EProst # 20160477

IND # 131448

Phase II Single Arm Study of Combination Pembrolizumab, Paclitaxel, and Carboplatin in Patients with Advanced Stage Ovarian, Fallopian Tube, or Peritoneal Carcinoma Receiving Neoadjuvant Chemotherapy

VERSION #	6.0
VERSION DATE	1 September 2023
NCT #	02834975

PRINCIPAL INVESTIGATORS (PI) Abdulrahman Sinno, MD
Division of Gynecologic Oncology

CONTACT INFORMATION

PRINCIPAL INVESTIGATOR	Abdulrahman Sinno, MD Division of Gynecologic Oncology University of Miami (UM)/ Sylvester Comprehensive Cancer Center (SCCC) Telephone: 305-243-2233 Email: ak.sinno@med.miami.edu
Protocol Writer	Norma Magallanes, MS, CCRP Sylvester Comprehensive Cancer Center University of Miami Phone: 305-243-3379 Email: nkm42@med.miami.edu
STATISTICIAN	Isildinha M. Reis, DrPH University of Miami Telephone: 305-243-5884 Email: ireis@med.miami.edu
FUNDING SOURCE	Merck, Inc.

Regulatory Sponsor	Abdulrahman Sinno, MD
Funding Source(s)	**Merck, Inc.**
Investigational Agent(s)	Pembrolizumab – provided by: Merck; commercial formulation
Other Agent(s)	Paclitaxel – commercial supply Carboplatin – commercial supply
IND Status	**IND Number: 131448** **IND Sponsor-Investigator:** Abdulrahman Sinno, MD

INVESTIGATOR AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Investigators' Brochure (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

eProst Number:	
Protocol Version Number:	Protocol Version Date:

Signature of Investigator:	Date:
Name of Investigator (printed):	Institution:

Table of Contents

ABBREVIATIONS & DEFINITIONS

Term	Abbreviation	Definition
Adjuvant chemotherapy	ACT	Treatment provided after the primary treatment to prevent cancer recurrence.
Neoadjuvant chemotherapy	NACT	Treatment given to shrink tumors prior to surgical removal.
Overall Survival	OS	The length of time from the date of first dose of study treatment until death due to any cause.
Progression-Free Survival	PFS	The length of time from the date of first dose of study treatment until date of disease progression or death due to any cause, whichever comes first.
Pathologic Objective Response Rate	pORR	The percentage of patients whose cancer shrinks or disappears after treatment (subjects that have achieved a pathologic complete response [pCR] or pathologic partial response [pPR]).
Time to Progression	TTP	The length of time from the date of diagnosis or the start of treatment for a disease until the disease starts to get worse or spread to other parts of the body.

Reference: National Cancer Institute (NCI) Dictionary of Cancer Terms: http://www.cancer.gov/dictionary

PROTOCOL SYNOPSIS

Protocol Title	Phase II Single Arm Study of Combination Pembrolizumab, Paclitaxel and Carboplatin in Patients with Advanced Stage Ovarian, Fallopian Tube, or Peritoneal Carcinoma Receiving Neoadjuvant Chemotherapy
Objectives	Primary Objectives • To determine the pathologic objective response rate (pORR) (complete response [CR] + partial response [PR]) of pembrolizumab in combination with paclitaxel and carboplatin in patients with advanced Stage III or IV epithelial ovarian, primary peritoneal or fallopian tube carcinoma (EOC). Secondary Objectives • To determine the progression-free survival (PFS) in patients with advanced Stage III or IV EOC treated with pembrolizumab, paclitaxel and carboplatin. • To confirm the safety and tolerability (rate of toxicity) of pembrolizumab, paclitaxel and carboplatin in patients with stage III or IV EOC. Exploratory Objectives • To determine if an immunologic profile (defined as an increased intra-tumor infiltration of perforin+ CD8+ T lymphocytes) may be a useful predictive biomarker of response and PFS. • To determine changes in tumor and blood biomarkers after treatment and its correlation with pathological response to therapy. Biomarkers include but are not limited to PD-L1, PD-1, CD8, FOXP3.
Targeted Patient Population	Women with primary advanced Stage III or IV EOC who are candidates for diagnostic laparoscopy (or interventional radiology [IR]-guided core biopsy), and dispositioned to receive neoadjuvant chemotherapy (NACT) with combination carboplatin and paclitaxel.
Expected Number of Patients	40
Study Design	This is a single arm, open-label, phase II study to assess pORR (CR + PR) in patients treated with pembrolizumab, paclitaxel and carboplatin for advanced stage III or IV EOC.
Treatment Schema	Eligible patients will undergo tissue biopsies to confirm diagnosis, followed by 3 to 4 cycles of NACT. NACT will be paclitaxel and carboplatin in combination with pembrolizumab. A cycle will consist of pembrolizumab at 200mg

	intravenous (IV), paclitaxel 175mg/m^2 IV, and carboplatin area under the curve (AUC) of 6 IV, on day 1 every 21 days. The length of each cycle is 21 days. This regimen will be followed by interval debulking surgery (IDS). Adjuvant chemotherapy (ACT) will consist of 3 to 4 more cycles of paclitaxel with carboplatin plus pembrolizumab once every 21 days. At the discretion of the treating physician, **dose-dense** paclitaxel may be administered weekly (instead of once every [q] 3 weeks) plus carboplatin once q21 days.
Duration of Treatment	Trial therapy may stop early due to withdrawal of consent, disease progression and/or other criteria for discontinuation is met (whichever occurs first). Treatment is considered complete following 6-8 cycles of NACT and ACT total (4 maximum for NACT and 4 maximum for ACT). See Section 8.0 for treatment discontinuation criteria.
Follow-up Required Post-Treatment	All patients will be followed at approximately 30 days (±7 days) after the last dose of study therapy as part of the Safety Evaluation. Patients without documented evidence of objective disease progression will have the same imaging studies used at Baseline and during Treatment as well as performed at the Safety Evaluation. Thereafter, all subjects will be followed for survival every 3 months for up to 24 months (i.e., 2 years) by phone call or standard of care visit.
Expected Number of Centers	Sylvester Comprehensive Cancer Center (SCCC) Note*:* SCCC is inclusive of the constituent satellite sites.
Expected Duration of the Protocol	Estimated time for accrual is approximately 36 months; estimated duration of the total protocol is approximately 60 months.

1.0 BACKGROUND AND RATIONALE

1.1 Epithelial Ovarian Cancer (EOC)

EOC collectively refers to ovarian, fallopian tube, and primary peritoneum cancers because of their similar biology.

Current standard treatment for advanced EOC in the US includes intravenous (IV) paclitaxel at 175mg/m^2 in combination with a platinum-containing (carboplatin area under the curve [AUC] of 6) agent or an intraperitoneal regimen. These regimens are effective with a significant clinical response rate (80%) that prolongs progression-free survival (PFS) and overall survival (OS). However, these therapies have a limited potential for cure and little progress has been made over the past 20 years in terms of cure rates. The likelihood of relapse after initial therapy in advanced stage disease is 80-85% with a median PFS of approximately 8-11 months. [1-3]

1.1.1 Neoadjuvant Chemotherapy (NACT) in Epithelial Ovarian Cancer (EOC)

Given the success of NACT in achieving less aggressive surgery without compromising survival benefit in other cancers, interest in NACT to treat EOC developed. The first prospective, randomized, controlled trial assessing the role of primary debulking surgery (PDS) in the treatment of advanced EOC was reported in 2010 (EORTC 55971). The study randomized 670 patients to either NACT followed by interval debulking surgery (IDS) or PDS followed by chemotherapy. The study demonstrated that NACT followed by IDS was not inferior to PDS followed by chemotherapy. [4] These results were then confirmed on a second randomized controlled phase III study (CHORUS). [5]

Retrospective studies examining the invasiveness of debulking surgery in patients receiving NACT compared to those undergoing PDS demonstrated that NACT groups had less blood loss, lower rate of bowel resection, splenectomy, surgical morbidities, shorter and less frequent intensive care unit (ICU) admissions, and shorter hospitalization. Additionally, the NACT groups had lower rate of permanent colostomy (6 vs 24%), lower rate of complications requiring surgery (3 vs 21%), and shorter duration of surgery. [6, 7]

Several advantages of NACT observed in these studies include (1) the identification of patients with chemoresistant disease; (2) no delay in up-front therapy; (3) lower incidence of surgical morbidity; and most importantly (4) higher interval surgical success by attaining no gross residual disease at the time of surgery. [8]

These advantages, in conjunction with a growing body of literature demonstrating non-inferiority of NACT as primary treatment, have led to a shift in practice patterns toward increasing utilization of this modality. Further, there is also significant data demonstrating that the previous definition of optimal response with a residual of <1cm may be inferior to no gross residual disease (R0). Patients that have an R0 at the completion of surgical cytoreduction have greater PFS and OS compared to patients with residual disease. [7, 8] Unfortunately, the selection criteria for this approach remains unclear

and there is currently no consensus as to which patients would benefit the most with this approach.

The vast majority of women with advanced stage EOC will have chemosensitive disease. However, the retrospectively reported magnitude of response to NACT is highly variable. This is likely due to the relatively new adoption of NACT as well as the reporting methodology. Petrillo *et al*. reported on pathologic response to NACT. Response was categorized as complete pathologic response, microscopic response and macroscopic partial response (6.5%, 32.3%, and 61.2%, respectively). [9] Colombo *et al*, examined cohorts separated by less than 4 cycles or greater than 4 cycles of NACT. In both groups, the rate of microscopic residual disease was 62-65%, and macroscopic disease was 35%-38%. Reported complete pathologic response has been as high as 23%. [10] Further, a recent study demonstrated that complete pathologic response may be a highly valuable prognostic tool. [9]

A system for grading response to NACT in advanced stage EOC based on minimal residual disease after IDS has been proposed by Bohm *et al.* [11] The study demonstrated that chemotherapy response score (CRS) has prognostic implications, particularly in patients achieving complete or near complete response. CRS was categorized as CRS 1 (no or minimal tumor response), CRS 2 (appreciable tumor response amid viable tumor that is readily identifiable), and CRS 3 (complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor). This system was then applied in a test cohort followed by a validation cohort, demonstrating reproducible results with prognostic significance. [11] Other studies have also shown that recurrences after clinical complete response are observed in about 75% of patients at a median of 10 months to as high as 28 months in the R0 cohort. [12-14] This emphasizes the urgent need for improvement(s) in current frontline therapy, as recurrent disease is largely incurable. As such, novel biological agents have been or are currently under investigation in the front-line setting in large phase III studies (GOG 218, ICON-7 with bevacizumab, nintedanib, trebananib, and veliparib). Thus far, there has been no significant improvement in OS and only modest impact on PFS.

1.2 Cancer Immune Surveillance and PD-1

The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, which is expressed on the cell surface of activated T-cells, is to down-modulate unwanted or excessive immune responses including autoimmune reactions. [15] PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and cytologic T-lymphocyte antigen (CTLA-4), which has been shown to negatively regulate antigen receptor signaling on engagement of its ligands, programmed death ligand-1(PD-L1) and/or programmed death ligand-2(PD-L2). [16] CTLA-4 and PD-1 normally function to counteract T-cell activation to self-antigens. [17-19]

In normal healthy individuals, PD-L1 expression is low (i.e., little, if any) while in a variety of cancers, it is richly expressed. Tumors can exploit this pathway to escape antitumor immunosurveillance. [18, 19] Blocking the PD-1/PD-L1 pathway may reduce the development of EOC tumor immune evasion and is an attractive target for therapeutic intervention especially in combination with standard lines of treatment. [20-22]

Invigorating tumor-specific T-cell immunity by inhibiting PD-L1/PD-1 signaling in conjunction with cytotoxic chemotherapy may result in deeper and more durable responses compared with standard chemotherapy alone. [23,24]In ovarian cancer patients, Polcher *et al.* observed a significant increase in $CD4^+$, $CD8^+$, and granzyme B^+ infiltration with the administration of NACT and no change in the accumulation of immunosuppressive $Foxp3^+$ cells. [25] Low immunosuppressive $Foxp3^+$ cell density was associated with longer PFS and improved OS. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors. [26]

These results suggest that the development of an immunogenic profile combining the absence of FOXP3 cells and the presence of high CD8+ and cytotoxic T cells result in the induction of pathologic complete response to NACT. [27] In light of these observations, we will evaluate whether boosting an immunological response by adding a PD-1 inhibitor, pembrolizumab, to NACT can result in a significant survival benefit and whether specific immune biomarkers could be identified that may predict overall response in patients with ovarian cancer.

1.3 Anti-PD-1/PD-L1 Agents

Clinical responses to agents targeting PD-1/PD-L1 and CTLA-4 have been observed in EOC patients enrolled in Phase I trials of solid tumors. The KEYNOTE-028 Phase Ib multi-cohort study of pembrolizumab in advanced solid tumors included 96 ovarian cancer patients, 49 of which had PD-L1 positive tumors (51%). In this study, pembrolizumab demonstrated antitumor activity and durability in a heavily pretreated metastatic ovarian cancer cohort with a manageable safety and toxicity profile. [28]

A multi-center Phase I study of pembrolizumab demonstrated durable tumor regression (objective response rate) and prolonged stabilization of disease in advanced cancers, including ovarian cancer. Responses lasted for 1 year or more in 8 of 16 patients with at least 1 year of follow-up. [27]

In another study, PD-L1 expression on monocytes in the ascites and blood of patients with malignant ovarian cancer was significantly higher than those with benign or borderline tumors suggesting that the PD-1 pathway may be a viable target for PD-1/PD-L1 directed antibody immunotherapy. [29]

1.3.1 Pembrolizumab

Pembrolizumab 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. Pembrolizumab can be administered intravenously or subcutaneously and is approved in the United States for many oncology indications alone and in combination with other chemotherapy regimens.[30]

1.3.2 Carboplatin/Paclitaxel plus Pembrolizumab

Safety data for the combination of paclitaxel/carboplatin and Pembrolizumab is available for multiple indications. Please refer to the Investigator Brochure for study details and results. [30]

1.4 Rationale for Chemotherapy Dose and Frequency of Administration

Rosenberg *et al.* demonstrated that weekly administration of paclitaxel was as effective as the equivalent dosed schedule every 3 weeks (Q3W) and had a better safety profile in patients with advanced ovarian cancer who were previously treated with one platinum-containing regimen. [31] Evidence suggesting that dose dense weekly paclitaxel is more effective than every 3 weeks paclitaxel emerged from the Japanese Gynecology Oncology Group (JGOG 3016). [32] In this phase III trial, women were randomized to either standard carboplatin (AUC 6 on day 1) and paclitaxel (180mg/m^2 on day 1) Q3W versus carboplatin (AUC 6 on day 1) and paclitaxel (80mg/m^2 on days 1, 8, and 15Q3W. Long term follow-up demonstrated improved survival with a median overall survival of 100.5 months in the dose dense group compared to 62.2 months in the standard arm. Interestingly, the study stratified patients by residual disease ≤1cm versus >1cm (suboptimal cohort) at the time of cytoreductive surgery. The median PFS for the suboptimal >1cm group receiving the dose dense regimen compared to standard Q3W therapy was 17.6mo vs 12.1mo, respectively. The median OS for the suboptimal group was 51.2mo vs 33.5mo favoring the dose dense regimen. This study suggests that women with a suboptimal cytoreductive surgery may benefit from a dose dense regimen of paclitaxel.

In studies conducted by the Gynecology Oncology Group (GOG, now NRG Oncology), the number of adjuvant cycles given to patients ranged from 6-9 cycles. GOG 182, which targeted patients with advanced stage (FIGO stage III or IV) ovarian or primary peritoneal carcinoma, 8 cycles of adjuvant treatment were administered.[33] Additionally, retrospective studies have looked at 6 vs 8, 9, and 12 cycles of adjuvant therapy and found no clear benefit. Thus, there is no standard of practice for the total number of cycles of adjuvant treatment in patients previously treated with neoadjuvant therapy. Boisen et al. presented an abstract at the 2015 annual Society of Gynecologic Oncology meeting which suggested that pathologic response based on the number of cycles of chemotherapy received may be a surrogate marker for survival in patients receiving NACT (patients received 6-8 cycles of chemotherapy). Thus, patients receiving treatment on this protocol will be given 6-8 cycles of chemotherapy at the provider's discretion depending on clinical assessment (i.e., CA 125 or computed tomography [CT] findings).

1.5 Rationale for Pembrolizumab Dose/Regimen Selection

Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

• Consistency in PK across tumor types

• Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose and exposure (or dose) and efficacy or safety relationships within the dose range of 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range.

• Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of fixed dose of 200 mg Q3W [refer to the Investigator's Brochure].

• Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications.

• Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

Based on this body of work, we have selected a fixed dose of 200 mg pembrolizumab to be administered Q3W in combination with paclitaxel and carboplatin. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.6 Correlative Studies

Although the immune system is suspected to play a role in tumor development and recurrence, the specific mediators of immune surveillance and suppression of tumor growth are largely unknown. Additionally, we have learned from analysis of patients treated thus far with PD-1-directed therapy that biomarkers of response to immunotherapy are extremely complex. Although PD-L1 expression in tumor cells and the presence of lymphocyte infiltration with PD-1/PD-L1 expression seem to be the best predictors of response, 10-15% of patients without tumor PD-L1 expression have responded to therapy, suggesting that other immunomodulatory factors must be playing a role. In addition to CTLA4 expression, other negative regulatory receptors have also been implicated, including LAG-3 and TIM-3, with pre-clinical blockade of some of these pathways resulting in improved anti-tumor response.[37,38] Finally, the presence of myeloid-derived suppressor cells (MDSCs) and regulatory T-cells have been shown to negatively impact response to therapy in many cancers, though these are also understudied in sarcomas. [39-42]

Thus, a key correlative component of our study will be to profile EOC tumors using pre-treatment tumor biopsies, surgical specimens and analysis of circulating peripheral blood mononuclear cells to better understand the immune environment in EOC patients and its modulation with treatment. We aim to define changes in intra-tumoral and peripheral blood lymphocyte phenotypes, activation and differentiation markers, and checkpoint ligand expression after NACT with pembrolizumab.

The tumor biomarkers include but are not limited to CD3, CD4, CD8, PD-1, PD-L1, and FOXP3, as defined by immunohistochemistry (IHC), quantitative real time polymerase chain reaction (qRT-PCR)[39,42-45], or other methods. Additional pharmacodynamic analyses will be conducted as appropriate. See Appendix D: Biomarker, Correlative and Special Studies for further information.

2.0 OBJECTIVES

2.1 Primary Objectives

- To determine the pathologic objective response rate (pORR), complete response (CR) and partial response (PR) of pembrolizumab in combination with paclitaxel and carboplatin in patients with advanced Stage III or IV EOC.

2.2 Secondary Objectives

- To determine PFS in patients with advanced Stage III or IV EOC treated with pembrolizumab, paclitaxel and carboplatin.
- To confirm the safety and tolerability (rate of toxicity) of pembrolizumab, paclitaxel and carboplatin in patients with stage III or IV EOC.

2.3 Exploratory Objectives

- To determine if an immunologic profile (defined as an increased intra-tumor infiltration of perforin+ CD8+ T lymphocytes) may be a useful predictive biomarker of response and PFS. To determine changes in tumor and blood biomarkers after treatment and its correlation with pathological response to therapy. Biomarkers include but are not limited to PD-L1, PD-1, CD8, and FOXP3.

3.0 ENDPOINTS

3.1 Primary Endpoints

Section 14.2 outlines pORR criteria for pembrolizumab in combination with paclitaxel and carboplatin. pORR will be calculated as the proportion of patients with best CR and PR overall.

3.1.1 Evaluable for pORR:

- Eligible subject(s) who receive at least one dose of pembrolizumab in combination with paclitaxel and carboplatin will have tissue collected at baseline and at IDS.

3.2 Secondary Endpoints

- Patients will be evaluated during treatment and by follow-up assessments post-treatment.

3.2.1 Evaluable for PFS:

Eligible patients who receive at least one dose of pembrolizumab in combination with paclitaxel and carboplatin.

- In progression-free patients, PFS will be censored at the last evaluable tumor assessment (RECIST v1.1).[46]

3.2.2 Evaluable for Safety and Tolerability:

Eligible patients who receive at least one dose of pembrolizumab in combination with paclitaxel and carboplatin.

- Treatment-related adverse events (AEs) and serious adverse events (SAEs) will be evaluated. AEs will be assessed by and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

3.3 Exploratory Endpoints

- The quantity of perforin^{+} CD8^{+} T lymphocytes in tumor tissue (baseline and debulking).

3.3.1 Evaluable for Predictive Biomarkers:

Eligible patients who receive at least one dose of pembrolizumab in combination with paclitaxel and carboplatin and successfully undergo at least one post-treatment tumor biopsy.

3.3.2 Evaluable for Health Status:

Patients who complete at least one assessment post baseline and who have received at least one dose of pembrolizumab in combination with paclitaxel and carboplatin. All causality AEs/SAEs will be evaluated in addition to treatment-related AEs.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

1. No prior treatment for primary advanced (Stage III or IV) high grade EOC, primary peritoneal, or fallopian tube carcinoma such as irradiation, chemotherapy, hormonal therapy, immunotherapy, investigational therapy, and/or other concurrent agents or therapies.
2. Patients must undergo diagnostic laparoscopy or IR core biopsy to collect tissue biopsies and to confirm diagnosis .

3. Patients must be appropriate candidates for planned NACT with combination carboplatin and paclitaxel administered IV Q3W.
4. Tissue from an archival sample or newly obtained core or excisional biopsy of a tumor lesion.
5. Age ≥ 18 years
6. Life expectancy > 3 months.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. See Appendix B: Performance Status Scores for more information.)
8. Patients must have normal organ and marrow function as defined below:

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

9. Negative urine or serum pregnancy ≤72 hours (i.e., 3 days) prior to receiving the first dose of study medication if not surgically sterilized. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential (have not been surgically sterilized or have not been without menses for >1 year) should be willing to use 2 methods of birth control at the same time or be surgically sterile or abstain from heterosexual activity for the course of the study and for at least 120 days after the last study dose. See Appendix F. Protocol-Approved Methods of Contraception for further details.
11. Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

1. Patients who are currently in or have participated in a study of an investigational agent or used an investigational device within 4 weeks of the first dose of treatment.
2. Histology showing mucinous or low grade epithelial ovarian cancer.
3. Patients who will not be likely to undergo IDS either secondary to performance status or sites of disease. If at the time of surgery, the patient is deemed to be surgically resectable to no gross residual, the patient will not be eligible for the study.
4. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of 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 28 days prior to study treatment.
5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer that has undergone potentially curative therapy.
6. Has received prior therapy with an anti-PD1, anti-PDL1, anti-CD137, 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) or anti-PDL2 agent.
7. Uncontrolled intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8. 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. Prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

10. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to previously administered event. Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for this study. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
11. Has active autoimmune disease that has required systemic treatment in the past two years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
12. Evidence of interstitial lung disease or active, non-infectious pneumonitis.
13. Is pregnant or breastfeeding or expecting to conceive 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.
14. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
16. Received live vaccine within 30 days prior to the first dose of study treatment. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
17. Patient has active bacillus tuberculosis (TB).
18. Patient with known hypersensitivity to pembrolizumab or any of its excipients (inactive ingredients).
19. Patient receiving concurrent additional biologic therapy.
20. Any other serious medical or psychiatric illness/condition likely in the judgment of the Investigator(s) to interfere or limit compliance with study requirements/treatment.

4.3 Strategies for Recruitment and Retention

Women of all races and ethnic groups are eligible for this trial. Prospective gynecologic subjects will be recruited at Sylvester Comprehensive Cancer Center (SCCC) inclusive of constituent satellite sites.

5.0 STUDY DESIGN

This is a single arm, open-label, phase II study to evaluate the effects of standard chemotherapy paclitaxel and carboplatin administered in combination with an anti-PD1 antibody, pembrolizumab, NACT for advanced stage III or IV EOC. Pathologic objective response rates (CR+ PR) will be assessed in patients treated with this combination.

Patients must undergo laparoscopy or IR-guided core biopsy to collect tissue biopsies and to confirm diagnosis. Tissue acquisition will consist of directed biopsies from the pelvis and

omentum (at least one metastatic peritoneal site). If at the time of surgery, the patient is deemed to be surgically resectable to no gross residual, the patient will not be eligible for the study.

Patients will be treated with 3-4 cycles of NACT. A cycle of NACT will consist of pembrolizumab at 200mg IV, paclitaxel 175mg/m^2 IV and carboplatin AUC 6 IV on day 1 as per institutional policies. This regimen will be followed by IDS at which time paired tissue samples will be collected. The IDS will be scheduled to take place within 8 to 10 weeks after last chemotherapy treatment.

Following IDS, patients will receive 3-4 cycles of adjuvant chemotherapy (ACT) consisting of paclitaxel with carboplatin plus pembrolizumab, Q3W. At the discretion of the treating physician(s), dose-dense chemotherapy (weekly paclitaxel with carboplatin Q3W) may be administered in place of the regimen received during NACT.

Blood collection will be performed before, during NACT and ACT, and at end of study. Blood samples for correlative studies will be collected before and after administration of pembrolizumab.

Forty subjects will be accrued and treated at Sylvester Comprehensive Cancer Center (SCCC) for approximately 36 months. Therapy will be administered until study completion, withdrawal of consent, disease progression and/or unacceptable toxicity, whichever occurs first.

All subjects will be followed for a Safety Evaluation at approximately 30-days (±7 days) after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever occurs first. Thereafter, subjects will be followed every 3-months for up to 24 months from treatment discontinuation.

6.0 TREATMENT PLAN

Patients may receive up to a maximum of 8 cycles on trial (4 cycles of NACT and 4 cycles of ACT).

6.1 Pembrolizumab

Pembrolizumab 200 mg flat dose shall be administered in the outpatient setting per standard of care procedures. For further information, please refer to the Investigator's Brochure.[30]

6.2 Paclitaxel (Taxol®)

In the neoadjuvant setting, paclitaxel 175mg/m^2 shall be administered as per institutional policy.

In the adjuvant setting, paclitaxel may be administered in the same way as in the neoadjuvant setting *OR* it may be administered as a dose dense treatment as in the JGOG 3016 study.[32] This decision will be at the discretion of the treating physician. For the dose

dense treatment, paclitaxel will be dosed at 80mg/m^2 and given as per institutional policy. Paclitaxel will be administered based on the patient's body surface area (BSA) in m^2 according to the manufacturer guidelines and institutional policy. Paclitaxel dose will be capped at a BSA of 2.0m^2. Premedications should be given as per institutional policy, such as, steroids, H1 and H2 blockers. For further information, please refer to the Investigator's Brochure.

6.3 Carboplatin

The carboplatin dose will be calculated using the Calvert formula using an estimated Cockroft and Gault-calculated creatinine clearance to present the GFR.

An antiemetic regimen is recommended for carboplatin.

Carboplatin dose (mg) = (Target AUC) x (GFR + 25)

For this protocol, GFR = CrCl (ml/min) = (140-age in years) x (ABW*) x (0.85) [female]/ (72 x serum creatinine mg/dL)

*ABW: actual body weight; In patients with an abnormally low serum creatinine (≤0.6 mg/dL), due to reduced protein intake and/or low muscle mass, the CrCl should be estimated using a minimum value of 0.7 mg/dL.

6.4 Treatment Schema

Table 6.4 Treatment Schema

Agent	Premedication(s)*	Dose	Route	Schedule	Cycle length
Pembrolizumab	Monitor for infusion reactions with hypersensitivity kit at bedside. Grade 2 infusion reactions will be premedicated with diphenhydramine 50 mg IV and acetaminophen 1000 mg PO prior to subsequent infusions. Diet: Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.	200 mg	IV (prior to TC)	Day 1 of each cycle***	21 days
Paclitaxel***	Dexamethasone, Diphenhydramine and Famotidine	175 mg/m^2	IV as per institutional practice		
Carboplatin	Zofran	AUC 6	IV as per institutional practice		

**May use other appropriate medications*

**** At the discretion of the treating physician, dose dense paclitaxel 80 mg/m^2 IV weekly plus carboplatin IV q21 days may be administered in the ADJUVANT setting.*

6.5 Concurrent Medications (as Applicable)

Because there is a potential for interaction of paclitaxel (Taxol®) with other concomitantly administered drugs through the cytochrome P450 system (Appendix E), the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The principal investigator (PI) should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

6.6 Acceptable 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 CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications from first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. .

6.7 Prohibited Medications

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

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

6.8 Duration of Treatment

Trial therapy will last until completion, withdrawal of consent, disease progression, unacceptable toxicity, study end and/or other criteria for treatment discontinuation is met, whichever occurs first. See Section 8.0 for treatment discontinuation criteria.

6.9 Duration of Follow-Up

All subjects will be followed for a Safety Evaluation at approximately 30-days (±7 days) after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever occurs first (See Section 9.4). Thereafter, subjects will be followed every 3 months for survival data for up to 24 months from the treatment discontinuation with either a telephone call or office visit as per standard of care.

7.0 TREATMENT/DOSE MODIFICATIONS

7.1 Assessment for Causality

Causality for all AE should be assessed and if deemed attributable, attempts should be made to attribute to pembrolizumab. Appendix A. Expedited AE Reporting Requirements.

7.2 General Procedure for Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. The AEs may occur shortly after the first dose or several months after the last dose of treatment The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab. Refer to Table 7.3.3 Supportive Care Guidelines.

Note: if after the evaluation. the event is determined not to be related, the Investigator does not need to follow the treatment guidance (as outlined below and in Table 7.3.3).

7.3 Dose Interruptions and Supportive Care Guidelines for AEs associated with Pembrolizumab

7.3.1 Dose Modifications

No dose modification is recommended for pembrolizumab.

7.3.2 Dose Interruptions

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

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.

7.3.3 Supportive Care Guidelines for Pembrolizumab AEs

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. Immune-mediated adverse reactions can occur after discontinuation of treatment. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the

adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA.

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis.

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis.

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA. Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA. Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis.

Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold

KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism.

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, and vasculitis. The following were reported in other clinical studies with KEYTRUDA or in postmarketing use: myocarditis and sclerosing cholangitis.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in postmarketing use.

Transplant-related adverse reactions

Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with KEYTRUDA has been reported in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Infusion-related reactions

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

Table 7.3.3: Pembrolizumab: Supportive Care Guidelines for Immune-Mediated Drug-Related Adverse Events

General instructions:

1. Based on the severity of the adverse reaction, withhold pembrolizumab and consider administration of corticosteroids. Administration of other systemic immunosuppressants can be considered for patients whose irAEs are not controlled with corticosteroid use.
2. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 1 month. Restart pembrolizumab if the AE remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue pembrolizumab.
3. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.

Immune-related AEs	**Toxicity grade or conditions (CTCAE v4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Severe Skin Reaction	Any	Withhold or permanently discontinue	Refer patient for specialized care for assessment and treatment.	If SJS or TEN confirmed, permanently discontinue pembrolizumab.
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and exclude other causes. Initiate corticosteroid treatment. •
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of colitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and exclude other causes •
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hepatitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor patients for changes in liver function with liver function tests (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. • Based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.
	Grade 3 or 4	Withhold or permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[1]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold until metabolic control is achieved.	• Initiate insulin replacement therapy for participants with T1DM. • Administer anti-hyperglycemic in participants with hyperglycemia.	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Adrenal insufficiency and hypophysitis (including hypopituitarism)[1]	Grade 2	Withhold	• Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated.	• Monitor patients for signs and symptoms of adrenal insufficiency and exclude other causes.
	Grade 3 or 4	Withhold or permanently discontinue		
Thyroid disorders (including hyperthyroidism, hypothyroidisim, and thyroiditis)1	Grade 2	Continue	• • Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. • Hyperthyroidism may be managed symptomatically.	• Monitor for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders..
	Grade 3 or 4	Withhold or permanently discontinue		
Renal failure and immune-mediated nephritis	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg/day or equivalent) followed by taper.	• Monitor changes of renal function and exclude other causes.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2	Withhold	• For grade 2 immune-mediated myocarditis, administer	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3 or 4	Permanently discontinue	prednisone corticosteroid or equivalent at an initial dose of 1-2 mg/kg/day followed by taper. • Permanently discontinue pembrolizumab for grade 3 or 4 myocarditis OR if toxicity does not resolve within 12 weeks of start of grade 2 toxicity or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.	

1.

[1]For participants with Grade 3 (severe) or 4 (life-threatening) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement or achieved metabolic control (in case of T1DM), continuation of pembrolizumab may be considered.

7.4 Paclitaxel (Taxol®) and Carboplatin

7.4.1 Dose Modifications

Treatment modifications regarding paclitaxel and carboplatin chemotherapy will be employed in a sequential manner using cycle delay and dose reduction.

Table7.4.1.1: Dose Reduction Sequence for Paclitaxel (Taxol(R)) and Carboplatin

Drug	Initial Dose	1st Reduction	2nd Reduction	Units
Paclitaxel	175	175	135	mg/m^2
Carboplatin	6	5	5	AUC

The following are criteria for carboplatin and paclitaxel treatment modifications and management of toxicities (in relation to pembrolizumab):

Table 7.4.1.2: Treatment Modifications and Management of Toxicities for Paclitaxel (Taxol(R)) and Carboplatin

Worst toxicity (CTCAE Grade)**	Recommended Dose Modifications & Management of Toxicities
None	
No Toxicity	Maintain dose level.
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC<lower limit of normal (LLN): $1.5x10^9$ cells/L) Grade 2 (ANC <1.5-1.0 $x10^9$ cells/L)	Hold treatment until ANC ≥ $1.5x10^9$ cells/L. May maintain dose level (i.e., no need to dose reduce or add GCSF at discretion of investigator).
Grade 3 (ANC<1-0.5 $x10^9$ cells/L) Grade 4 (ANC<$0.5x10^9$ cells/L)	First occurrence: Hold all treatment (chemotherapy & pembrolizumab) until ANC ≥ 1.0 x 10^9 cells/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 ≥$1.0x10^9$ cells/L, then ↓dose level (all treatment).
Febrile neutropenia (ANC< $1.0x10^9$ cells/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 ↓dose level (all treatment) or discontinue patient from study treatment at the investigator's discretion.
Thrombocytopenia	
Grade 1 (platelets (PLT)<LLN: $75x10^9$ cells/L) Grade 2 (PLT <75-50 $x10^9$ cells/L)	Hold treatment until Platelets >100K. May maintain dose level.
Grade 3 (PLT<50-25 $x10^9$ cells/L)	First occurrence: Hold all treatment until resolved to ≤Grade 1, then: • If resolved in ≤7 days, then maintain dose level.

Worst toxicity (CTCAE Grade)**	Recommended Dose Modifications & Management of Toxicities
	• If resolved in >7 days, then ↓1 dose level (all treatment). Second occurrence: Hold all treatment until resolved to ≤ Grade 1, then ↓dose level (all treatment).
Grade 4 (ANC<25x10^9 cells/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 ↓dose level (all treatment) or discontinue patient from study treatment at the investigator's discretion.
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 liver function tests (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.**
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).
Drug induced liver injury	
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,	

Worst toxicity (CTCAE Grade)**	Recommended Dose Modifications & Management of Toxicities
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 4.03	

7.4.2. Dose Interruptions

Under certain conditions, a dose interruption of carboplatin or paclitaxel may be required. Should the dose interruption last for greater than 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.

8.0 TREATMENT DISCONTINUATION

Treatment may be discontinued for any of the following reasons:

- The patient demonstrates progression of disease. (Exception: patients may remain on the study if in the opinion of the investigator, he/she is deriving clinical benefit from study treatment.)
- The patient (or legally authorized representative) withdraws consent from the study.
- Study treatment for participant is past due for >28 days due to an AE (or other such toxicity).

- The patient experiences an adverse event that in the opinion of the investigator makes continued study treatment an unacceptable risk.
- The patient becomes pregnant.
- The patient requires continuous treatment with a prohibited concomitant drug(s) for which no safe alternatives can be substituted.
- The patient is significantly noncompliant with the requirements of the protocol.

Should discontinuation of study therapy occur, all efforts should be made to execute/report End-of-Treatment and Follow-up Evaluations as completely as possible and to determine/ document the reason for discontinuation (unless the patient withdraws consent for follow-up).

Although unexpected termination of study treatment may occur, it is possible the subject may still agree to follow-up. This is particularly important to distinguish if the protocol has a defined follow-up period. Therefore, in such a scenario, the end of treatment (EOT) visit and procedures shall occur, but it is important to understand that the subject is still in Follow-up.

If, however, a subject withdraws consent to participate in the study, this constitutes the end of study for the patient. Even so, attempts should be made to obtain permission to record at least record survival data up until the protocol-specified end of follow-up period. Methods used for attempted contact must also be documented properly (e.g., number of telephone calls to subject, certified letters, etc.).

If a patient wishes to withdraw consent from the study, the principal investigator (PI) must be notified. The information regarding withdrawal (i.e. subject identifiers and date of withdrawal) should be documented in the subject's record and updated within any other research database(s).

9.0 SCHEDULE OF CLINICAL & LABORATORY EVALUATIONS

Prior to performing any study-specific procedures or evaluations, written informed consent and authorization for the use of protected health information (HIPAA) must be obtained in accordance with all applicable policies, regulations and laws. Correlative evaluations must also be performed at specified visits for patients who consent to these correlative evaluations. Please refer to Section 10.0 Schedule of Correlative Evaluations for specific details.

All evaluations should be completed as detailed below and prior to the administration of trial treatment on Day 1 of each cycle. All evaluations will be administered on an outpatient basis.

9.1 Pre-Treatment Evaluations (Screening)

The following must be collected/performed within 28 days prior to Cycle 1, Day 1 of treatment unless otherwise specified. Clinical and laboratory evaluations performed as part of routine standard of care do not need to be repeated if performed within the appropriate window.

- Informed Consent Form (ICF)

- Eligibility
- Demographic data (age, gender, and race)
- Medical History
- Complete physical examination (PE)
- Height
- Weight
- Vital signs (V/S)
    - Oral temperature
    - Blood pressure
    - Heart rate
    - Respiratory rate
- ECOG Performance Status (PS)
- 12-Lead Electrocardiogram (ECG)
- Urine or serum pregnancy test for women of child-bearing potential (WoCBP).
- Laboratory Evaluations:
    - CA 125
    - Complete Blood Count (CBC) with differential (diff)
    - Comprehensive Serum Chemistry Panel
    - Coagulation studies:
        - Prothrombin Time (PT)/International Normalized Ratio (INR)
        - Activated partial thrombobplastin time (aPTT)
    - Thyroid Tests
        - Triiodothyronine (T3)
        - Thyroxine (T4)
        - Thyroid-stimulating hormone (TSH)
    - Urinalysis (U/A)
- Correlative Studies: Diagnostic laparoscopy for tissue or IR-guided core biopsy. See Section 10.0 Schedule of Correlative Evaluations.
- Correlative Studies: Blood (optional). See Section 10.0 Schedule of Correlative Evaluations.
- Imaging studies for tumor assessment for all known sites of disease (including computed tomography (CT) or magnetic resonance imaging (MRI) of abdomen and pelvis with contrast): the same method of assessment and technique used at baseline will be used during treatment and follow-up at the discretion of the treating physician.
- Concomitant medications

9.2 Evaluations on Treatment

Collection of Concomitant Medications and AE should occur throughout the study as described. Any SAE, or follow up to an SAE, 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 30 days following end of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. All subjects with SAEs must be followed up for outcome. (See Section 13.0 Adverse Events and Appendix A. Expedited AE Reporting Requirements for details).

9.2.1 All Cycles, Day 1 (±3 days)

- Medical History
- Complete PE; pelvic exam done at the discretion of the Investigator.
- Weight
- Vital signs (V/S)
    - Oral temperature
    - Blood pressure
    - Heart rate
    - Respiratory rate
- ECOG PS
- Laboratory Evaluations:
    - CA 125
    - CBC with diff
    - Comprehensive Serum Chemistry Panel
    - Thyroid Tests
        - T3
        - T4
        - TSH
- Correlative Studies: Blood (optional). Blood samples will be collected before and after administration of pembrolizumab. See Section 10.0 Schedule of Correlative Evaluations.
- Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen and pelvis with contrast) prior to IDS per institutional standard of care procedures: the same method of assessment and technique used at baseline will be used during treatment and follow-up at the discretion of the treating physician.
- Genetic testing results per standard of care procedures
- Correlative Studies; Tissue Sample (newly obtained at IDS). See Section 10.0 Schedule of Correlative Evaluations.
- Urine or serum pregnancy test for women of child-bearing potential (WoCBP) ≤72 hours (i.e., 3 days) prior to day 1 all cycles.
- AE reporting
- Concomitant medications

Patients may receive up to a maximum of 8 cycles of combination treatment (4 as NACT and 4 after IDS [ACT]) while on study.

9.3 Early Treatment Discontinuation Evaluations

If discontinuing treatment early, these subjects should then proceed to the Safety Evaluation Visit (Section 9.4) and Follow-Up Evaluation Visit(s) (Section 9.5) of the study.

9.4 Safety Evaluation Visit

The following safety assessments must be performed at 30 days (±7 days) after the last dose of study treatment for all subjects. These subjects should then proceed to the Follow-Up Evaluation Visit(s) of the study (Section 9.54).

- Medical History
- Complete PE, pelvic exam done at the discretion of the Investigator.
- Weight
- V/S
    - Oral temperature
    - Blood pressure
    - Heart rate
    - Respiratory rate
- ECOG PS
- Laboratory Evaluations
    - CA 125
    - CBC with diff
    - Comprehensive Serum Chemistry Panel
    - Coagulation studies:
        - PT/INR
        - aPTT
    - Thyroid Tests
        - T3
        - T4
        - TSH
- Correlative Studies: Blood (optional). See Section 10.0 Schedule of Correlative Evaluations.
- Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen and pelvis with contrast): the same method of assessment and technique used at baseline will be used during treatment and follow-up at the discretion of the treating physician.
- AE reporting
- Concomitant Medications

9.5 Follow-up Evaluations

All subjects will be followed for a Safety Evaluation at approximately 30 days (±7 days) after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever occurs first (See Section 9.4). Thereafter, subjects will be followed every 3 months for survival data for up to 24 months from the date of treatment discontinuation with either a telephone call or office visit as per standard of care.

.

9.6 Calendar of Clinical and Laboratory Evaluations

	Screening	**Treatment Cycle(s)** q21 days	**Safety Evaluation** [M]	**Follow-Up** [N]
	≤28 days prior [A]	Day 1 (±3 days unless specified)	30 days (±7 days) after treatment discontinuation	Q3mos x 2 years after Safety Evaluation [N]
ICF	X			
Eligibility	X			
Demographics [B]	X			
Medical History & Physical, [C]	X	X	X	
Height	X			
Weight	X	X	X	
Vital Signs [D]	X	X	X	
ECOG PS	X	X	X	
12-Lead ECG	X			
CA 125	X	X	X	
CBC with diff [E]	X	X	X	
Comp Serum Chemistry Panel [E]	X	X	X	
PT/INR, aPTT	X		X	
T3, T4 and TSH	X	X	X	
Urinalysis	X			
Correlative Studies: Diagnostic laparoscopy OR IR-guided core biopsy [F]	X			
Correlative Studies: Blood [G]	X	X [G]	X [G]	
Imaging [H]	X	X (prior to Interval Debulking Surgery)	(X)[H]	
Baseline Symptoms	X			
Genetic Testing [I]		X		
Correlative Studies: Tissue Sample [J] (newly obtained)		X (at IDS)		
Urine or serum pregnancy test [K]	X	X		
Pembrolizumab IV		X		
Paclitaxel IV		X (or dose-dense option: every (q) 7 days in adjuvant setting plus carboplatin q21 days)		
Carboplatin IV		X		
Adverse Events		X		(X) [L]

	Screening	**Treatment Cycle(s)** q21 days	**Safety Evaluation** [M]	**Follow-Up** [N]
	≤28 days prior [A]	Day 1 (±3 days unless specified)	30 days (±7 days) after treatment discontinuation	Q3mos x 2 years after Safety Evaluation [N]
Concomitant Medications	X			
Post-Study Status [O]				X

[A] Screening evaluations should be done within 28 days prior to initiation of study treatment unless otherwise specified.
[B] Demographic data includes age, gender and racial/ethnic background.
[C] Complete Medical History includes disease history and prior medical treatments.
[D] Vital signs include oral temperature, blood pressure, respiratory rate and heart rate.
[E] Complete Blood Count (CBC) with differentials and Comprehensive Serum Chemistry Panel.
[F] Tumor specimens (archival or fresh – tissue or core) will be obtained at baseline diagnostic surgery (laparoscopy or IR-guided) at baseline/screening (28 days prior to Cycle 1, day 1).
[G] Blood (20 mL) will be collected at baseline/screening, on day 1 of NACT and ACT, prior to pembrolizumab and following pembrolizumab, and prior to IDS to characterize serum biomarkers.
[H] Imaging for tumor assessment for all known sites of disease (including CT or MRI of abdomen or pelvis with contrast) prior to IDS per institutional standard of care procedures: the same method of assessment and technique used at baseline will be used during treatment and follow-up at the discretion of the treating physician. Imaging will be done at baseline, prior to IDS, at the end of treatment and during follow-up, as per standard of care.
[I] Genetic panel testing will be performed as per institutional practice.
[J] Tissue sample collection during Treatment (i.e., at IDS) is optional and for correlative studies (see Section 10.0 for details). IDS to be scheduled within 10 weeks from the last chemotherapy treatment. If longer than 10 weeks, it must be discussed with the PI.
[K] Urine or serum (beta-HCG) pregnancy test is required for women of childbearing potential at screening and **within 3-days prior to Day 1** of each cycle treatment and should be conducted until women have surgery.
[L] AE/SAE collections should continue for at least **30 days** after the last dose of treatment. All subjects with SAEs must be followed up for outcome. (See Section 13.0 and Appendix A for details).
[M] Safety Evaluation visit for all patients; these safety assessments must be performed at 30 days (±7 days) after the last dose of study treatment.
[N] All subjects will be followed for a Safety Evaluation at approximately 30 days (±7 days) after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever occurs first (See Section 9.4). Thereafter, subjects will be followed every 3 months for survival data for up to 24 months from the treatment discontinuation with either a telephone call or office visit as per standard of care.
[O] To follow-up on patients' post-study anticancer therapy and survival status by means of a phone call or office visit per standard of care.

10.0 SCHEDULE OF CORRELATIVE EVALUATIONS

For those patients who consent to additional correlative evaluations, the following procedures will be performed: collection of blood will be performed on each cycle of neoadjuvant treatment before and after pembrolizumab infusion.

In addition to the study laboratory evaluations (i.e., CBC with differential, comprehensive serum chemistry panel), the patient's immune phenotyping (markers including but not limited to CD3, CD4, CD8, PD-1, PD-L1, FOXP3) will be determined. Intracellular cytokine levels in circulating blood and other evaluations based on available modalities at time of evaluation.[39, 42, 45]

Tumor specimens will be obtained at baseline diagnostic surgery (laparoscopy or IR-guided) and at IDS.

Immunohistochemistry and additional interrogations will be performed to determine tumor expression of biomarkers (including but not limited to CD3, CD4, CD8, PD-1, PD-L1, FOXP3), on formalin fixed paraffin embedded tumor specimens.[45]

Immune gene expression profiling via qRT-PCR and/or other evaluations will be performed on available snap frozen tumor specimens.[45]

10.1 Pre-Treatment Specimen Collection

The following should be collected at baseline/screening (28 days prior to Cycle 1, Day 1):

- Tumor specimens (archival or fresh – tissue or core)
- Blood (20 mL)

10.2 On Treatment Specimen Collection (during Neoadjuvant *and* Adjuvant treatment)

10.2.1 All Cycles, Day 1 prior to infusion and following completion of pembrolizumab infusion prior to chemotherapy initiation

- Blood (20 mL)

10.2.2 Interval Debulking Surgery (IDS)

- Blood (20 mL) just **prior** to IDS
- Tumor specimens

10.3 Off Treatment Specimen Collection

10.3.1 Safety Evaluation

- All subjects will be followed for a Safety Evaluation at approximately 30-days (±7 days) after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever occurs first (See Section 9.4). The following sample collection activities for correlative studies are performed during the Safety Evaluation visit. Blood (20 mL)

10.3.2 Follow-Up

Subjects will be followed every 3 months for survival data for up to 24 months from the treatment discontinuation with either a telephone call or office visit as per standard of care.

10.4 Specimen Collection for Correlative Studies

Timepoints	Tumor Collection	Blood
Screening	X*	X
All NACT and ACT Treatment Cycles, Day 1		X**
Interval Debulking Surgery (IDS)	X	X
Safety Evaluation		X
Follow-Up (q3mo x 2 years after last treatment)		
*Tumor sample collected laparoscopically or IR-guided core biopsy. **Blood samples for correlative studies will be collected before and after administration of pembrolizumab.		

11.0 AGENTS (DRUG FORMULATION AND PROCUREMENT)

11.1 Pembrolizumab

Refer to the FDA-approved package insert and current version of the Investigator's Brochure (IB) for more information.[30]

11.1.2 Mechanism of Action

MK-3475 is a potent and highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 potently blocks binding to both ligands with half maximal inhibitory concentration (IC_{50}) values below 1 nM in humans and cynomolgus monkey.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune-mediated adverse events are of primary concern.

11.1.4 Composition

The commercial formulation of pembrolizumab is being used in this study. Pembrolizumab drug product (DP) (solution for infusion, 100 mg/vial) is packaged in vials that contain 4 mL of sterile solution for IV infusion and 25 mg/mL pembrolizumab.

11.1.5 Storage Recommendations and Dosage Forms

Two Drug Product (DP) dosage forms are available for pembrolizumab (MK-3475): a subcutaneous injection form and an IV form. For the purposes of this study, only the IV form of pembrolizumab will be used. For instructions on dose preparation and administration, refer to the KEYTRUDA® package insert.

Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. If the diluted pembrolizumab solution is not used immediately, it may be stored at room temperature for no more than 6 hours from the time of dilution. This hold time includes room temperature storage of the diluted solution and the duration of infusion. The product can also be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, the diluted solution must be allowed to come to room temperature prior to administration. Do not shake. The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

Do not freeze the diluted solution!

11.1.1 Dispensation and Accountability

For this study, pembrolizumab will be provided by Merck as the commercial formulation of pembrolizumab at 100 mg/4 mL vial (25 mg/mL) as a solution for injection which is labeled as for investigational use. For further details on drug preparation, please refer to the most recent version of the KEYTRUDA® (MK-3475) Pharmacy Manual. See Section 8.5 Treatment Dispensation, Compliance and Accountability for Pembrolizumab for instructions on dispensing, accounting, and disposal.

12.0 MEASUREMENT OF EFFECT

Patient's response(s) to study treatment will be assessed pathologically.

12.1 Pathologic Response

The main specimen will be sampled uniformly with intervals of at least one section per centimeter. The secondary specimens (e.g., omentum, colon, appendix) will be grossly evaluated for the presence of macroscopic disease, and representative sections will be taken. For this protocol, pathologic complete response (pCR) will be defined as no residual macroscopic or (viable) microscopic disease. Pathologic partial response (pPR) will be defined as the presence of residual (viable) microscopic tumor, and the size of the largest focus will be provided for possible outcome correlation. A percentage (residual tumor/background of necrosis and fibrosis) will also be documented for the main specimen.

12.2 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response after completion of 3-4 cycles of NACT and after 3-4 cycles of ACT. In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guideline (version 1.1)https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf.[47] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.[47]

12.2.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with pembrolizumab, paclitaxel and carboplatin.

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

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

12.2.2 Disease Parameters

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

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

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

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

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

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

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

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

12.2.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA 125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.[47-49] In addition,

the Gynecologic Cancer Intergroup has developed CA 125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[50]

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

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

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

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of progressive disease (PD) based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

12.2.4 Response Criteria – Evaluation of Target Lesions

Table 12.2.4: Response Criteria (Target Lesions)

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute

	increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.2.5 Response Criteria – Evaluation of Non-Target Lesions

Table 12.2.5.1: Response Criteria (Non-Target Lesions)

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.2.6 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease):

Table 12.2.5.2: Best Overall Response- Measurable Disease

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	

Any	PD***	Yes or No	PD	no prior SD, PR or CR
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.[46]
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease):

Table 12.2.5.3: Best Overall Response-Non-measurable Disease

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

12.2.7 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

12.2.8 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of disease progression or death, whichever occurs first.

13.0 ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for adverse event (AE) reporting.

13.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events (AEs) are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner for timelier monitoring of patient safety and care.

13.2 Adverse Event

Adverse Event (AE): Can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, medical treatment, or procedure without judgment about causality. An AE can arise from any use and from any route of administration, formulation, or dose including an overdose. This includes any newly occurring event or a previous condition that has increased in severity or frequency since initiation of a drug, medical treatment, or procedure.

Abnormal Findings

In any clinical assessment, a value outside the normal or reference range (such as a clinical laboratory, vital sign, or ECG) will **not** be reported or assessed as an AE unless that value is considered to be of clinical significance by the investigator. A value of clinical significance is one that leads to discontinuation or delay in protocol treatment, dose modification, therapeutic intervention*, or is considered to be a clinically significant new finding or change from baseline by the investigator.

*Transfusion support administered to offset clinical symptoms of anemia or thrombocytopenia will not be considered therapeutic intervention.

Signs and Symptoms

Signs/symptoms resulting from an underlying clinical diagnosis should be documented as one comprehensive AE. If no underlying clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event. (A new or worsening event resulting from an underlying clinical diagnosis or a reaction to concurrent medications should be documented as a separate independent AE unless it is within the normal range of fluctuation for that patient.)

Grade Changes/Fluctuations

AEs will be reported at the maximum grade/severity experienced for the duration of the event. Should one particular event warrant further investigation, additional details may be collected at the discretion of the PI.

Progression of Disease

Progression of disease (PD), if documented in accordance to standard of care, should not be reported as an AE.

Tests and Procedures

Tests and procedures should not be reported as AEs. The underlying clinical diagnosis (or sign/symptom in the event an underlying clinical diagnosis is not known) requiring testing or a procedure should be reported as an AE if it meets criteria for reporting.

13.3 Serious Adverse Events (See also Appendix A.)

Serious AE (SAE) means any untoward medical occurrence that occurs at any dose:

1. **Results in death.**
2. **Is life-threatening.**
   The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
3. **Requires inpatient hospitalization or prolongation of present hospitalization.**
   Elective hospitalization to simplify protocol treatment/evaluations or to treat a baseline condition that did not worsen from baseline will not be considered an SAE.
4. **Results in persistent or significant disability/incapacity.**
   Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect.**
6. **Is a medically important event.**
   A medically important event may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, or involves suspected transmission via a medicinal product of an infectious agent. 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; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT synonymous. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually

associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

13.4 Adverse Event Collection Period

In this protocol, AE include only treatment-emergent AEs. A treatment-emergent adverse event (TEAE) is defined as any event that begins or worsens after the start of protocol treatment. All baseline-emergent AEs, any event that begins or worsens after completion of the informed consent but prior to the start of protocol treatment, should be reported as a Baseline/Comorbid Condition.

All AEs that occur ≤ 30 days of the last dose of study therapy will be reported as well as until end of treatment or end of safety follow up visit whichever occurs last. Resolution is defined as a return to baseline status or the stabilization of an event with the expectation that it will remain chronic. (Exception: If a patient begins an alternative therapy that confounds accurate assessment of AEs within ≤ 30 days of the last dose of study therapy, all AE collection will stop and any ongoing events closed out.)

13.5 Adverse Event Reporting Requirements

The information to be reported in AEs will be assessed by and assigned severity using the NCI CTCAE, Version 4.03. The NCI CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the NCI CTCAE v 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
Information to be reported in the description of each AE may be included, but is not limited to:

1. Clinical Diagnosis of the event as determined by NCI CTCAE, Version 4.03 descriptive terminology. If no clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event.
2. Date of onset of the AE (start date).
3. Date of resolution of the AE (end date).
4. Severity of the event as determined by NCI CTCAE, Version 4.03 grading scale.
5. Relationship of the AE to study therapy. Refer to NCI Guidelines for Investigators https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf which are categorized as follows:

Definite	The adverse event is clearly related to the investigational agent(s)
Probable	The adverse event is likely related to the investigational agent(s)
Possible	The adverse event may be related to the investigational agent(s)
Unlikely	The adverse event is doubtfully related to the investigational agent(s)
Unrelated	The adverse event is clearly not related to the investigational agent(s)

6. Whether or not the AE is Serious or Not Serious as defined in Section 13.3 Serious Adverse Events.
7. Whether the AE is Suspected and/or Unexpected. Refer to FDA Title 21 part 312. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

Suspected	Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
Unexpected	Any AE for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure or Package Insert.

8. Action taken as a result of the AE.
9. Outcome.

13.6 Expedited Adverse Event Reporting Requirements

All AEs, regardless if serious or not, will be described in the source documents, reported on the applicable AE page of the CRFs, and entered into *Velos*. However, certain AEs must also be reported in an expedited manner for timelier monitoring of patient safety and care. Appendix A provides information about these expedited reporting requirements.

13.7 Events of Clinical Interest

Not applicable.

14.0 STATISTICAL CONSIDERATIONS

14.1 Overview

The primary objective of this single-arm, open label, phase II study is to determine the pathologic objective response rate (CR + PR) in patients treated with pembrolizumab, paclitaxel and carboplatin for advanced stage III or IV EOC. Pathologic objective response will be assessed at time of IDS.

Secondary objectives of this study include (1) determine treatment-related toxicity and (2) PFS in patients with advanced Stage III or IV EOC treated with pembrolizumab, paclitaxel and carboplatin.

In addition, the study exploratory objectives are as follows: (1) determine if an immunologic profile (defined as an increased intra-tumor infiltration of perforin+ CD8+ T lymphocytes) may be a useful predictive biomarker of response and PFS; (2) define changes in tumor and blood biomarkers such as but not limited to, CD3, CD4, CD8, PD-L1, PD-1, FOXP3) after treatment and its correlation with pathological and radiological response to therapy.

Analysis of primary and secondary endpoints will be based on all evaluable patients as defined in Section 14.2. Sample size justification of 40 patients is provided in Section 14.3.

In addition, Section 15.2 provides early stopping guidelines for monitoring toxicity and pathologic response on a continuous basis throughout the course of the trial. The stopping boundaries were determined using Bayesian posterior probability methodology; thus, they can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed or the number of evaluable patients at the time such assessments are made.[51, 52] The early stopping guidelines are offered for the Data Safety and Monitoring Committee (DSMC) consideration in its review of accumulating study data assessing AEs and treatment response. The number of interim analyses is unknown, but they occurred at times requested by the DSMC. The DSMC may recommend to stop enrollment to a study if at an interim analysis there is evidence of harm that is, evidence of high rate of unacceptable toxicity or low response rate (lack of efficacy).

14.2 Definitions and Study Endpoints

Evaluable for safety and toxicity: Study eligible patients who receive at least one dose of pembrolizumab in combination with paclitaxel and carboplatin.

Evaluable for pathologic objective response: Study eligible patients who receive at least one dose of pembrolizumab in combination with paclitaxel and carboplatin and have tissue collected at baseline and at IDS.

***Exclusions*:** Any patient who is enrolled on study but does not receive any dose of proposed NACT (pembrolizumab in combination with paclitaxel and carboplatin) will be excluded from all efficacy analyses. Any patient who initiates treatment and is later found to be ineligible for study (e.g., protocol violation) will be withdrawn from study but will be followed for toxicity and disease progression; the experience of such patients will be characterized separately from that of evaluable patients. Reasons for exclusion of enrolled patients from the analysis set for safety will be characterized.

Main Endpoints (see more details in sections 3 and 14):

Pathologic objective response rate (pORR): the proportion of patients with best overall response of pathologic complete or partial responses; that is, pORR = (pCR + pPR)/n.

Progression-free survival (PFS): Measured from date of start of treatment to the earliest occurrence of any of the following events: documented disease progression or death from any cause. Patients who are alive and progression-free will be censored at the date of last documented progression-free status which is the date of last tumor assessment according to RECIST v1.1.[47]

14.3 Patient Enrollment, Follow-Up, and Sample Size Justification

In this single-arm phase II study, we plan to enroll a **maximum of 40 evaluable patients.** Based on our institution's enrollment capacity, we anticipate successful enrollment of 40 patients in approximately 36 months with an estimated 1-2 patients per month. The expected study duration is 4 years including a desirable minimum follow up of 2 years. Of note, as described in Section **15, *enrollment to study will stop early*** with less than 40 patients if there is evidence of high rate of unacceptable toxicity at any interim monitoring as determined by the SCCC DSMC.

The **planned sample size of 40 evaluable patients** provides reasonable precision as illustrated by considering the width of the 95% confidence interval (CI) estimate for the rate of pathologic objective response, pORR = (pCR + pPR)/n. Based on available literature, we estimate that the pORR for carboplatin and paclitaxel is about 4-6%.[3,32] We expect that the addition of pembrolizumab to paclitaxel and carboplatin will improve pORR to 10-15%. Table 14.3.1 illustrates point estimates and corresponding precisions for possible outcomes in the expected range for the true pathologic objective response rate (pORR).

Table 14.3.1. Precision on potential study findings for pORR with 40 evaluable patients

Number of pCR + pPR	pORR	95% CI
5	12.5%	4.2 – 26.8%
6	15%	5.7 – 29.8%
7	17.5%	7.3 – 32.8%
8	20%	9.1 – 35.6%
9	22.5%	10.8 – 38.5%

95% CI: 95% confidence interval using binomial method.

In terms of study power, our study size of 40 patients provides 74% power to detect a difference of 10% between pORRs of 5% and 15% under the null and alternative hypotheses respectively using a one-sided binomial test at a target 5% significance level. The actual significance level achieved by this test is 4.8%. Our study with 40 patient provides 85% power to detect a difference of 12.5%, comparing pathologic

objective response rates 5% versus 17.5% for null and alternative hypotheses, respectively. [53]

Note: We plan one interim analysis after enrollment of 20 evaluable patients to assess futility. See Section 14.2.2. This power calculation does not take into account this planned interim analysis and the unknown number of interim analysis of pathologic response, which are determined by the DSMC. In addition, the DSMC may also recommend to stop enrollment to the study if at an interim analysis there is evidence of harm that is, evidence of high rate of unacceptable toxicity.

14.4 Planned Statistical Analysis

Statistical analysis will be based on evaluable patients as defined in Section 14.2. Baseline characteristics will be summarized using descriptive statistics: counts and percentages, ranges, median, mean, and standard deviation as appropriate. This will include demographics (age, weight, and race/ethnicity), performance status, time since diagnosis, and prior treatment.

Safety analysis will include detailed tabulation of worst toxicity and toxicity by type, grade, duration, and attribution to treatment (unrelated, unlikely, possible, probable, or definite) using the NCI CTCAE version 4.03.

Pathologic objective response rate, pORR = (pCR + pPR)/n, and the rates of individual categories pCR and pPR as defined in section 14.0, will be reported with corresponding 95% confidence intervals (95% CIs) using the binomial method.[54]

The Kaplan-Meier method will be used to estimate and plot PFS.[55] Point estimates with corresponding 95% CI for the proportion of progression-free and surviving patients will be given for selected times, such as 6 and 12, 18, and 24 months. Median time to progression and median survival time, if attained, will also be reported.

Logistic regression will be utilized to assess the effect of patient prognostic factors on the pORR and endpoints.[56] To the extent that it is possible with small sample size, comparison of PFS by important subgroups will be made using the log-rank test, and Cox proportional hazard regression will be employed for univariate and multivariable analysis of PFS. [57] Potential prognostic factors also include endpoints addressing exploratory objectives; for example, change in in perforin^{+}CD8^{+} tumor infiltrating T cells measured in tissue or blood at laparoscopy and at debulking surgery and change in tumor/blood biomarker (such as but not limited to CD3, CD4, CD8, PD-L1, PD-1, FOXP3).

Methods for analysis of longitudinal data, such as repeated measures analysis of variance (ANOVA), linear models, generalized mixed models, and profile plots will be employed to assess differences over time and to compare subgroups defined by key patient characteristics. [58] Genetic panel testing will be descriptive and evaluated in all patients as per institutional practice.

15.0 DATA REPORTING

Data must be submitted according to the protocol requirements for all patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

15.1 Data and Safety Monitoring

The SCCC DSMC will monitor this clinical trial according to the SCCC's data and safety monitoring (DSM) plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. DSMC oversight of the conduct of this trial includes ongoing review of accrual and AE data and periodic review of the study therapy efficacy. The guidelines appearing in the Section 17.2 are offered for DSMC consideration in assessing AEs and pathologic objective response. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The SCCC DSM Plan to which this study is subject can also be found at www.sylvester.org.

15.2 Stopping Rules

We propose the following guidelines for DSMC consideration in its review of accumulating study data. The proposed guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of evaluable patients at the time such assessments are made. [51, 52] Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true response rate and similarly a prior distribution for the true toxicity rate. As treatment response and toxicity data on study patients become available, each of these prior probability distributions is revised and the resulting posterior probabilities become the basis for recommending either early termination or continuation of the study. The following sections provide specific stopping guidelines and underlying assumptions for the prior distributions.

15.2.1 Early Stopping Due to Toxicity

The clinical investigators and the SCCC DSMC will monitor the study patients for study-related toxicities. Toxicities encountered in this trial will be reported according to the NCI CTCAE, version 4.03.

If a treatment-related (possible, probable, or definite) death occurs, enrollment will be suspended and continuation of the study will be reassessed by the DSMC.

For the purposes of safety monitoring, we define unacceptable toxicity to be any treatment-related (possible, probable, or definite) grade 3 or higher toxicity **due to pembrolizumab.** For instance, SJS or TEN would be considered unacceptable and would be assigned treatment-related attribution either possible, probable or definite**.** Toxicity due to chemotherapy alone occurs commonly including grades 3/4 (neutropenia, anemia,

etc.) and is acceptable. Unacceptable toxicity is expected to occur in no more than 25% of patients. If there is evidence that the true rate of unacceptable toxicity exceeds 25%, then the study will be suspended and possibly terminated early. Specifically, we suggest as a guideline for early termination a posterior probability of 80% or higher that the true rate exceeds 25%. The table below shows specific instances where this guideline is met, suggesting early termination due to evidence of excessive unacceptable toxicity.

Table 15.2.1.1. Stopping boundaries for toxicity

(Stop if the number of unacceptable toxicity in N evaluable patients is more than or equal to X.)

X: Number (%) of patients with unacceptable toxicity*	**N: total evaluable patients assessed for toxicity**	**Observed unacceptable toxicity rate ≥**
3	4 to 7	42.9%
4	8 to 10	40.0%
5	11 to 13	38.5%
6	14 to 17	35.3%
7	18 to 20	35.0%
8	21 to 23	34.8%
9	24 to 27	33.3%
10	28 to 31	32.3%
11	32 to 34	32.4%
12	35 to 38	31.6%
13	39 to 39	33.3%

*: Possible, probable, or definite treatment-related grade 3 toxicity.

To illustrate the stopping guidelines, suppose that 10 evaluable patients have been assessed for toxicity and 5 of them have experienced grade 3 treatment-related toxicity (row 2 of the above table). Under this circumstance, the observed rate of grade 3+ of such toxicity is 50%, resulting in a posterior probability of >90% that the true underlying rate exceeds 25%, thereby suggesting early termination.

Posterior probabilities for the above table are calculated under a weak prior beta distribution with parameters $\beta_1 = 0.5$ and $\beta_2 = 1.5$, which corresponds to an expected unacceptable-toxicity rate of 25% based on very limited information roughly equal to having studied 2 patients. This prior distribution implies also *a priori* chance of 39.1% that true rate of unacceptable toxicity is 25% or greater.

15.2.2 Early Stopping Due to Lack of Efficacy.

We plan one interim analysis to assess futility. Available literature indicates that the pORR = pCR + pPR) for carboplatin and paclitaxel is about 4-6%, and we expect that the addition of pembrolizumab to paclitaxel and carboplatin will improve pORR to 10-15%. Based on conservative stopping rule of ≥90% posterior probability that pORR is less than 4%, the study will be terminated early when there are no pORR observed among the first 20 evaluable patients. This posterior probability was calculated under a weak prior beta distribution with parameters $\beta 1 = 0.3$ and $\beta 2 = 1.7$, which corresponds to an expected

response rate of 15%, and roughly equal to having studied 2 patients. This prior distribution implies a priori chance of 46.2% that true response rate is 4% or less.

16.0 STUDY AUDITING AND MONITORING

This study will be audited and/or monitored (as applicable) according to the University of Miami requirements. See also http://researchedu.med.miami.edu/regulatory-compliance-services and http://research.med.miami.edu/clinical-research/crors.

17.0 INVESTIGATOR RESPONSIBILITIES

17.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects. The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

17.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

17.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian. The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor-Investigator, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

17.4 Source Documentation and Investigator Files

The Investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. Subject clinical source documents may include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, electroencephalogram (EEG), radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file.

17.5 Recording and Processing of Data

If using hard copies of CRFs, study center personnel will complete individual CRFs in black ink. All corrections to entered data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. The use of "white-out" or obscuring correction tape will be prohibited. A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRFs are accurate, complete, legible and timely. Separate source records are required to support all CRF entries except those for which use of the CRF as source document is clearly allowed per note in the investigator study file.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

17.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

17.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

UM Ethics Programs' Research Ethics Consultation Service (RECS) is a free resource for UM Researchers. See the website for further information: https://bioethics.miami.edu/clinical-and-research-ethics/research-ethics-consultation-service/index.html.

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. This study will

create, utilize and file all essential documents following Good Clinical Practice (GCP) and the institution's standard operating procedures.

REFERENCES

1. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1994; **12**(9): 1748-53.
2. Trimble EL, Adams JD, Vena D, et al. Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1993; **11**(12): 2405-10.
3. Seewaldt VL, Greer BE, Cain JM, et al. Paclitaxel (Taxol) treatment for refractory ovarian cancer: phase II clinical trial. *American journal of obstetrics and gynecology* 1994; **170**(6): 1666-70; discussion 70-1.
4. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *The New England journal of medicine* 2010; **363**(10): 943-53.
5. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015; **386**(9990): 249-57.
6. Morice P, Brehier-Ollive D, Rey A, et al. Results of interval debulking surgery in advanced stage ovarian cancer: an exposed-non-exposed study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2003; **14**(1): 74-7.
7. Hou JY, Kelly MG, Yu H, et al. Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease. *Gynecologic oncology* 2007; **105**(1): 211-7.
8. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. *Gynecologic oncology* 2013; **130**(3): 493-8.
9. Petrillo M, Zannoni GF, Tortorella L, et al. Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer. *American journal of obstetrics and gynecology* 2014; **211**(6): 632 e1-8.
10. Colombo PE, Labaki M, Fabbro M, et al. Impact of neoadjuvant chemotherapy cycles prior to interval surgery in patients with advanced epithelial ovarian cancer. *Gynecologic oncology* 2014; **135**(2): 223-30.
11. Bohm S, Faruqi A, Said I, et al. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(22): 2457-63.
12. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? *Gynecologic oncology* 2006; **103**(2): 559-64.
13. Tian WJ, Jiang R, Cheng X, Tang J, Xing Y, Zang RY. Surgery in recurrent epithelial ovarian cancer: benefits on Survival for patients with residual disease of 0.1-1 cm after secondary cytoreduction. *Journal of surgical oncology* 2010; **101**(3): 244-50.

14. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecologic oncology* 2009; **112**(1): 265-74.
15. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunological reviews* 2010; **236**: 219-42.
16. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunological reviews* 2008; **224**: 166-82.
17. Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. *Seminars in oncology* 2010; **37**(5): 430-9.
18. Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. *Nature reviews Drug discovery* 2015; **14**(8): 561-84.
19. Gubin MM, Zhang X, Schuster H, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature* 2014; **515**(7528): 577-81.
20. Ngiow SF, Young A, Jacquelot N, et al. A threshold level of intratumor CD8+ T cell PD1 expression dictates therapeutic response to anti-PD1. *Cancer research* 2015.
21. Gowrishankar K, Gunatilake D, Gallagher SJ, Tiffen J, Rizos H, Hersey P. Inducible but not constitutive expression of PD-L1 in human melanoma cells is dependent on activation of NF-kappaB. *PloS one* 2015; **10**(4): e0123410.
22. Hersey P, Gowrishankar K. Pembrolizumab joins the anti-PD-1 armamentarium in the treatment of melanoma. *Future oncology* 2015; **11**(1): 133-40.
23. Merritt WM, Lin YG, Han LY, Kamat AA, Spannuth WA, Schmandt R, Urbauer D, Pennacchio LA, Cheng JF, Nick AM, Deavers MT, Mourad-Zeidan, A, and 10 others. Dicer, Drosha, and outcomes in patients with ovarian cancer. New Eng. J. Med 2008; 359: 2641-2650. Note: Erratum: New Eng. J. Med. 363: 1877 only, 2010.
24. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Maiuri MC, Ullrich E, Saulnier P, Yang H, Amigorena S, Ryffel B, Barrat FJ, Saftig P, Levi F, Lidereau R, Nogues C, Mira JP, Chompret A, Joulin V, Clavel-Chapelon F, Bourhis J, André F, Delaloge S, Tursz T, Kroemer G, Zitvogel L Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat. Med.* 2007; **13**, 1050–105910.1038/nm1622
25. Polcher M, Braun M, Friedrichs N, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer immunology, immunotherapy: CII 2010; 59(6): 909-19.
26. Ladoire S, Mignot G, Dabakuyo S, et al. In situ immune response after neoadjuvant chemotherapy for breast cancer predicts survival. The Journal of pathology 2011; 224(3): 389-400.
27. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *The New England journal of medicine* 2012; **366**(26): 2455-65.
28. Varga A, Piha-Paul S, Ott PA, Mehnert JM, Berton-Rigaud D, Morosky A, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. *Gynecol Oncol* 2019; **152**(2): 243-250.

29. Maine CJ, Abdul Aziz NH, Chatterjee, J, Hayford C, Brewig, N, Whilding, L, George, AJT, Ghaem-Maghami, S. Programmed death ligand-1 over-expression correlates with malignancy and contributes to immune regulation in ovarian cancer. *Cancer Immunol Immunother* 2013; **63**(3): 215-224.
30. Investigator's Brochure. Investigator's Brochure for Pembrolizumab (Keytruda). Merck; 2 Sept 2021, 2021.
31. Rosenberg P, Andersson H, Boman K, Ridderheim M, Bengt S, Puistola U, Parö G. Randomized Trial of Single Agent Paclitaxel Given Weekly Versus Every Three Weeks and with Peroral Versus Intravenous Steroid Premedication to Patients with Ovarian Cancer Previously Treated with Platinum, Acta Oncologica 2002; 41:5, 418-424.
32. Katsumata N, Yasuda M, Isonishi S, Takahashi F, Michimae H, Kimura E, Aoki D. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol 2013; 14: 1020–26.
33. Rodriguez N, Miller A, Richard SD, Rungruang B, Hamilton CA, Bookman MA, et al. Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: An analysis of Gynecologic Oncology Group (GOG) 182. *Gynecol Oncol* 2013; **130**(3): 487-92.
34. Robert C, Ribas A, Wolchok JD, Hodi S, Hamid O, Kefford R, Weber JS, Joshua AM, Hwu WJ, Gangadhar TC, Patnaik A, Dronca R, Zarour H and 10 others. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *The Lancet*, 2014; **384**(9948):1109-1117.
35. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, Hodi FS, Schachter J, Pavlick AC, Lewis KD, Cranmer LD, Blank CU, O'Day SJ, Ascierto PA, Salama AKS, Margolin KA, Loquai C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* 2015; 16: 908–18
36. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, et al for the KEYNOTE-001 Investigators. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *N Engl J Med* 2015; 372:2018-2028.
37. Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov. 2015 Aug;14(8):561-84.
38. Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, Ivanova Y, Hundal J, Arthur CD, Krebber WJ, Mulder GE, Toebes M, Vesley MD, Lam SS, Korman AJ, Allison JP, Freeman GJ, Sharpe AH, Pearce EL, Schumacher TN, Aebersold R, Rammensee HG, Melief CJ, Mardis ER, Gillanders WE, Artymov MN, Schreiber RD. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. Nature 2014 Nov 27;515(7528):577-81.

39. Budiu RA, Mantia-Smaldone G, Elishaev E, et al. Soluble MUC1 and serum MUC1-specific antibodies are potential prognostic biomarkers for platinum-resistant ovarian cancer. *Cancer immunology, immunotherapy : CII* 2011; **60**(7): 975-84.
40. Katoh H, Watanabe M. Myeloid-derived suppressor cells and therapeutic strategies in cancer. *Mediators Inflamm* 2015; 2015: 159269.
41. Qian F, Liao J, Villella J, et al. Effects of 1-methyltryptophan stereoisomers on IDO2 enzyme activity and IDO2-mediated arrest of human T cell proliferation. *Cancer immunology, immunotherapy : CII* 2012; **61**(11): 2013-20.
42. Vlad AM, Budiu RA, Lenzner DE, et al. A phase II trial of intraperitoneal interleukin-2 in patients with platinum-resistant or platinum-refractory ovarian cancer. *Cancer immunology, immunotherapy : CII* 2010; **59**(2): 293-301.
43. Budiu RA, Elishaev E, Brozick J, et al. Immunobiology of human mucin 1 in a preclinical ovarian tumor model. *Oncogene* 2013; **32**(32): 3664-75.
44. Budiu RA, Diaconu I, Chrissluis R, Dricu A, Edwards RP, Vlad AM. A conditional mouse model for human MUC1-positive endometriosis shows the presence of anti-MUC1 antibodies and Foxp3+ regulatory T cells. *Disease models & mechanisms* 2009; **2**(11-12): 593-603.
45. Suryawanshi S, Vlad AM, Lin HM, et al. Plasma microRNAs as novel biomarkers for endometriosis and endometriosis-associated ovarian cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2013; **19**(5): 1213-24.
46. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.
47. Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst* 2004; **96**(6): 487-8.
48. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999; **17**(11): 3461-7. doi: 10.1200/JCO.1999.17.11.3461. Erratum in: *J Clin Oncol* 2000; **18**(13): 2644. Erratum in: *J Clin Oncol* 2007; **25**(9): 1154. Erratum in: *J Clin Oncol* 2013; **31**(13): 1702.
49. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **26**(7): 1148-59.
50. Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. *J Natl Cancer Inst* 2000; **92**(18): 1534-5.
51. Spiegelhalter DJ, Freedman LS, Parmar MK. Bayesian approaches to randomized trials (with discussion). J Royal Stat Soc Ser A 1994; 157:357-416.

52. Fayers PM, Ashby D, Parmar MKB. Tutorial in biostatistics: Bayesian data monitoring in clinical trials. Stat Med 1997;16:1413 - 30.
53. Hintze, J. (2014). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.
54. Hosmer DW and Lemeshow S. Applied Logistic Regression, 2nd ed. Wiley, New York, 2000.
55. Armitage P, Berry G, and Matthews J N. Statistical Methods in Medical Research, Fourth Edition. Oxford: Blackwell Scientific, 2001.
56. Machin D, Cheung YB, and Parmar MKB. Survival Analysis: A Practical Approach. Second Edition, Cambridge, UK: John Wiley & Sons, 2006.
57. Brown H, Prescott. Applied Mixed Models in Medicine. New York: Wiley, 1999.
58. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993 Mar; **85**(5):365-76.

APPENDIX A: EXPEDITED ADVERSE EVENT (AE) REPORTING REQUIREMENTS

For all AEs that meet criteria for expedited reporting, the PI is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached (i.e., for the duration specified in the protocol) or the patient is lost to follow-up.

The PI and all applicable research study team members should become familiar with the safety profile of the investigational agent(s) and/or intervention at the start of the study and for the duration of the research, e.g., by reviewing the Investigator's Brochure and any Safety Reports released by the Sponsor as applicable.

I. FDA Expedited Reporting

A. Sponsor-Investigators i.e., IND Holders, have additional reporting requirements to the FDA and other committees and should consult the applicable regulations and agency guidelines for these requirements.

B. Since this protocol involves the use of FDA IND agent(s), completion of the FDA MedWatch 3500A Reporting Form is required for Sponsor-Investigators. The Form can be obtained electronically at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

1. All serious, unexpected (unanticipated) and suspected adverse events must be directly reported to the FDA within 15 calendar days of being made known to the PI.

2. All fatal or life-threatening AEs must be directly reported to the FDA within 7 calendar days of being made known to the PI.

C. For more information regarding reporting to the FDA, please refer to the FDA website for REPORTING GUIDELINES: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

II. IRB Expedited Reporting

A. All Investigators should also be aware of local Institutional requirements for AE reporting. For more information regarding the IRB policy, please refer to the University of Miami's Human Subjects Research Office (HSRO)'s Investigator Manual: https://hsro.uresearch.miami.edu/_assets/pdf/hrp-103---investigator-manual---rev022717.pdf and the UM HSRO SOP on New Information (HRP-024) https://eprost.med.miami.edu/eProst/Doc/0/HLJ5OTJVQEH419E0I6QPT3B199/HRP-024%20-%20SOP%20-%20New%20Information.docx

B. All AEs that are serious, unanticipated and possibly related will be reported to the IRB within ten (10) working days of being made known to the PI.

C. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the PI.

D. All unanticipated deaths must be reported to the IRB within 24 hours of being made known to the PI.

III. Merck Expedited Reporting

A. In addition to the mandatory MedWatch 3500A Form, the PI is also required to comply with all reporting requirements as supplied by the Investigational Drug Sponsor: Merck.

B. Any SAE or follow up to an SAE 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, and whether or not related to Merck product must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety.

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

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

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

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

APPENDIX B: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX C: NYHA CLASSIFICATION OF HEART DISEASE

New York Heart Association (NYHA) classification of heart disease;
https://manual.jointcommission.org/releases/TJC2016A/DataElem0439.html

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

APPENDIX D: BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

Samples will be processed and stored at the University of Miami's (UM) Biospecimen Shared Resource (BSSR). Biomarker analysis (PDL-1) will be performed by QualTek Molecular Laboratories. Additional biomarker analysis will be performed as deemed by Abdulrahman Sinno, MD.

1. Email Notification

Abdulrahman Sinno, MD (PI) should be contacted via email to notify her of all specimen submissions for banking. The subject line should read "NACT+Pembro_EOC_Biospecimen Banking".

PI: ak.sinno@med.miami.edu to

Tissue Banking Facility: bssr@med.miami.edu

2. Blood samples collection

Collection of blood will be performed pre-treatment, on treatment (before pembrolizumab infusion) and post-treatment.

Plasma and blood monocytes will be obtained, aliquoted and stored following the Standard Operating Procedures (SOP) for handling the blood samples.

3. Tissue samples collection

Collection of tissue samples will be performed pre-treatment (laparoscopy or needle core biopsy) and at IDS.

For each time point, two specimens will be collected. The first one will be fixed in formalin and submitted to the Pathology Department for paraffin embedding and the second one will be immediately frozen for molecular profiling.

A sample of normal tissue will be also collected preferable at pre-treatment (laparoscopy or needle core biopsy). Alternatively, this sample can be collected at IDS.

4. Sample Banking

Upon collection of the tissue samples from the patients, a code system will be used to de-identify all samples, assigning a unique code to each specimen. The samples will be tied to patient-identifying information only at the time of sample collection. The patient's name will be written on the specimen collection case. Once the samples are de-identified, which will happen as soon as the specimen arrive in the BSSR, the patient's name will be blacked out on the original sample

case and the original casing will be discarded in biohazardous waste, which is subsequently sent for incineration. Samples will be then identified with a code identified (study number). The list where patient's names will be tied to their code will be kept on a password protected computer in the BSSR. The only information that will be stored with the actual samples in the bank is the code identifier used to identify each sample. No samples will be accepted into the bank unless the subject's signed consent form has first been submitted. The only investigator who will have access to samples and data being kept in the bank is Abdulrahman Sinno, MD.

Samples in the bank will be stored indefinitely, or until the patient withdraws consent for inclusion in the protocol. At that time, all samples and data will be destroyed.

Specimen Storage Conditions

- FFPE blocks will be stored at room temperature 15-25°C
- Plasma and blood monocytes will be stored in a -80°C freezer
- Flash frozen samples will be stored in liquid nitrogen (-150°C)
- DNA/RNA will be stored in a -80°C freezer

Contact Information
Biospecimen Shared Resource
Rosenstiel Medical Science Building
1600 NW 10th Avenue, Suite 4051
Miami, FL 33136
Phone: 305-243-6777
Email: bssr@med.miami.edu

5. Biomarker Analysis

PDL1 biomarker measurements will be performed at the end of study. Five (5) unstained slides cut from an FFPE block will be provided to QualTek as described below.

5.1 Sample Requirements

1. For patient samples, the provided positively charged ProbeOn Plus slides **(Fisher ProbeOn Plus Catalog Number 22-230-900)** must be used for tissue sections. Slide measurements are 75mm x 25mm x 1mm (other slide sizes cannot be accommodated). In the event this requirement cannot be met, please contact QualTek to discuss alternative options.

2. Tumor tissue for biomarker analysis must be provided as **five (5) unstained slides** cut from an FFPE tissue block. Five (5) sectioned slides per patient are *required* for PD-L1 testing. If additional markers beyond PD-L1 are required to be tested as per the service contract established between QualTek and the Investigator Site, 5 additional sections per marker will be required.

3. Samples may be held as blocks indefinitely at the site and then cut in batches. Slides must be shipped to QualTek immediately after sectioning to comply with the protocol's testing requirements. If patient slides are not received by QualTek within seven (7) days of sectioning, new sections may be requested and additional processing charges may be assessed.

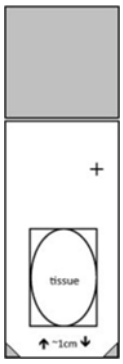
4. As per Merck protocol requirements, sectioned slides must be shipped cold (2-8°C) and in the dark using the shipping materials provided by QualTek **pages 7-8**. Be advised that slides received that do not meet these conditions may affect PD-L1 staining.

5. Sectioned slides provided should contain tumor specimen sufficient for pathology review and analysis of tumor sample. If available, greater than 50% tumor content is preferred.

6. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, lavage specimen, frozen sample, plastic embedded sample, or formalin fixed sample that was frozen at any point **will not be accepted** for IHC analysis. Needle core biopsies that are formalin-fixed and paraffin-embedded are acceptable.

5.2 Sectioning of Tissue onto ProbeOn Plus Slides from Formalin-Fixed, Paraffin-Embedded (FFPE) Block(s)

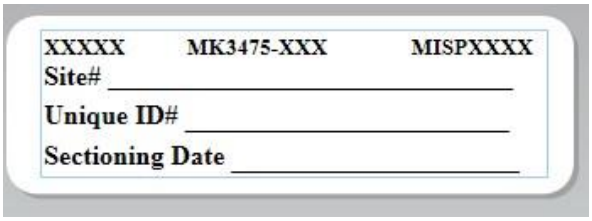
1. Prepare exactly **five (5)** freshly-cut serial sections at 4 micron thickness onto the provided Fisher ProbeOn Plus Slides, Cat Number 22-230-900. Sections must be placed on the painted/textured side of the slide.
    - Other standard-sized positively-charged slides (75mm x 25 mm x 1mm) are acceptable as a last resort, however, QualTek must be notified as there is a risk that outside slides cannot be stained. The slides must be sized as described above or the sample **cannot be tested and will be returned.**
    - No adhesives should be used in the water bath since the slides are positively-charged.
2. Ensure that the sample has the institutional block ID clearly marked on each slide as well as the slide section levels, if possible.
    - **Ensure that the block ID is referenced on the manifest**
    - Note that the sample must be labeled with 2 patient identifiers (Refer to the label provided for the slide holder)



3. When placing the sections onto the slides, ensure that the tissue is towards the bottom third of the slide as pictured at right.
    - Ensure tissue sections are oriented the same direction on all slides.
    - No adhesive labels directly on slides. Slide / patient identifiers must be hand written with indelible / chemical proof ink.
    - Number the slides sequentially (serially), one section per slide.
4. **DO NOT OVEN DRY SLIDES.** Air dry until completely dry (12-24 hours).
5. Complete an electronic Sample Manifest for each shipment (Excel Spreadsheet provided by QualTek to the Site Contact at study initiation).
    - Email the completed electronic manifest prior to shipment to: **MISPsamples@qmlabs.com**
    - Make a copy of the manifest to include with the sample(s)
    - Retain the original at the site for your records
6. Email or a de-identified (redacted) pathology report(s) if available. Write the block ID on the top of each page of the pathology report
7. Prepare samples for shipping as detailed on **pages 5-6.**

5.3 Packaging Instructions for Formalin-Fixed Paraffin Embedded Slides

1. Affix and complete the label provided for the slide holder with Unique Patient ID number, Site Number/Identifier and Sectioning Date using indelible ink. Ensuring that the patient identifiers on the slide holder match the patient slides.



Top line of the label are the Study Identifiers and will be pre-printed for the specific study
Left - Investigator Study Number
Center – Merck Protocol Number
Right – QualTek Project Number

2. Place the newly sectioned slides (air dried until completely dry (12-24 hours), exactly five (5) slides, into the labeled slide holder. Ensure only one patient per slide holder.
3. Place the piece of small foam between the top of the slides and the holder's lid to prevent the slides from breaking. Tape the lid closed.
4. Insert the slide holders into the Amber UV bag labeled as "Biohazard" and seal the bag.
5. Place the Amber UV bag into a bubble wrap bag, or wrap in a sheet of bubble wrap.
6. More than one shipping box size may have been provided, choose the appropriate size as follows:
    - If shipping 1 patient slide holder:

      Use a 9x12 Insulated Shipping mailer. Place 1 freezer pack in the cooler liner, place the bubble wrap bag containing slides on top of the freezer pack.
    - If shipping between 2 and 10 patient slide holders:

      Use a 10x10x10 Shipping box and cooler box liner. Place 1 freezer pack on the bottom of the cooler liner, place the bubble wrap bag containing slides on top of the freezer pack and include 1 freezer pack on top of the bubble wrap bag.
    - If shipping between 11 and 20 patient slides holders:

      Use a 12x12x12 shipping box and cooler box liner. Place 2 freezer packs on the bottom of the cooler liner place the bubble wrap bag containing the slides on top of the freezer pack and include 2 freezer packs on top of the bubble wrap bag.
7. Fill remaining space with appropriate cushioning, i.e., additional bubble wrap or other packing material. For extreme temperature conditions, additional ice packs may be required. Samples must be shipped cold (2-8°C) and in the dark.
8. Enclose the de-identified (redacted) pathology report and the Sample Manifest, ensure that an electronic copy of the Manifest has been emailed to MISPsamples@qmlabs.com
9. Seal the mailer/box to ensure it will not open during shipping. Package & ship same day to QualTek.

10. Complete the pre-printed air bill provided by QualTek with sender information.
11. Verify correct shipping address as:

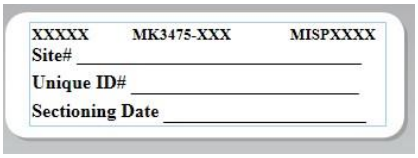
QualTek Molecular Laboratories
MISP Receiving
300 Pheasant Run
Newtown, PA USA 18940

12. Adhere the pre-printed air bill to the top of the shipping mailer/box.
13. Ship **Standard Overnight** Monday through Thursday, do not ship Friday, Saturday or Sunday.

5.4 Investigator Studies Supply List for FFPE Sectioned Slides Shipping to QualTek

The following supplies, or their equivalent, will be provided by QualTek:

Positively charged microscope slides used for sectioning of slides (5 per patient) Fisher ProbeOn Plus 25mm x 75mm x 1mm Capillary Gap Microscope Slides catalog 22-230-900 http://www.fishersci.com	
Plastic slide holders (1 per patient, each hold maximum of 5 slides) Catalog 12-587-17B http://www.fishersci.com	
Paraffin embedding cassette sponge to cushion slides in the plastic slide holder during shipping "square" biopsy foam pad sized 1 7/8" x 1" x 1/16" (catalog 60872-492) http://us.vwr.com	
Amber UV bags with biohazard sticker (to keep the slides in dark) Amber UV bag (6x8 Inches) – catalog 89005-326 http://us.vwr.com Biohazard Sticker – catalog ML1022 http://www.marketlab.com	

Shippers 9x12 (Mailer) *For shipping 1 sample holder* – catalog S18306 (http://www.uline.com) 10x10x10 *(Small) For shipping between 2 to 10 patient slide holders* – catalog s4105 (http://www.uline.com) 12x12x12 *(Large) For bulk shipments, between 11 to 20 patient slide holders* – catalog s18283 (http://www.uline.com) Insulated shippers – catalog s18282 (http://www.uline.com)	  
Cold Packs (12 oz. Ice Packs, 1 for the Mailer, 2 for the Small Shipper, 4 for the Large Shipper) Catalog s7889 http://www.uline.com	
Bubble wrap Catalog s-683 http://www.uline.com	
Miscellaneous Labels for the slide holders FedEx Pre-Printed Air bills Site Supply Inventory Sample Manifest Template (Excel Spreadsheet provided electronically to site contact)	

5.5 (EXAMPLE) Site Supply Inventory

Date	
QualTek Project #	
Investigator Study #	
Merck Protocol #	
Site Name	
Site Address	
Address Continued	

Quantity	**Description**	**Quantity**	**Description**
	Positively Charged Capillary Gap (ProbeOn Plus) Microscope Slides		Freezer Packs
	Plastic Five (5) Slide Holder (with small Foam Pad)		Fed-Ex Pre-Printed Air bill(s)
	Labels for Slide Holder		10x10x10 Shipping Box with Cooler Box Liner
	Amber UV Bags (labeled Biohazard)		12x12x12 Shipping Box with Cooler Box Liner
	Bubble Wrap Bags		Other (If Applicable)

5.6 Unpacking Instructions

1. Confirm material counts and check for breakage.
2. Remove freezer packs and place in freezer as soon as possible.
3. Retain all other materials for return of samples to QualTek Molecular Labs.
4. When ready to section, remove Positively Charged Capillary Gap (ProbeOn Plus) Microscope Slides from slide holder and use only this slide type for sectioning. Retain foam pad for repackaging.

APPENDIX E: CYP1A2, CYP2C8, CYP2C19, CYP3A4 SUBSTRATES, INHIBITORS & INDUCERS *

SUBSTRATE(S)				
1A2	*2C8*	*2C19*	*3A4,5,7*	
Amitriptyline caffeine clomipramine clozapine cyclobenzaprine duloxetine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine naproxen olanzapine ondansetron phenacetin→ acetaminophen→NAPQI propranolol riluzole ropivacaine tacrine theophylline tizanidine triamterene verapamil (R)warfarin zileuton zolmitriptan	[paclitaxel] torsemide amodiaquine cerivastatin repaglinide sorafinib	Proton Pump Inhibitors (PPIs): esomeprazole lansoprazole omeprazole pantoprazole rabeprazole Anti-epileptics: diazepam→Nor phenytoin(O) S-mephenytoin phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine chlopidogrel cyclophosphamide hexobarbital imipramine N-DeME indomethacin labetalol R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin→8-OH voriconazole	Macrolide antibiotics: clarithromycin erythromycin (not 3A5) *NOT azithromycin* telithromycin Anti-arrhythmics: quinidine→3OH (not 3A5) Benzodiazepines: alprazolam diazepam→3OH midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Antivirals: indinavir nelfinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine terfenadine Calcium Channel Blockers: amlodipine diltiazem felodipine lercanidipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin NOT pravastatin NOT rosuvastatin	Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone Miscellaneous: alfentanyl aprepitant aripiprazole boceprevir buspirone carbamazepine cafergot caffeine→TMU cilostazol cocaine codeine-N-demethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone nateglinide nevirapine ondansetron pimozide propranolol quetiapine quinine risperidone romidepsin NOT rosuvastatin salmeterol sildenafil sirolimus sorafenib tamoxifen taxol telaprevir

SUBSTRATE(S)			
1A2	*2C8*	*2C19*	*3A4,5,7*
			simvastatin terfenadine torisel trazodone vemurafenib vincristine zaleplon ziprasidone zolpidem
INHIBITORS			
1A2	*2C8*	*2C19*	*3A4,5,7*
fluvoxamine ciprofloxacin cimetidine amiodarone efavirenz fluoroquinolones fluvoxamine furafylline interferon methoxsalen mibefradil ticlopidine	gemfibrozil trimethoprim glitazones montelukast quercetin	<u>PPIs</u>: Esomeprazole lansoprazole omeprazole pantoprazole <u>Other</u>: rabeprazole chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oral contraceptives oxcarbazepine probenicid ticlopidine topiramate voriconazole	<u>HIV Antivirals</u>: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem cimetidine amiodarone NOT azithromycin Chloramphenicol boceprevir ciprofloxacin delaviridine diethyldithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir voriconazole
INDUCERS			
1A2	*2C8*	*2C19*	*3A4, 5, 7*
broccoli brussel sprouts carbanazepine char-grilled meat insulin methylcholanthrene modafinil	rifampin	carbamazepine nevirapine phenobarbital rifampin secobarbital St. John's Wort	<u>HIV Antivirals</u>: efavirenz nevirapine barbiturates carbamazepine glucocorticoids modafinil

INDUCERS			
1A2	*2C8*	*2C19*	*3A4, 5, 7*
nafcillin beta-naphthoflavone omeprazole rifampin tobacco			oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort troglitazone

*Reference): http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX F: PROTOCOL-APPROVED METHODS OF 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.

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range which may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female subjects of reproductive potential must agree to avoid becoming pregnant while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Combination method (requires use of **two** of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered

acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor-Investigator.

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.