Confidential

A Pilot Study Investigating the Effect of Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers of Müllerian Origin

DUKE CANCER INSTITUTE
A National Cancer Institute-designated Comprehensive Cancer Center

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1.0 TRIAL SUMMARY

Abbreviated Title	Change in immunoprofile after Pembrolizumab dose in gynecologic cancers
Trial Phase	0
Clinical Indication	Newly diagnosed gynecologic cancers of müllerian origin
Trial Type	Biomarker study
Type of control	None
Route of administration	IV
Trial Blinding	Unblinded
Treatment Groups	1
Number of trial subjects	15
Estimated enrollment period	18 months
Estimated duration of trial	2 years
Duration of Participation	18 months

2.0 TRIAL DESIGN

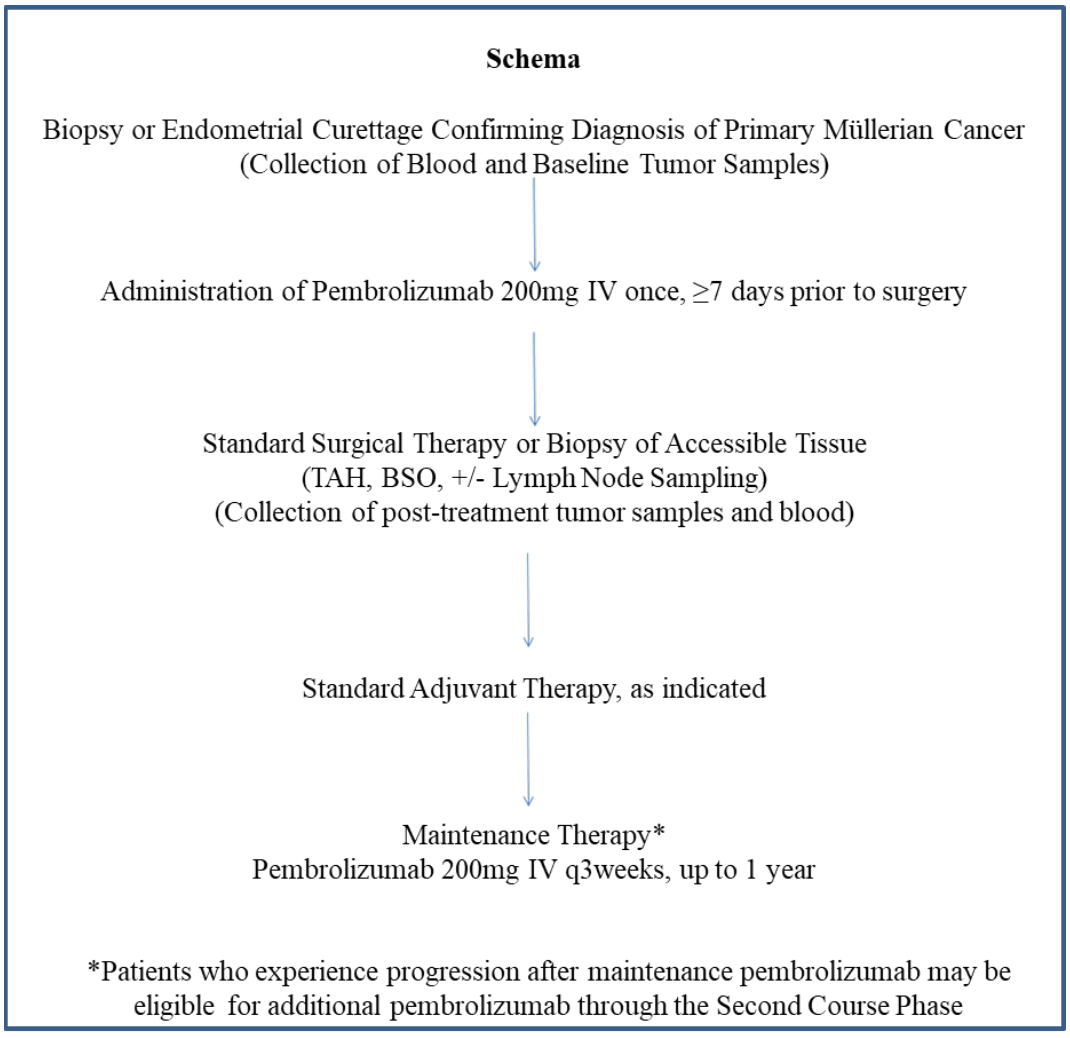
2.1 Trial Design

Patients with a gynecologic tumor of müllerian origin and no prior therapy for their current diagnosis will be eligible for the study. Patients will receive one dose of pembrolizumab at least 7 days prior to post-treatment surgery or biopsy. Patients will undergo standard surgical cytoreductive surgery as deemed appropriate by their gynecologic oncologist, followed by standard chemotherapy for their cancer as deemed appropriate by their treating physician. Follow-up after completion of therapy will be per institutional standard practice.

Patients already enrolled prior to amendment 5 will have the option of receiving maintenance pembrolizumab following completion of chemotherapy. Patients enrolled subsequent to the amendment will be required to receive maintenance pembrolizumab if they meet eligibility for pembrolizumab maintenance. Patients who experience radiographic disease progression after completion of maintenance pembrolizumab may be eligible for up to one year of additional

treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Efficacy Objective**: To assess the change in tumor immune infiltrates after administration of pembrolizumab.

Hypothesis: Tumor immune infiltrates will increase after administration of pembrolizumab.

Safety Objective: To evaluate the feasibility and toxicity profile of pembrolizumab when given to patients with newly diagnosed gynecologic cancers of müllerian origin prior to standard therapy and as maintenance therapy after completion of chemotherapy.

Hypothesis: Pembrolizumab will be well tolerated when given prior to standard chemotherapy +/- surgery and as maintenance after completion of chemotherapy in patients with gynecologic cancers of müllerian origin.

3.2 Exploratory Objective

(1) Objective: To characterize changes in the tumoral and circulating blood immunoprofile after administration of pembrolizumab. Levels of immune and inflammatory mediators, profile of tumor immune infiltrates, and the expression of PD-L1 in pre-administration samples will be compared to post-administration surgical resection (including ascites) or biopsy samples.

(2) Objective: For patients who enroll on the second course phase: To evaluate changes in the tumoral and circulating blood immunoprofile at time of recurrence. Levels of immune and inflammatory mediators, profile of tumor immune infiltrates, and the expression of PD-L1 in samples at time of recurrence will be compared to pre-administration and surgical or biopsy samples.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation

between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

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

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United

States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Epithelial gynecologic malignancies are tumors of müllerian origin, which include ovarian, endometrial, fallopian tube, and primary peritoneal cancers, and account for >70,000 new diagnoses and >22,000 deaths per year in the United States alone[1]. Treatment typically consists of a thorough cytoreductive and staging surgery in combination with platinum/taxane chemotherapy. Newer approaches adding anti-angiogenic therapies to chemotherapy have resulted in moderate improvements in recurrence free survival. However, despite these aggressive treatments, the majority of women with advanced stage at diagnosis will experience relapse. Unfortunately, relapsed disease is incurable and women ultimately die of their disease despite maximal efforts at cancer control using subsequent chemotherapy or targeted agents. There has been significant interest in incorporating immune checkpoint therapies in the treatment of gynecologic malignancies, especially given the durable remissions associated with these therapies in the treatment of melanoma and early indications of durable responses in recurrent ovarian cancer[2,3]. At this time, little is known about whether or how to combine chemotherapy, anti-angiogenic therapies, and immunologic therapies for maximal benefit. Understanding the tumor microenvironment, particularly immune and angiogenic factors that contribute to tumor survival, as well as the changes that occur in response to immunotherapy is critical to identify favorable biomarker profiles which could lead to improved prognostic outcomes and inform the development and sequencing of therapies to maximize benefit.

In this study, we propose to use immunohistochemical and molecular approaches to expand our current understanding of the effects of tumor immune checkpoint inhibition on cancers of müllerian origin. The ultimate goal of the study is to identify potential biomarkers, immune gene expression signatures, and co-stimulatory pathways that may be used to develop future clinical trials. Following the pathologic diagnosis of a cancer of müllerian origin, baseline blood and tumor samples would be obtained. Women would receive a single dose of Pembrolizumab then treated conventionally with surgical therapy including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymph node sampling as indicated. This design affords the opportunity to obtain a significant post-administration tumor sample (including ascites) for analysis. In cases where surgery is not performed, a post-treatment biopsy specimen should be obtained. While the short-term administration of Pembrolizumab may have a therapeutic benefit, all women will go on to receive standard therapy which may include chemotherapy +/- surgery, if indicated.

Amendment 5: Encompassed two major changes to the protocol: the addition of maintenance therapy and the allowance of a Second Course Phase of therapy with pembrolizumab for subjects who experience radiographic disease progression after completion of initial treatment. The rationale for the inclusion of maintenance therapy after completion of chemotherapy in this study is predicated on scientific, practical, and ethical considerations. Several current studies are evaluating the combination of chemotherapy with pembrolizumab followed by pembrolizumab maintenance. However, while the combination is feasible, it is unclear that giving concurrent chemotherapy and pembrolizumab is necessary; maintenance therapy following initial chemotherapy may be sufficient. Thus, in this amendment in addition to the primary objectives of evaluating the safety and immune profile after a pre-surgical dose of pembrolizumab, we propose to evaluate whether there are any safety concerns with administering pembrolizumab as maintenance therapy after receiving an initial dose prior to surgery and after completion of chemotherapy. As part of this, we will evaluate the circulating immune profile after completion of chemotherapy and during pembrolizumab maintenance therapy to determine the immune effect of therapy.

This change should also obviate a practical/ethical concern we have encountered with this study thus far. As there are currently other studies combining chemotherapy and immunotherapy for this patient population, physicians and patients have been reluctant to consider this protocol as the patient would only receive one dose of pembrolizumab. This study was not originally designed with a therapeutic intent, however exposure to the single dose of pembrolizumab in this study would make patients ineligible for any other anti-PD-1 study. It stands to reason that one dose is unlikely to provide substantial therapeutic benefit, thus the allowance of maintenance therapy with pembrolizumab in this amendment would provide reasonable exposure to pembrolizumab to maintain anti-tumor response and is in keeping with currently FDA-approved approach to maintenance adjuvant therapy with ipilimumab in malignant melanoma.

The second major change of amendment 5 is the allowance of a Second Course Phase of therapy with pembrolizumab for subjects who experience radiographic disease progression after completion of initial treatment. This approach is in keeping with current pembrolizumab protocols that allow for a Second Course Phase if radiographic progression is observed after discontinuation for complete response. Biopsy samples will be obtained from patients who opt for the Second Course Phase to evaluate the immunoprofile in recurrent disease.

Amendment 6: Allows for patients to participate if they have disease that is amenable to post-treatment biopsy

Amendment 8: Allows for collection of additional tumor specimen and blood collection at the time of interval debulking surgery for exploratory translational research analysis.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab (MK-3475): 200mg once at least 7 days prior to surgery or biopsy will be used to assess changes in immune markers pre- and post-study drug administration.

An open-label Phase I trial (Protocol 001) has been conducted to evaluate the safety and clinical activity of single agent MK-3475 in locally advanced or metastatic carcinoma, melanoma, or non-small cell lung carcinoma (NCT01295827). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). 10.0 mg/kg Q2W, the highest dose tested in P001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W on P001 showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB).

Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients enrolled on P001. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either

2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

For the maintenance portion of the study, subjects will receive 200mg IV every 3 weeks. This is the dose used in ongoing studies evaluating maintenance therapy.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

In this biomarker study the main focus is to identify potential biomarkers, immune gene expression signatures, and co-stimulatory pathways that may be used to develop future clinical trials. We have established the following efficacy and safety endpoints. Because of the small sample size in this pilot study, statistical analyses will be descriptive.

(1) **Efficacy Endpoint:** Fold change in tumor immune infiltrates after administration of pembrolizumab.

(2) **Safety Endpoint:** Frequency and severity of adverse events associated with pembrolizumab when given to patients with newly diagnosed gynecologic cancers of müllerian origin prior to standard surgical therapy, and as maintenance therapy after completion of chemotherapy, as assessed by CTCAE.

Immune checkpoint inhibitors have not been given to patients with gynecologic cancer prior to standard surgical therapy. While immune checkpoint inhibitors have been safely given in patients with recurrent gynecologic cancers and in a neoadjuvant setting in other cancers, establishing the safety profile of pembrolizumab for patients newly diagnosed with gynecologic malignancies is essential.

4.2.3.2 Biomarker Research

(1) Changes in the tumoral and circulating blood immunoprofile after administration of pembrolizumab. Levels of immune and inflammatory mediators, profile of tumor immune infiltrates, and the expression of PD-L1 in pre-administration samples will be compared to post-administration surgical resection (and ascites) and biopsy samples.

Further biomarker analysis will be performed in a subset of patients who undergo neoadjuvant chemotherapy followed by standard-of-care interval debulking. In this subset, tumor and blood specimens will be collected from the day of surgery +/- 1 day.

Immune markers may predict response to immunotherapy agents, however the early changes that occur in response to PD-1 inhibition have not been assessed. It is our hypothesis that characteristics of the immunomodulatory cells in the blood or tumor may be associated with clinical response of gynecologic malignancies to pembrolizumab. The identification of the markers expressed in gynecologic malignancies, and the change in immunophenotype in response to pembrolizumab, will inform the development of future clinical trials.

The specific phenotypic markers comprising the Immune Profiling Panels (Table 1) were selected based upon key cellular subsets proven important in the assessment of immune checkpoint blockade therapeutic strategies for various human cancers, including melanoma, NSCLC, and renal cell carcinoma. These panels are currently in use to evaluate effects of immune checkpoint blockade in several clinical trials. Within the Tumor Reactive Panel, maturational subsets of CD4+ and CD8+ T cells (defined by CD197 and/or CD45RA expression) will be monitored for co-expression of 'regulation' and 'exhaustion' markers such as CTLA-4, TIM3, PD-1, and LAG3. The coexpression of the latter 3 markers identifies tumor-reactive TILs[4]. We will also examine the expression of T cell activation markers HLA-DR and ICOS previously shown to be upregulated in patients responding to ipilimumab therapy, identifying them as potential pharmacodynamic biomarkers[5,6]. Lastly, we will track proliferating T cell subsets expressing the intracellular marker Ki67.

Table 1 Immune Profile Panels

	Marker	Stain	Purpose
Tumor Reactive T cells (13c)	amine	Surface	Dead cell exclusion
	CD3	Intracellular	T- cells
	CD4	Intracellular	CD4+ (helper) T cells
	CD8	Intracellular	CD8+ (cytotoxic) T cells
	Lag3 (CD223)	Surface	Exhaustion
	HLA-DR	Surface	Activation
	CCR7 (CD197)	Surface	Maturation
	CD45RA	Surface	Maturation
	TIM3	Surface	Regulation
	PD1 (CD279)	Surface	Exhaustion
	CTLA4 (CD152)	Intracellular	Regulation
	Ki67	Intracellular	Proliferation
	ICOS (CD278)	Surface	Co-stimulation
Treg & MDSC (12c)	amine	Surface	Dead cell exclusion
	CD3	Intracellular	T- cells
	CD4	Intracellular	CD4+ (helper) T cells
	CD8	Intracellular	CD8+ (cytotoxic) T cells
	CD16	Surface	Lineage exclusion channel
	CD19		
	CD20		
	CD56		
	CD25	Surface	Tregs
	CD127	Surface	Tregs
	Ki67	Surface	T-regs
	CTLA4 (CD152)	Intracellular	Regulation
	FoxP3	Intranuclear	Tregs
	CD14	Surface	MDSC's
	HLA-DR	Surface	MDSC's

The Treg and MDSC panel monitors levels of immunosuppressive cells shown to predict response to ipilimumab[6]. For these studies, Tregs will be defined as CD3+/CD4+/CD25hi/FoxP3+/CD127low-neg, and MDSC will be defined as lineage negative/CD14+/HLA-DRlow-neg. Additionally, intracellular expression of CD152 and FoxP3 will be monitored on Treg cells.

A multiplex ELISA approach has been developed to analyze over 25 tumor angiogenesis, growth factors, and inflammatory cytokines in less than 0.5 ml of plasma or ascites. Coefficients of variation for most analytes are <20%. This platform has been successfully used to analyze samples from several phase I to III studies. Markers of inflammation will be analyzed in our Phase I biomarker lab, which serves as a core lab for these analyses for the US Alliance Cooperative Group. Samples will be evaluated for soluble angiogenic factors (including but not limited to bFGF, HGF, PlGF, VEGF A-D, ANG1-2, PDGF, IGFBP1-3, sVEGFR1-3, sTie2), matrix-derived angiogenic factors (including but not limited to MMP2, MMP9, TGFβ1-2, osteopontin, sEndoglin), markers of coagulation (e.g. CRP, d-dimer, VWF, tissue factor), and markers of vascular activation and inflammation (including but not limited to IFNγ, IL1β, IL6, sILR6R, sGP130, IL4, IL7, IL10, IL12, IL17A, IL17E, and IL23).

The actual analytes tested may be adapted based on current knowledge at the time of collection.

5.0 METHODOLOGY

5.1 Entry Criteria

Before patient screening begins, each site must submit the following documents to Duke University, Division of Gynecologic Oncology Clinical Trials via mail or email (Attn: Regulatory Department, Protocol Pembro Merck):

- IRB approval.
- IRB-approved informed consent.
- IRB Membership list or FWA assurance letter.
- Study-specific signed original FDA Form 1572 for institution PI.
- Current CV (signed and dated within one year) for institution PI and sub-investigators listed on FDA Form 1572.
- Medical license for institution PI and sub-investigators listed on the FDA Form 1572.
- Lab license, certificates, and required Normal Lab Values (NLV) for labs listed on FDA Form 1572.
- Signed original Signature Page for PI.
- Signed original Financial Disclosure Form for all investigators listed on FDA Form 1572.
- Delegation of Authority log.
- Human Subject Protection Certificates for investigators and personnel who will be seeing and consenting study participants.

Please allow 7-10 days for processing of regulatory documents before screening the first patient. All copies of the above should be filed into a study-specific regulatory binder at your institution.

The initial supply of study drug cannot be shipped until all the regulatory documents have been reviewed and approved. Duke University may require copies of the regulatory documentation prior to any shipment of drug.

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients newly diagnosed with a gynecologic tumor of müllerian origin, specifically epithelial ovarian, fallopian tube, primary peritoneal, or uterine endometrial cancer.

5.1.2 Subject Inclusion Criteria

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

1. Have histologically or cytologically confirmed gynecologic tumor of müllerian origin, specifically epithelial ovarian, fallopian tube, primary peritoneal, or uterine endometrial cancer.

2. Have disease amenable to surgical resection or biopsy.

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

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

5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion or ascites or pleural effusions via paracentesis or thoracentesis. *Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement of the investigator.*

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

7. Demonstrate adequate organ function as defined in Table 2, all screening labs should be performed within 10 days of study drug administration.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion dependency or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subjects of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication.

9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity until planned hystecterectomy/oopherectomy (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving a study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the study drug administration.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study drug administration.

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

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

6. Has received prior chemotherapy, targeted small molecule therapy, or radiation therapy for the current gynecologic malignancy.

    - Note: Subjects who have received treatment for a prior unrelated malignancy must have recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

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

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

11. Has an active infection requiring systemic therapy.

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

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

14. Is pregnant or breastfeeding.

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

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

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

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

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

5.1.4 Patient Entry and Registration

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

- An approved consent form must be signed by the patient or guardian. The consent must contain language permitting the release of personal health information. Current FDA and institutional regulations concerning informed consent will be followed
- All eligibility requirements indicated must be satisfied
- Eligibility checklist data should be gathered and faxed to (919) 681-7689
- Subject entry will take place after the fax is received and verification of the Eligibility Checklist data completed.
- The institution will enter the patient's name into a log book to verify the patient's entry

The study drug and dose to be used in this trial is outlined below.

Table 3 Trial Treatment

	Drug	Dose/ Potency	Dose Frequency	Route	Regimen/ Treatment Period	Use
Pre-surgical or biopsy dose	Pembrolizumab	200 mg	Once	IV infusion	Day 1	Experimental
Maintenance	Pembrolizumab	200mg	Every 3 weeks up to 1 year	IV infusion	Maintenance post-chemotherapy (MC1-MC18)*	Experimental

Study drug administration should begin as close as possible to the date of enrollment on study.

* Patients who experience dose delays of maintenance pembrolizumab will receive up to 12 months of therapy, which may be less than 18 cycles of pembrolizumab maintenance therapy

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

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

5.2.1.2 Dose Modifications and Interruptions

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after or several months after the last dose of pembrolizumab. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below. No dose modifications are allowed.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General Instructions:

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

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

General Instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST, ALT, or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	3-4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[1]		

General Instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor for changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other Immune-Related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillan-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

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

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

5.2.2 Timing of Dose Administration

Study drug will be administered on an outpatient basis. The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion once. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, for reporting sites may follow their institutional standard guidelines.

Day 1: Study drug is planned to be administered at least 7 days prior to standard surgery or research biopsy. Study drug should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Maintenance Phase: Study drug should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

5.2.3 Trial Blinding/Masking

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

5.3 Criteria for Entry into Maintenance Phase

Demonstrate adequate hematologic, renal, and hepatic function as defined in Table 2 in Section 2.1.2.

5.4 Stratification

There is no powered stratification for enrollment. Post-hoc analyses will be performed based upon histology of tumor, whether patient received steroids, and exploratory biomarkers.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before and 30 days after study drug administration should be recorded. Concomitant medications administered after 30 days after study drug administration should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Study Drug Administration Phase (up until and including time of surgery or biopsy) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to study drug administration and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Table 4 in section 5.2.1.2 and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

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

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

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

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

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Intercurrent illness that prevents administration of treatment.
- Investigator's decision to withdraw the subject.
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- The subject is lost to follow-up.
- Administrative reasons.

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

5.8.1 Discontinuation of Study Therapy

Maintenance therapy will be discontinued after 1 year for subjects who do not discontinue for unacceptable adverse experiences as in Section 5.2.1.2 or progression of disease during the treatment phase of the study. Subjects who subsequently experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.6.6.

5.9 Subject Replacement Strategy

In the event a patient is deemed ineligible or is not assessable for the primary endpoint assessment, the patient may be replaced at the discretion of the study PI in consultation with Merck.

5.10 Clinical Criteria for Early Trial Termination

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

1. The study will be stopped if adequate tissue is not obtained in more than 2/3 of paired samples with a maximum accrual of 20 patients.
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
5. Plans to modify or discontinue the development of the study drug

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

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6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Pre-surgery or Biopsy Administration [a]**					**Maintenance (M)[k]**			**Post-Administration SAE Monitoring**	**Survival Follow-up[c]**
Title:		Day 1	Phone f/u post-dose	Surgery or Biopsy	Interval Surgery or Biopsy[p]	Safety Follow-up	M-C1	M-C2 to C18[q]	Safety Follow-up		
Scheduling Window (Days):	-10 to -1		± 3	≥7 days post-Day1	During SOC chemo	30 ± 7 post-Day1	≤ 3 mo after last chemo[h,l]	Q3wks -1+3D	30 ± 7 post-study drug	90 days following last dose of pembrolizumab	every 16 weeks ± 4 weeks
Administrative Procedures											
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics/Medical History	X										
Prior/Concomitant Medications	X	X	X			X	X	X	X		
Post-study anticancer therapy						X			X		X
Survival Status						X			X		X
Clinical Procedures/Assessments											
Review Adverse Events			X[g]	X[b]		X	X	X	X	X	
Physical Examination[d]	X	X[o]				X	X	X[i]	X		
Vital Signs and Weight	X	X[o]				X	X	X[m]	X		
ECOG Performance Status	X	X[o]				X			X		
Administration of Pembrolizumab		X					X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Pregnancy Test – β-HCG		X[a]									
PT/INR and aPTT	X										
CBC with Differential	X					X	X[l]	X	X		
CA125	X					X	X[l]	X	X		
Comprehensive Serum Chemistry	X					X	X[l]	X	X		
Urinalysis	X										
FT3, FT4 and TSH	X					X	X[l]	X	X		

Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood											
Newly Obtained Tissue or Fluid Collection (or archival if permitted at discretion of investigator)[e]	X										
Correlative Studies Blood Collection	X			X[b]	X[p]	X[f]	X[j]	X[j]			
Surgical or Biopsy Specimen Collection[e]				X	X[p]		X[n]	X[n]			

[a] Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
[b] Correlative studies blood collection and adverse events review may be performed up to 3 days prior to surgery or biopsy.
[c] Survival follow-up may be performed by chart review or phone survey within 16 weeks, ± 4 weeks.
[d] Full physical exam is to be performed during screening; directed physical exams may be performed in subsequent visits.
[e] Tissue or fluid will be collected and processed according to the laboratory manual and sent to Qualtek for PD-L1 IHC and to the Weinhold lab for immune profiling.
[f] Collection of a blood sample (30ml) at the next scheduled visit after completion of chemotherapy. If this coincides with start of maintenance phase, only one blood sample (30ml) need be collected.
[g] Check of adverse events by phone ≥3 days after study drug but prior to surgery or biopsy to assess for adverse effects and/or changes to medications.
[h] Patients who enrolled prior to Amendment 5 have the option to start maintenance phase within a 6 month window from last chemotherapy if they choose.
[i] MD visits and physical exams will be required every other cycle.
[j] Collection of blood for correlative studies during maintenance phase must occur prior to M-C1 and at least once prior to subsequent cycles.
[k] Patients who have radiographic progression after completion of maintenance phase may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the eligibility requirements for Second Course Phase, and the trial is open. Tissue biopsy and blood samples are required prior to start of second course phase. See Section 7.1.6.6.
[l] There is a 10 day window for labs prior to start of Maintenance Phase or Second Course Phase.
[m] Weight is only required every other cycle
[n] Tissue collection is required at time recurrence
[o] Screening procedures may be used if collected within 10 days of C1D1
[p] Interval biopsy and correlative studies are optional and done **only** if clinically indicated **at any time during standard of care treatment**; subjects must opt-in or opt-out of collection
[q] Patients who experience dose delays of maintenance pembrolizumab will receive up to 12 months of therapy, which may be less than 18 cycles of pembrolizumab maintenance therapy

6.2 Second Phase Flow Chart

Patients who have radiographic progression after completion of maintenance phase may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the eligibility requirements for Second Course Phase, and the trial is open. Tissue biopsy and blood samples are required prior to start of second course phase. See Section 7.1.6.6.

Trial Period:	**Second Course Phase (SC)**			**Post-Administration SAE Monitoring**	**Survival Follow-up[c]**
Title:	SC-C1[l]	SC-C2 to C18	Safety Follow-up		
Scheduling Window (Days):	Radiographic recurrence[l]	Q3wks -1+3D	30 ± 7 post- study drug	90 days following last dose of pembrolizumab	every 16 weeks
Administrative Procedures					
Informed Consent					
Inclusion/Exclusion Criteria					
Demographics and Medical History					
Prior and Concomitant Medication Review	X	X	X		
Post-study anticancer therapy status			X		X
Survival Status			X		X
Clinical Procedures/Assessments					
Review Adverse Events	X	X	X	X	
Physical Examination[d]	X	X[i]	X		
Vital Signs and Weight	X	X	X		
ECOG Performance Status			X		
Administration of Pembrolizumab	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory					
PT/INR and aPTT					
CBC with Differential	X[l]	X	X		
CA125	X[l]	X	X		
Comprehensive Serum Chemistry Panel	X[l]	X	X		
Urinalysis					
FT3, FT4 and TSH	X[l]	X	X		
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood					
Newly Obtained Tissue or Fluid Collection	X[m]				
Correlative Studies Blood Collection	X[m]				
Surgical and Biopsy Specimen Collection[e]					

[c] Survival follow-up may be performed by chart review or phone survey.
[d] Full physical exam is to be performed during screening; directed physical exams may be performed in subsequent visits.

[e] Tissue or fluid will be collected and processed according to the laboratory manual and sent to Qualtek for PD-L1 IHC and to the Weinhold lab for immune profiling.
[i] MD visits and physical exams will be required every other cycle.
[l] There is a 10 day window for labs prior to start of Maintenance Phase or Second Course Phase.
[m] Patients who have radiographic progression after completion of maintenance phase may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the eligibility requirements for Second Course Phase, and the trial is open. Tissue biopsy and blood samples are required prior to start of second course phase.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after study drug administration. If a subject initiates a new anti-cancer therapy, other than planned chemotherapy, within 30 days after study drug administration, the Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy, other than planned chemotherapy, has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

As they are enrolled in the study, subjects will be assigned a unique consecutive number.

7.1.1.7 Assignment of Randomization Number

Not applicable

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

The investigator or qualified designee will administer study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. Subjects will be supervised at the time of study drug administration.

A requirement for enrollment on study is a fresh biopsy (or collection of ascites fluid or pleural effusions via paracentesis or thoracentesis). Subjects whose sample is found to be inadequate for study purposes (e.g. could not be obtained or insufficient) may continue on study at the discretion of the investigator.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Adverse events will not be collected during standard of care treatment. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical

interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study drug administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of study drug as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging and/or disease assessment will occur per NCCN guidelines during treatment on this protocol.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

All samples will be collected through the Duke Biospecimen Repository and Processing Core (BRPC). A biopsy (or one of the following: endometrial curettage, paracentesis for ascites fluid, or thoracentesis for pleural effusions) and baseline correlative studies blood collection will be performed within 10 days prior to study drug administration on Day 1. After administration on day 1, peripheral blood will be collected within 3 days prior to surgery or biopsy, prior to start of maintenance therapy, and at least once during maintenance therapy

(prior to infusion) Tumor samples and ascites/pleural effusions will be collected at the time of surgery or biopsy, and at time of recurrence. Samples will be collected, delivered, and stored according to standard operating procedures, detailed in separate lab manual.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Comprehensive Serum Chemistries	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free thriiodothyronine (FT3)
Absolute Neutrophil Count	Carbon Dioxide *(CO_2 or biocarbonate)*	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count		Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Creatinine		
	Glucose		CA-125
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

Laboratory tests for screening, entry into the Maintenance Phase, or entry into the Second Course Phase should be performed within 10 days prior to study drug administration. After Maintenance Cycle 1 (M-C1) or Second Course Phase Cycle 1 (SC-C1), pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of study drug administration.

7.1.3.2 Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for Serum Pembrolizumab

Not applicable.

7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies

Not applicable.

7.1.4 Immunohistochemistry for PD-L1 expression on tumor cells

Immunohistochemistry for PD-L1 expression will be performed on the pre-treatment biopsy tissue or collected fluid, post-treatment surgical and biopsy specimens, and recurrence biopsy tissue. Sample collection, storage and shipment will be performed by the Duke BRPC as per instructions in the Qualtek MISP Sample Handling Manual.

7.1.5 Other Procedures

Not applicable.

7.1.5.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.5.2 Blinding/Unblinding

Not applicable.

7.1.6 Visit Requirements

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

7.1.6.1 Screening

Screening will only be performed after an initial pre-eligibility determination is made using those requirements that are part of the medical history (disease and treatment history, recent labs or scans, etc.), do not require specific testing, where it appears the patient may be eligible for study, and after an informed consent is made.

Screening studies and labs are performed in accordance with the sections listed above.

7.1.6.2 Pre-Surgery/Biopsy Administration Period

The treatment period will consist of the time from study drug administration until the time of surgery or biopsy. A single dose of pembrolizumab will be administered on this study. The subject will be contacted at least once by phone ≥3 days after dose administration and prior to surgery or biopsy to assess for adverse effects and/or any changes in medications.

7.1.6.3 Maintenance Phase

Subjects who complete chemotherapy per local guidelines without unacceptable adverse experience (Section 5.2.1.2) attributable to Pre-Surgery/Biopsy Administration of pembrolizumab or progression of disease may be eligible for up to one year of maintenance pembrolizumab therapy. Maintenance therapy may be initiated if the subject meets the following conditions:

- No radiographic evidence of disease progression after chemotherapy

AND

- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who receive treatment during the maintenance phase will receive therapy according to Section 5.2.1.1 Maintenance treatment will be administered for up to one year. Patients who experience dose delays of maintenance pembrolizumab will receive up to 12 months of therapy which may be less than 18 cycles of pembrolizumab maintenance therapy.

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

7.1.6.4 Safety Follow-up Visits

Safety Follow-Up Visits will occur after completion of each phase of treatment (i.e. Pre-surgery/biopsy Administration, Maintenance Phase, and Second Course Phase, if applicable). The Safety Follow-Up Visits should be conducted approximately 30 ± 7 days after last study drug administration for each phase, as outlined in Section 6.0 - Trial Flow Chart. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy (other than planned adjuvant chemotherapy), whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have three safety follow-up visits, one after the Pre-Surgery/biopsy Administration Period, one after the Maintenance Phase, and one after the Second Course Phase.

7.1.6.4.1 Post-Administration SAE Monitoring

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

7.1.6.5 Survival Follow-up

After completion of post-administration monitoring, the subject moves into the survival follow-up phase and should be contacted by telephone every 16 weeks (+/- 4 weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.6.6 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab after completion of the maintenance phase without unacceptable adverse experience or progression may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Stopped initial treatment with pembrolizumab after completion of maintenance phase without disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. No adverse events will be collected while subjects are receiving standard of care chemotherapy The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor's designated safety reporting system, the Duke Safety Desk by fax (919-681-9357) or by secure email (dcccsafe@dm.duke.edu). The Duke Safety Desk will report to Merck Global Safety within 2 working days hours. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial treatment period. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor's designated safety reporting system, the Duke Safety Desk by fax (919-681-9357) or by secure email (dcccsafe@dm.duke.edu). The Duke Safety Desk will report to Merck Global Safety within 2 working days. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

7.2.3.1 Serious Adverse Events

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through at least 90 days following administration of study drug, except when subjects are solely receiving standard of care chemotherapy, or the initiation of new anti-cancer therapy (other than planned chemotherapy), whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor's designated safety reporting system, the Duke Safety Desk, by fax (919-681-9357) or by secure email

(dcccsafe@dm.duke.edu). The Duke Safety Desk will report to Merck Global Safety within 2 working days.

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor's designated safety reporting system, the Duke Safety Desk, by fax (919-681-9357) or by secure email (dcccsafe@dm.duke.edu). The Duke Safety Desk will report to Merck Global Safety.

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

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 the Duke Safety Desk, which will send a copy to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor's designated safety reporting system, the Duke Safety Desk by fax (919-681-9357) or by secure email (dcccsafe@dm.duke.edu). The Duke Safety Desk will report to Merck Global Safety within 2 working days. (Attn: Worldwide Product Safety; FAX 215 993-1220) Events of clinical interest for this trial include:

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

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the

upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

1. Additional adverse events:

   Events of Clinical Interest can be found in section 5.4.5 and tables 32 and 33 of the Pembrolizumab Investigator's Brochure.

   ECIs (both non-serious and serious adverse events) identified in these sections from the date of study drug administration through at least 90 days following study drug administration, except when subjects are solely receiving standard of care chemotherapy, or 30 days after the initiation of a new anticancer therapy (not including planned chemotherapy), whichever is earlier, need to be reported within 24 hours to the Sponsor's designated safety reporting system, the Duke Safety Desk by fax (919-681-9357) or by secure email (dcccsafe@dm.duke.edu). The Duke Safety Desk will report to Merck Global Safety within 2 working days. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

7.2.4 Evaluating Adverse Events

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

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

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Table 7 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

We expect to enroll 15 patients with epithelial gynecologic malignancies over a period of 18 months from the time of approval of Amendment 5 (22 Dec 2017). Since this is a pilot study with a limited sample size, statistical analyses will be descriptive. The information gained from this study will help inform the development of future studies.

8.2 Statistical Analysis Plan

Analysis of toxicity data: The number of participants with adverse events will be determined and each observed toxicity will be tabulated by type, grade, and frequency.

Biomarker statistics: Descriptive statistics will be used to summarize baseline, post-administration, and change from pre-to post-administration for each biomarker. Ninety-five percent confidence intervals will be constructed to describe the change in the levels of each marker between pre- and post-administration. Correlation coefficients will be calculated and graphical displays of biomarker data will be generated to determine correlation between biomarkers. Waterfall plots will be used to illustrate changes from baseline. Coefficients of variation will be used to assess the dispersion of each analyte. PFS and OS will be estimated for analyte levels and changes (both will be dichotomized).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 8 .

Table 8 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

All data for patients and this trial are subject to all applicable federal, state, local, and institutional policies that may be applicable during the conduct of the trial.

10.2 Compliance with Financial Disclosure Requirements

The investigator and study team members will follow federal and institutional regulatory standards, including compliance with required financial disclosure reporting.

10.3 Compliance with Law, Audit and Debarment

All investigators and sites must be in agreement to allow reasonable access by study designated personnel to all study data and study related patient data necessary in order to allow the proper conduct and demonstrate compliance with applicable laws, regulations and statutes. Any investigator or site under investigation or receiving disbarment should notify the sponsor of this study as soon as possible, but no later than 5 days.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. External site monitoring will be performed in accordance with the **External Site Monitoring Plan**, which accompanies this protocol. Please refer to this document for specifics regarding monitoring procedures.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

The Duke School of Medicine Clinical Trials Quality Assurance (CTQA) office may conduct audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the CTQA auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the CTQA auditor(s) in order to discuss findings and any relevant issues.

CTQA audits are designed to protect the rights and well-being of human research subjects. CTQA audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

CTQA audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

10.6 Data Management

Data will be collected and reported through a Medidata RAVE database that will be designed specifically for this study. Data will be analyzed and reported after the trial has completed accrual. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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

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

11.3 Events of Clinical Interest Guidance Document

Refer to section 5.4.5 and Tables 32 and 33 in the Pembrolizumab Investigator's Brochure.

11.4 Standard Operating Procedures for Blood, Ascites, and Tissue Specimen Collection

For instructions regarding specimen processing please refer to the Specimen Processing Manual and the QualTek Sample Handling Manual.

11.5 Eligibility Checklist

Study #: Pro00068544	Subject ID #:		
Inclusion Criteria	**Yes**	**No**	**N/A**
Patient has histologically or cytologically confirmed gynecologic tumor of müllerian origin, specifically epithelial ovarian, fallopian tube, primary peritoneal, or uterine endometrial cancer			
Patient has disease amenable to surgical resection			
Patient is willing and able to provide written informed consent for the trial			
Patient is ≥ 18 years of age on day of signing informed consent			
Patient is willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion or ascites or plural effusions via paracentesis or thoracentesis. • Patients for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement of the investigator			
Patient has an ECOG Performance status of 0 or 1.			
Patient has adequate bone marrow function: • **Absolute Neutrophil Count** ≥ 1,500/mcl • **Platelets** ≥ 100,000/mcl. • **Hemoglobin** ≥ 9.0 g/dL or ≥5.6 mmol/L without transfusion dependency or EPO dependency (within 7 days of assessment)			
Patient has adequate renal function: • **Creatinine** ≤ 1.5 x institutional upper limit of normal **OR** • **Measured or calculated creatinine clearance** (GFR can also be used in place of creatinine or CrCl) ≥60mL X ULN			
Patient has adequate hepatic function: • **Bilirubin** ≤ 1.5 X ULN **OR** • **Direct bilirubin** ≤ ULN for subjects with total bilirubin levels > 1.5 X ULN • **ALT/AST** ≤ 2.5 x ULN *If patient has liver metastases*: **ALT/AST** ≤ 5 x ULN. • **Albumin** ≥ 2.5 mg/dL			
Patient has adequate blood coagulation: • **International Normalized Ratio (INR) or Prothrombin Time (PT)** ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants • **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			
If patient is of child-bearing potential: negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication.			
If patient is of childbearing potential: should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity until planned hysterectomy/oophorectomy. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year			

Study #: Pro00068544	Subject ID #:		
Exclusion Criteria	**Yes**	**No**	**N/A**
Patient is currently participating and receiving a study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the study drug administration			
Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study drug administration			
Patient has a known history of active TB (Bacillus Tuberculosis).			
Patient has hypersensitivity to pembrolizumab or any of its excipients			
Patient has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1, or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier			
Patient has received prior chemotherapy, targeted small molecule therapy, or radiation therapy for the current gynecologic malignancy • Patients who have received treatment for a prior untreated malignancy must have recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent • If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy			
Patient 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 that has undergone potentially curative therapy, or in situ cervical cancer			
Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to study drug administration and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study drug administration. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.			
Patient has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.			
Patient has known history of (non-infectious) pneumonitis that required steroids or current pneumonitis			
Patient has active infection requiring systemic therapy.			
Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator			
Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial			
Patient is pregnant or breastfeeding			
Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.			
Patient has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)			
Patient has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).			
Patient has received a live vaccine within 30 days of planned start of study therapy • Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed			

Subject eligibility verbally reviewed with PI/delegated physician and subject was deemed eligible on: _____
Date and Time

_____
Signature of Coordinator/Research Nurse
PI/Delegated physician agrees that the above statement is true and the subject was eligible:

_____ _____
Signature of Investigator/Sub-Investigator **Date**

Original version:	October 8, 2015	Amended version 5:	September 18, 2017
Amended version 1:	April 12, 2016	Amended version 6:	March 29, 2018
Amended version 2:	July 25, 2016	Amended version 7:	August 28, 2018
Amended version 3:	November 11, 2016	Amended version 8:	December 27, 2018
Amended version 4:	February 27, 2017	Amended version 9:	October 17, 2019

11.6 Registration Form

Subject Registration Form

Section 1: SUBJECT INFORMATION

First Name: _____ **Middle Initial:** ____ **Last Name:** _____

Sex: ☐ **Male** ☐ **Female** **Date of Birth:** ____ / ____ / _____ **Duke MRN (if applicable):** _____

Date Consent Signed: ____ /____ / _____ **Version Date of Site Consent:** ____ /____ / _____

Type of Cancer Diagnosis: _____ **Protocol Name:** _____

RACE:	**ETHNICITY**:
☐ White	☐ Hispanic or Latino
☐ Black or African American	☐ Non Hispanic or Latino
☐ Native Hawaiian or other Pacific Islander	☐ Not Reported
☐ Asian	☐ Unknown
☐ American Indian or Alaska Native	
☐ Not Reported	
☐ Unknown	

Section 2: SITE INFORMATION

Site Name: _____ **Site Fax #:** _____

Study Coordinator Name: _____ **Phone #:** _____ **Pager #:** _____

Study Coordinator Email: _____

Treating MD Name: _____ **Phone #:** _____ **Pager #:** _____

Treating MD Email: _____

Section 3: ELIGIBILITY

☐ **Subject meets all eligibility criteria.** ***(Please note: If subject meets all eligibility criteria, please provide completed eligibility checklist along with supporting source documentation to the Duke Team.)***

Date of expected Cycle 1 Day 1: ____ / ____ / _____

☐ **Subject does not meet all eligibility criteria.**

If subject does not meet eligibility, please explain below.

_____

Study Coordinator Signature: _____ **Date:** _____

Section 4: TO BE COMPLETED BY DUKE STUDY TEAM

Subject Study Number		**Cohort Number**	**N/A**

11.7 Investigator Signature Page

Investigator Signature Page

Product: Pembrolizumab (Keytruda)

Protocol: A PILOT STUDY INVESTIGATING THE EFFECT OF PEMBROLIZUMAB ON THE TUMORAL IMMUNOPROFILE OF GYNECOLOGIC CANCERS OF MÜLLERIAN ORIGIN

Investigator's Agreement

I have read the attached protocol entitled "A PILOT STUDY INVESTIGATING THE EFFECT OF PEMBROLIZUMAB ON THE TUMORAL IMMUNOPROFILE OF GYNECOLOGIC CANCERS OF MÜLLERIAN ORIGIN", and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in **21 CFR Parts 11, 50, and 56.**

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

12.0 REFERENCES

1. Siegel, R, Naishadham, D *et al.* Cancer statistics, 2013. *CA Cancer J. Clin.* (2013) **63**, 11-30.
2. Topalian, SL, Sznol, M *et al.* Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J. Clin. Oncol.* (2014) **32**, 1020-1030.
3. Hamanishi, J, Mandai, M *et al.* in *SGO 2015 Annual Meeting on Women's Cancer.*
4. Gros, A, Robbins, PF *et al.* PD-1 identifies the patient-specific CD8(+) tumor-reactive repertoire infiltrating human tumors. *J. Clin. Invest.* (2014) **124**, 2246-2259.
5. Weber, JS, Hamid, O *et al.* Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J. Immunother.* (2012) **35**, 89-97.
6. Tarhini, AA, Edington, H *et al.* Immune monitoring of the circulation and the tumor microenvironment in patients with regionally advanced melanoma receiving neoadjuvant ipilimumab. *PLoS One* (2014) **9**, e87705.