated with pre- and post-chemotherapy will yield 80% power with a 2-sided significance level of 0.05 using a 2-sample t-test to detect a difference of 0.74 standard deviations between treated and untreated patients with respect to the change in biomarker expression. No adjustment for multiple testing is made, as these analyses are considered exploratory in nature. These sample size calculations were performed using nQuery Advisor ® 8.0 (Copyright © 1995-2007, Statistical Solutions, Saugus, MA). We will also use Cox proportional hazards regression to model PFS and OS as a function of biomarker expression.

11.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

11.1 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 8.

Table 8 Product Descriptions

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

12.0 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 Confidentiality

The data will be kept in a database on a password protected computer in a secure office. This information will only be accessible to the study investigators. Once the clinical information is obtained, all patient identifying information will be deleted from the database. No patient identifiers will be used when analyzing the data, or reporting the results.

12.2 Compliance with Financial Disclosure Requirements

12.3 Compliance with Law, Audit and Debarment

This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. E6 Good Clinical Practice: Consolidated Guidance
   www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

2. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

   - Title 21 Part 11 – Electronic Records; Electronic Signatures
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
   - Title 21 Part 50 – Protection of Human Subjects
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
   - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
   - Title 21 Part 56 – Institutional Review Boards
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

3. State laws: It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.4 Compliance with Study 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 MDACC of the Study is solely responsible for determining whether the Study and its results are subject to the requirements for submission to the Clinical Studies Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate Studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate Study locations and Study site contact information.

12.5 Quality Management System

The study team, including the PIs, research nurse, and data coordinator, will perform monthly reviews of case histories and regulatory documents. Audits will be performed as per institutional standard.

12.6 Data Management

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

Study data will be collected and managed using Data Management Initiative (DMI) electronic data capture tools hosted at MD Anderson. DMI is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies DMI uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. DMI is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. DMI has undergone a Governance Risk & Compliance Assessment (May 2014) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. External collaborators are given access to the database once approved by the PI, with their access expiring in 6 months but renewable in 6 months increments at the request of the PI. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from DMI for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. Following publication study data will be archived in DMI.

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