Immunotherapy with MK-3475 in surgically resectable endometrial carcinoma

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Protocol Revision History

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SCHEMA

Patients must have a FIGO grade 3 endometrioid cancer, serous, clear cell, or mixed high grade endometrial cancer and stage III or IV by radiographic imaging

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An endometrial biopsy will be obtained after enrollment in trial

⇩

Receive two doses of MK-3475 200mg q 3 weeks pre-operatively and have a blood draw prior to each dose of MK-3475

⇩

Surgery for endometrial cancer staging 3-4 weeks after last dose of MK-3475. Blood and tumor samples will be obtained at surgical procedure

⇩

Complete adjuvant chemotherapy of Paclitaxel 175mg/m2 intravenously over 3 hours on day 1 and Carboplatin AUC 5 intravenously on day 1 +/- radiation therapy. Collect blood sample prior to re-administering MK-3475 4-6 weeks post completion of adjuvant therapy.

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Receive MK-3475 every 3 weeks x 4 cycles

⇩

Collect blood prior to 2nd and 4th cycle of MK-3475

Glossary of Abbreviations

AE/irAE	Adverse event/immune-related adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
CBC	Complete blood count
CMP	Complete metabolic panel
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DM	Distant metastases
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECI/irECI	Event of clinical interest/immune-related event of clinical interest
FDA	Food and Drug Administration
GOG	Gynecologic Oncology Group
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
PBMC	Peripheral blood mononuclear cell
PI	Principal investigator
PT	Prothrombin time
PTT/aPTT	Partial thromboplastin time
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RNA	Ribonucleic acid
SAE	Serious adverse event
SCC	Siteman Cancer Center
SUSAR	Suspected unexpected serious adverse reaction
TSH	Thyroid stimulating hormone
UPN	Unique patient number

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1.0 BACKGROUND AND RATIONALE

1.1 Endometrial Adenocarcinoma

Endometrial adenocarcinomas are the most common gynecologic malignancy in developed countries. Although current therapies result in a five-year survival of 80-90% for low risk patients with Stage I disease, patients with high-risk (serous or clear cell – any stage or Stage III grade 2 or 3 endometrioid histology) disease have poor survival ranging from 18-74% with Stage I-IV disease. For those who recur, multi-modality treatment options are not successful. Thus, there is a pressing need for development of novel therapeutics for high-risk endometrial cancer (1).

Standard of care treatment for locally advanced disease includes surgical resection followed by adjuvant radiation, and for advanced, metastatic disease, the standard of care includes surgical resection followed by chemotherapy with or without adjuvant radiation. Despite the addition of these modalities, a portion of locally advanced and metastatic disease patients will suffer disease specific mortality and could benefit from novel therapeutic approaches.

Endometrial cancer has distinct features that make it ideal for checkpoint blockade based immunotherapeutic approaches. First, there has been positive PD-L1 immunohistochemical expression detected in 83% of primary, 67% of recurrent, and 100% of metastatic endometrial cancers (2). As seen in the MK-3475 melanoma and NSCLC trials, tumors with PD-L1 expression had better progression-free survival compared to PD-L1 negative tumors. Additionally, the genomic landscape of these cancers has shown at least 48 genes with differential mutation frequencies that can lead to an array of antigenic targets for immune based therapeutics (3). Such high mutational frequencies in tumors have been hypothesized to be a factor in patient response to checkpoint inhibitors, as in the case of lung and bladder cancers. Thus, we believe that anti-PD1 therapy will have signal in endometrial carcinoma.

1.2 MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (4). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (5-9) . 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) (10, 11). The structure of murine PD-1 has been resolved (12). 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 (11, 13-15). 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 (7, 16). 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 (17, 18). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (19). 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 (4-8). 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 (18). 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) (20) . 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 Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Please refer to the IB for preclinical and clinical data.

1.2.1 Rationale for Dosing

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. 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). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the 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 showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of 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.

1.3 Study Rationale

Women with early stage and FIGO grade 1 and 2 endometrial cancer have a relatively good prognosis with surgery alone or surgery plus radiation (21). However, 10-15% of patients are diagnosed with stage III disease at the time of surgery, and have an estimated 5 year survival rate of 40-70% (22). Lastly, the remaining 10-15% of patients are diagnosed with stage IV disease and have a very poor 5 year survival of 0-10% (23).

Those patients with advanced disease are unlikely to be cured by surgery, chemotherapy and/or radiation alone. In addition, the prognosis for recurrent disease is even more dismal, with expected overall survival of only 14-15 months. It is well-known that more aggressive histologies such as serous and clear cell carcinoma cause a disproportionate amount of recurrent cases and ultimately deaths therefore requiring more aggressive treatment even in early stage disease.

The Cancer Genome Atlas Research Network published that uterine serous carcinomas and approximately 25% of high-grade endometrioid cancers had extensive copy number alterations and frequent TP53 mutations. Additionally, there were frequent mutations in PTEN, CNNB1, PIK3CA, ARID1A, ARID5B and KRAS. Uterine serous carcinomas shared genomic features with ovarian serous carcinomas (3).

Much work needs to be done with regards to managing patients with advanced stage or recurrent disease. The current standard is systemic treatment with paclitaxel and carboplatin. A large phase III non-inferiority study performed by the Gynecologic Oncology Group (GOG) compared paclitaxel/carboplatin versus a three drug regimen of paclitaxel, doxorubicin and cisplatin (TAP) and showed that paclitaxel/carboplatin was not inferior to TAP in terms of PFS and OS.

Overall, paclitaxel and carboplatin also had a favorable toxicity profile (24, 25). According to the Surveillance, Epidemiology and End Results (SEER) study of cases diagnosed from 1998-2001, the five-year survival rate (26):

- Among women with stage III cancers, it was 33, 48, 48 for serous, clear cell, and grade 3 endometrioid cancers respectively.
- Among women with stage IV cancer, it was 18, 18, 37 percent for serous, clear cell, and grade 3 endometrioid respectively.

Thus no other adjuvant therapies have been identified to improve this dismal statistic of survival for patients with stages III/IV endometrial cancer.

Vanderstraeten et al. used a composite immunohistochemistry scoring which included the subparts of the percentage of total tumor cells showing expression and the intensity of the staining to evaluate indoleamine 2,3 dioxygenase, PD-L1, and PD-L2 in mainly grade 3 endometrioid, clear cell and papillary serous uterine cancers. Eighty-three percent of primary endometrial tumors showed high expression of PD-L1, and there was a trend to improved overall survival in patients with high expression of PD-L1. Sixty-seven and one hundred percent of recurrent and metastatic endometrial cancers had high expression of PD-L1 (2). Gatalica and colleagues surveyed several common cancer types and confirmed in 16 cases of endometrial cancer that there was 88% PD-L1 expression in tumor cells and concurrent PD-1 and PD-LI expression in 79% (27). Interferon-gamma and $CD8^+$ T cells cause upregulation of PD-L1. Therefore, PD-L1 expression could be viewed as a result of ongoing endogenous anti-tumor

immune response and may represent a negative feedback loop dependent on an infiltrating immune response (2).

Due to the high expression of PD-L1 in endometrial cancers as well as in ovarian cancers which are molecularly similar to uterine serous cancers, using pembrolizumab should be beneficial in this patient population. Since we are able to get a pre-treatment research- related endometrial biopsy as well as the surgical specimen post two cycles of pembrolizumab, we will be able to evaluate the mechanism of action of this drug on the endometrial cancer tumor environment. Please see below for more details.

1.4 Correlative Studies Background

The goal of the correlative work will be to determine if there is any correlation between the primary endpoint and biomarkers within peripheral blood or in the tumor specimens. The key advantage of this study is the availability of not only matched pre- and post-treatment peripheral blood but also pre- and post-treatment tumor tissue from treatment naïve patients. Existing data suggest that tumor expression of PD-L1 correlates with patient responses. However, the understanding of predictive biomarkers is incomplete. Thus, we propose to not only incorporate PD-L1 tumor staining on the neoadjuvant biopsies of pre- and post-treatment tumors, but to also analyze molecular signatures in peripheral blood and tumor tissues. RNA profiling of the pre- and post- pembrolizumab treated specimens will also be performed using either FFPE tumors or flash frozen tumors. Together, these data will lead to an improved understanding of those endometrial cancer patients who may benefit most from MK-3475 therapy.

We hypothesize that MK-3475 will result in increased T cell responses in peripheral blood as detected by multiparameter analysis and will define a unique biomarker molecular signature of MK-3475 activity (28). MK-3475 treatment will reveal an intratumoral signature of an immune response to advanced stage endometrial cancer. The goal will be to determine if there is any correlation between the primary endpoint and biomarkers within peripheral blood or in the tumor specimens. The key advantage of this study is the availability of not only matched pre- and post-treatment peripheral blood but also pre- and post-treatment tumor tissue from treatment naïve patients. In addition to standard IHC methodology, we will aim to generate biomarkers that will be linked to patient outcomes identified in the primary endpoint. Using our immunomonitoring core, we will apply CyTOF or FACS based multiparameter analysis of PBMCs pre- and post- MK-3475 treatment to delineate immune cell subsets and cell surface activation markers. Additionally, pre-treatment tumor tissue is available, FACS or CyTOF will also be applied to tumor infiltrating immune cells.

A next generation of single-cell analysis technology called mass cytometry overcomes limitations of flow cytometry of measuring a maximum of ten markers per panel. The CyTOF (Cytometry of Time Of Flight) is a mass spectrometer-flow cytometer hybrid instrument that uses stable isotopes instead of fluorophores as reporters. Due to the discrete read-outs of mass cytometry, use of isotopes as reporters enables a significant increase in the number of measurable parameters per cell. CyTOF will be used to detect changes in immune populations and markers. Additionally panels can be designed with up to 45 antibodies focused completely on surface markers to delineate cellular hierarchy and intracellular signaling molecules. This will allow us to focus on the activation states of intracellular signaling pathways (29).

Additionally, T cell immune repertoire diversity based on the detection of V-J arrangements of the T cell receptor (TCR) will allow monitoring of immune diversity in blood or tumors (30).

2.0 OBJECTIVES

2.1 Primary Objective

To determine the safety of treatment with MK-3475 in women with advanced endometrial adenocarcinoma.

2.2 Secondary Objective

To determine progression-free survival of women with endometrial adenocarcinoma treated with MK-3475.

2.3 Exploratory Objective

To compare the anti-endometrial tumor immune response before and after treatment with MK-3475 as measured by PD-L1 IHC expression, immune function in blood and tumor tissue, and immune correlates.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Diagnosis of FIGO grade 3 endometrioid cancer, serous, clear cell, or mixed high grade endometrial cancer with confirmation on research-related endometrial biopsy.

2. Radiographically confirmed endometrial adenocarcinoma of stages III-IV requiring adjuvant therapy. If stage III disease is suspected, there should be multiple pelvic and/ and or lymph nodes involved.

3. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with CT scan, as $\geq$20 mm by chest x-ray, or $\geq$10 mm with calipers by clinical exam by RECIST 1.1.

4. Treatment plan must include primary site biopsy followed by resection of the primary tumor site and any metastatic sites at time of surgery.

5. At least 18 years of age.

6. GOG performance status $\leq$ 2 (see Appendix A).

7. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count $\geq$ 1,500/mcl
   b. Platelets $\geq$ 100,000/mcl
   c. Hemoglobin $\geq$ 9 g/dL
   d. Total bilirubin $\leq$ 1.5 x IULN OR direct bilirubin $\leq$ IULN for patients with total bilirubin > 1.5 x IULN

e. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN (or ≤ 5 x IULN for patients with liver metastases)
f. Serum creatinine ≤ 1.5 x IULN OR creatinine clearance by Cockcroft-Gault ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels > 1.5 x IULN
g. INR or PT ≤ 1.5 x IULN unless patient is receiving anticoagulant therapy as long as INR or PTT is within therapeutic range of intended use of anticoagulants
h. aPTT ≤ 1.5 x IULN unless patient is receiving anticoagulant therapy as long as INR or PTT is within therapeutic range of intended use of anticoagulants

8. Sexually active women of childbearing potential must agree to contraceptive methods as described in Section 5.5 prior to study entry, for the duration of pre-operative study participation and until definitive hysterectomy/bilateral salpingo-oophorectomy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

9. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. FIGO grade 1 or 2 endometrioid cancer.

2. Radiographic imaging demonstrating uterine cancer that is probably stage I or II.

3. Prior treatment for endometrial cancer.

4. Prior treatment with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

5. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to first dose of MK-3475 or has not recovered (i.e., to ≤ grade 1 or baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the first dose of MK-3475 or has not recovered (i.e., to ≤ grade 1 or baseline) from adverse events due to a previously administered agent. Note, subjects with ≤ grade 2 neuropathy are an exception to this criterion and may qualify for the study. Note, if a subject received major surgery, she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Received a live vaccine within 30 days prior to the first dose of MK-3475. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist) are live attenuated vaccines and are not allowed.

8. A history of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only.

9. Known active central nervous system 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 4 weeks prior to the first dose of MK-3475 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 trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

10. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of MK-3475.

11. Currently receiving any other investigational agents or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of MK-3475.

12. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-3475 or other agents used in the study.

13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring systemic therapy, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, immunosuppression, autoimmune conditions, underlying pulmonary disease, or psychiatric illness/social situations that would limit compliance with study requirements.

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

15. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

16. Pregnant and/or breastfeeding. Patient must have a negative serum or urine pregnancy test within 72 hours of study entry.

17. Known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus defined as HCV RNA [qualitative] is detected).

18. Known history of HIV (HIV 1/2 antibodies).

19. Known history of active TB.

3.3 Inclusion of Women and Minorities

Women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

All patients must be registered through the Siteman Cancer Center database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

Patients will undergo endometrial biopsy followed by two doses of neoadjuvant MK-3475 three weeks apart. Three to four weeks after the second dose of MK-3475, the standard of care surgical resection will take place, followed by standard of care adjuvant therapy (chemotherapy ± radiation). Tissue and blood will be collected at the time of surgical resection for immune analysis. Patients confirmed to have high-risk endometrial cancer will begin additional treatment with adjuvant MK-3475 4 to 6 weeks after the end of adjuvant chemotherapy +/- radiation for a total of 4 doses and will undergo evaluations for toxicity and response.

5.1 Premedication Administration

No premedications are required for MK-3475, but antiemetics will be given as per institutional practice for the adjuvant chemotherapy with or without radiation.

5.2 Agent Administration

MK-3475 will be given intravenously at a dose of 200 mg over the course of 30 minutes (-5 min/+10 min) on an outpatient basis. MK-3475 will be given twice prior to surgery at three week intervals, with the second dose given 3 to 4 weeks pre-op. After surgery, all patients will receive standard of care adjuvant therapy (chemotherapy ± radiation). For patients whose pathology confirms high-risk features and advanced stage, MK-3475 will be given every 3 weeks starting 4 to 6 weeks after completion of adjuvant therapy for a maximum of 4 doses post-surgery.

5.2.1 Post-operative Chemotherapy Regimen

This will consist of 6 cycles of paclitaxel 175mg/m^2 and carboplatin AUC 5 every 3 weeks if patient has adequate blood and chemistry values for 6 cycles. Docetaxel can be substituted for paclitaxel per institutional guidelines if a patient suffers a hypersensitivity reaction. Chemotherapy cycles may be delayed per treating physician's discretion.

Paclitaxel will be infused over approximately 3 hours.

Carboplatin will be infused over approximately 30 minutes, following paclitaxel.

For all cycles where paclitaxel is to be administered, it is recommended that a preparative regimen be employed, to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an equivalent dose of an alternate H1blocker such as loratadine or fexofenadine), and a standard dose of antihistamine H2 IV (Famotidine is preferred, but ranitidine can also be used). The preparative regimen can be altered at the discretion of the treating physician.

Dosing of Carboplatin: See Appendix B for Carboplatin Dose Calculation Instructions.

Chemotherapy administration: See Appendix C for General Chemotherapy Guidelines.

5.2.2 Post-operative Radiation Therapy

The decision to administer radiation therapy will be per the treating physician. If the patient does not receive radiation therapy, then the patient will start MK-3475 every three weeks x four doses after the completion of chemotherapy.

5.3 Evaluability

All patients who receive any treatment with MK-3475 are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment due to treatment related adverse events(s) before any disease assessment. Patients will be followed

every 3 months post-completion of MK-3475 adjuvant therapy for two years and every 6 months for three additional years (unless patient recurs sooner).

5.4 General Concomitant Medication and Supportive Care Guidelines

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Patients are prohibited from receiving the following therapies while in screening for and enrolled in this trial:

- Antineoplastic systemic chemotherapy other than as dictated in the post-operative setting or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy other than as dictated in the post-operative setting
- Live vaccines within 30 days prior to the first dose of treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Steroids may be used as anti-emetics around the time of chemotherapy delivery, which may occur more than 10 weeks after the pre-operative single dose MK-3475 and 4 weeks before post-operative dosing. In the immediate perioperative period patients receive steroids to help with wound edema from surgery. The use of physiologic doses of corticosteroids may be approved.

Patients may receive myeloid growth factors either filgrastim or pegfilgrastim) can be used per institutional guidelines. This may only be used during administration of chemotherapy ± radiation therapy and **not** during the pre-operative or post-adjuvant therapy of MK-3475.

5.4.1 Supportive Care Guidelines for Infusion Reactions

Pembrolizumab may cause severe or life-threatening reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

The table below shows treatment guidelines for patients who experience an infusion reaction associated with MK-3475.

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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 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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.5 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum or urine pregnancy test within 72 hours prior to the first dose of MK-3475.

Pembrolizumab may have adverse effects on a fetus in utero.

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). Women in the following categories are not considered of childbearing potential:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described below) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below during the protocol-defined timeframe.

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*

● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, after the last dose of study treatment, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for up to 4 doses of MK-3475 in the adjuvant setting following surgery plus adjuvant chemotherapy +/- radiation therapy or until one of the following criteria applies:

- Documented and confirmed disease progression

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.7 Duration of Follow-up

All patients will be followed for at least 5 years for cancer surveillance following completion of postoperative treatment with MK-3475 (i.e. up to 5 years after surgery) or for 5 years after surgery for patients who did not receive post-op MK-3475 or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event or up to 5 years as dictated by the treating physician. Case report forms will be filled in every 3 months for the first 24 months post-completion of therapy and then every 6 months for the following 3 years until progression.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 MK-3475 Dose Modifications

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. In case any toxicity listed below does not resolve to grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued. However patients with a laboratory adverse event still at grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled and with PI approval. For information on the management of adverse events, see the table below.

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

Pembrolizumab will be withheld for drug-related toxicities and severe or life-threatening AEs as per the table below.

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 ≤ 10 mg 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 (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation 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
	Grade 3 or 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 (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. 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 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

6.2 Dose Modifications for Chemotherapy

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study.

6.2.1 Individual Dose Modification Levels

All modifications are relative to the actual starting doses for the specific Regimen. For application of individual dose modifications, see specific guidelines below.

Allowable drug dose levels and instructions are summarized in Tables A, B, and C.

General Guidelines for Hematologic Toxicity

- Hematologic Nadirs, Table A
- Delayed Hematologic Recovery, Table B
- Non-Hematologic Toxicity, Table C

6.2.2 General Guidelines for Hematologic Toxicity

Initial treatment modifications will consist of cycle delay and/or dose reduction as directed. Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

6.2.3 Lower Limits for ANC and Platelet Count

Subsequent courses of treatment which contain any cytotoxic chemotherapy (carboplatin, paclitaxel) will not begin (**day 1 of each cycle**) until the ANC is ≥1,500 cells/ mcl and the platelet count is ≥ **100,000**/ mcl. Such treatment will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive any protocol-directed therapy.

Exceptions:
Patients who received filgrastim or pegfilgrastim prior to the current cycle may begin (day 1 of cycle) with ANC ≥ 1000 cells/mcl, if clinically appropriate, to allow for transient reductions in ANC after discontinuation of myeloid growth factors. Patients who are delayed more than 7 days may begin with ANC ≥ 1000 cells/ mcl, if clinically appropriate; and if they will receive filgrastim or pegfilgrastim with subsequent therapy.

6.2.4 Modifications for Hematologic Toxicity (Nadirs)

Initial occurrence of dose-limiting neutropenia (defined in 6.15) or dose limiting thrombocytopenia (defined in 6.16) will be handled according to Table A.

Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile

neutropenia or prolonged Grade 4 neutropenia persisting ≥ 7 days. There will be no modifications for uncomplicated Grade 4 neutropenia lasting less than 7 days. Febrile neutropenia is defined as a disorder characterized by an ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour. Dose reductions will be handled according to Table A.

Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia or bleeding associated with Grade 3 thrombocytopenia. There will be no modifications for uncomplicated Grade 3 thrombocytopenia. Dose reductions will be handled according to Table A.

Table A: Modification Instructions for Dose-Limiting Hematologic Toxicity

DLT ANC	DLT PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes±	No	Reduce paclitaxel one dose level	Reduce carboplatin one AUC unit*	Discontinue protocol-directed cytotoxic chemotherapy
Yes±	Yes	Reduce paclitaxel one dose level and carboplatin one AUC unit*	Reduce paclitaxel one dose level	Discontinue protocol-directed cytotoxic chemotherapy
No	Yes	Reduce carboplatin one	Reduce paclitaxel one dose level	Discontinue protocol-directed cytotoxic chemotherapy

*Minimum carboplatin dose = AUC 4.
±Myeloid growth factors (either filgrastim or pegfilgrastim) can be used (it is recommended that ASCO, NCCN and/or your institutional guidelines be consulted).

6.2.5 Modifications for Delayed Hematologic Recovery:

Delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is less than 1,500 cells/mcl within 24 hours prior to scheduled day 1 therapy, or less than 1,000 cells/mcl, if the patient received filgrastim or pegfilgrastim during the previous cycle.

Delay on the basis of thrombocytopenia (Delay-PLT) is defined if the platelet count is less than **100,000**/mcl within 24 hours prior to scheduled day 1 therapy.

Modifications noted below are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT (as noted above). In other words, if the patient experiences DLT-ANC and Delay-ANC, make the modifications as indicated for the nadir counts without additional modifications based on delayed recovery.

Table B: Modifications for Delayed Hematologic Recovery

Category	Delay (days)	Modification
Delay - ANC†	1-7	No Change mandated
	8-21	Decrease paclitaxel one dose level
	>21	Discontinue Protocol Directed Cytotoxic Chemotherapy
Delay-PLT	1-7	No Change
	8-21	Decrease carboplatin one AUC unit*
	>21	Discontinue Protocol Directed Cytotoxic Chemotherapy

*Minimum carboplatin dose = AUC 4.
†Myeloid growth factors (either filgrastim or pegfilgrastim) can be used (it is recommended that ASCO,

NCCN and/or your institutional guidelines be consulted).

6.2.6 Adjustments for Non-Hematologic Toxicity

Table C: Adjustments for Non-Hematologic Toxicity			
Drug	**Regimen -2 Level**	**Regimen -1 Level**	**Regimen Starting Dose**
Paclitaxel	110 mg/m2	135 mg/m2	175 mg/m2
Carboplatin	Discontinue	AUC = 4	AUC = 5

The development of Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel. If CTCAE Grade 3 or 4 peripheral neuropathy occurs then subsequent doses of paclitaxel will be delayed for a maximum of three weeks until recovered to CTCAE Grade ≤2. If peripheral neuropathy fails to recover to Grade ≤2 by a maximum delay of three weeks from time therapy is due, then all paclitaxel should be withheld from all subsequent chemotherapy cycles.

Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this chemotherapy naive patient population using the prescribed dose and schedule of each regimen. See Appendix C (Carboplatin Dose Calculation Instructions).

Hepatic toxicity is not expected as a direct complication of chemotherapy in this chemotherapy naive patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in AST, ALT, alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

There will be no dose modifications for alopecia or controllable nausea, vomiting, constipation, or diarrhea. It is recommended that routine medical measures be employed to manage nausea, vomiting, constipation, and diarrhea.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.4. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Merck requires that all SAEs or SUSARs be reported as outlined in Section 7.5.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.

- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.5 Reporting to Merck & Co., Inc.

The PI shall forward to Merck's Global Safety group (FAX 215-661-6229) any SAE and SUSAR information, including, but not limited to, all initial and follow-up information

involving any study subject in the study within 2 business days or 3 calendar days (whichever comes first) of learning of the SAE or SUSAR.

"Adverse Event" or "AE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

"Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious."

"Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

7.5.1 Reporting Overdose

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 and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

7.5.2 Reporting Pregnancy and Lactation

Although pregnancy and infant exposure during breastfeeding 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.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

7.5.3 Reporting Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

Events of clinical interest for this trial include:

1. an overdose of Merck product that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is $\geq$ 3 x IULN and an elevated total bilirubin lab value that is $\geq$ 2 x IULN and, at the same time, an alkaline phosphatase lab value that is < 2 x IULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

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

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

7.6 Timeframe for Reporting Required Events

Adverse events will be tracked for 30 days following the last day of study treatment. For the purposes of this protocol, reportable adverse events are events thought to be possibly, probably, or definitely related to MK-3475. Events thought to be probably or definitely related to surgery or adjuvant therapy need not be recorded. Please note that patients must be followed for events of clinical interest for 90 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

8.1 MK-3475

8.1.1 MK-3475 Description

MK-3475 is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, MK-3475 has high affinity and potent receptor blocking activity for PD-1. MK-3475 has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies.

8.1.2 Clinical Pharmacology

Refer to Section 5.2 of the IB.

8.1.3 Pharmacokinetics and Drug Metabolism

Refer to Section 5.2 of the IB.

8.1.4 Supplier

MK-3475 will be provided free of charge by Merck & Co., Inc.

8.1.5 Dosage Form and Preparation

Merck will provide MK-3475 as a liquid drug product.

8.1.6 Storage and Stability

MK-3475 should be stored under refrigerated conditions (2°C - 8°C).

If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours.

8.1.7 Administration

MK-3475 will be given intravenously over the course of 30 minutes (-5 min/+10 min) on an outpatient basis.

8.2 Paclitaxel

8.2.1 Formulation

Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi-dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel In addition to 6mg of paclitaxel, each mL of sterile nonpyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

8.2.2 Storage

Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

8.2.3 Stability

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

8.2.4 Preparation

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

8.2.5 Supplier/ How Supplied

Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

8.3 Carboplatin (Paraplatin®)

8.3.1 Formulation

Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin.

8.3.2 Storage

Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

8.3.3 Preparation

Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

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

8.3.4 Supplier

Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

9.0 CORRELATIVE STUDIES

9.1 Tumor Tissue

9.1.1 Collection of Specimens

An endometrial biopsy will be performed at baseline for research purposes only since majority of patients will have already had either an endometrial biopsy or dilatation and

curettage performed to confirm diagnosis prior to seeing the gynecologic oncologist. At least 1 ml of tissue will be needed and placed in saline. We will try to collect metastatic disease if possible for research purposes if the treating clinician decides to get a biopsy of a metastatic site prior to initiation of any therapy. Dr. Ian Hagemann will confirm the histology, tumor presence and viability of the research endometrial biopsy and if there is a metastatic site. Tissue from the surgical resection of both primary uterine tumor and a metastatic site will also be harvested for analysis of intratumoral changes. Routinely a pathology resident or fellow comes to the operating room intraoperatively to evaluate the uterus for viable tumor and will provide the samples of both the primary uterine tumor and metastatic site. Dr. Hagemann will then confirm the tumor histology, cellularity and viability of these samples by H&E.

In the event that the research biopsy does not yield sufficient tissue to be able to perform the correlative studies required, the FFPE archival block from the original diagnostic procedure will be requested. Consent and release of records will be utilized to obtain the block which is required from the pathology department of origin. Laboratory personnel will use to block to cut up to 10 slides to include 1 slide for H&E staining and the rest (5μm, charged slides) to be used to complete the correlative studies. The block will then be returned to the originating pathology department. Additionally, RNA will be obtained from FFPE slides or fresh frozen tumors for RNA profiling of pre- and post-pembrolizumab treated tumors.

Up to 10 additional tissue samples from patients with either advanced stage endometrial or ovarian cancer, and some normal endometrium or ovarian tissue samples will be requested from our Gynecologic Oncology Tissue Bank (IRB#:201105400) at Washington University in St. Louis.

In addition, up to 10 samples of whole blood from patients with either advanced stage endometrium or ovarian cancer, and some normal pathology will also be requested from our tissue bank.

Both the blood and tissue samples will have been collected under the tissue bank consent for that study, and per division policy, a request for these samples will be made to the bank and approval received by the appropriate faculty before they are used. These samples will be de-identified prior to submission to Dr. Fuh's lab and no identifying except some minimal clinical data to confirm histology and advanced stage cancer will be associated with the samples. These matched blood and tissue samples will be used as controls for the CyTof testing as well as optimization as described below.

9.1.2 Handling of Specimens

The specimens will be taken to the laboratory of Katherine Fuh, MD, PhD. and tissue digestion will be performed in preparation for CyTof. Paired pre- and post-treatment blood will be analyzed by multiparameter CyTOF mass cytometer based analysis in CHiiPS for changes in immune populations and markers including ICOS and PD-1. CD3+ infiltrates in tumors and TCR repertoire expansion, and antibody arrays will also be performed. IHC on pre-and post-treatment tumor samples to examine for immune cell infiltrates will be performed which include but are not limited to T cells: CD3, CD4,

CD8, CD25, Foxp3; B cells: CD19, CD20, MDSC: Siglec-3/CD33, Lineage negative, HLA-DR negative, CD14+; DC: CD11c HLA-DR lineage +/- CD123 +/- CD8; NK: CD16, CD5, CD107, CD3-; Macrophages/TAMs: CD11b+, CD11c-, CD68.

IHC intensity will be graded by 2 blinded reviewers for both intensity and frequency of staining by microscopy. IHC staining for PD-L1 will be performed PD-L1 assessment with the prototype assay as developed by Merck. The following scoring system will be used as performed in the pembrolizumab paper in NSCLC. The intensity of the infiltrates will be graded by using a proportion score (PS), defined as the percentage of cells with membranous PD-L1 staining at any intensity. A proportion score of 2+ or 3+ (P2S) is defined as the percentage of cells with membranous PD- L1 staining at moderate (2+) or strong (3+) intensity. A proportion score 3+ (P3S) is defined as the percentage of cells with membranous PD-L1 staining at strong intensity (3+). A modified H-score (HS) provides a numerical value that accounts for the proportion of cells staining for PD-L1 at each of the 3 intensities.

In addition to standard IHC methodology, we will be applying approaches for biomarker generation that can be linked to patient outcomes through next-generation sequencing and CyTOF. Using the immunomonitoring core of ChiiPs, we will apply CyTOF multi parameter analysis of endometrial cells pre- and post-MK-3475 treatment to delineate immune cell subsets and cell surface activation markers. Tissue samples requested from the tissue bank of the Division of Gynecologic Oncology will be used as controls. CyTOF will also be applied to analyze the tumor infiltrating immune cells (eg. CD3+TIL). The breadth of the immune response will be evaluated by TCR repertoire expansion (for the cellular arm), and antibody array (for the humoral response).

9.2 Peripheral Blood for Biomarkers

9.2.1 Collection of Specimens

Blood samples (10-15 mL) will be collected and fixed using a fixation/stabilization buffer (Smart Tube Inc.) within 30 min of phlebotomy and stored at −80°C. Collection will be performed prior to first dose of MK-3475, prior to second dose of MK-3475, day of surgery, after adjuvant therapy and prior to resuming first dose of MK-3475 after adjuvant therapy, and every other administration of MK-3475 in adjuvant setting (pre-dose 2 and 4 of MK-3475).

9.2.2 Handling of Specimens

Samples will be thawed on the day of processing. Red blood cells will be lysed using a hypotonic buffer (Smart Tube Inc.). Peripheral blood leukocytes will be washed and resuspended in cell staining medium. This will be performed in the laboratory of Katherine Fuh, MD, PhD. Using the immunomonitoring core of CHiiPs, we will apply CyTOF multiparameter analysis of PBMCs pre- and post- MK-3475 treatment to delineate immune cell subsets and cell surface activation markers (similar markers as was performed for the endometrial tumors as for blood). Blood samples from the tissue bank of the Division of Gynecologic Oncology will be used as controls. CyTOF will also be applied to analyze the tumor infiltrating immune cells (e.g. CD3+ TIL). The breadth

of immune response will be evaluated by TCR repertoire expansion (for the cellular arm), and antibody array (for the humoral response).

10.0 STUDY CALENDAR

10.1 Calendar for All Participants

There is a +/- 2-day window for all assessments with the exception of surgery.

	Screening[11]	Baseline[12]	Day 1	Day 22	Days 42-46 (Surgery)	Adj. Tx[4]	Maint. MK-3475	Follow-Up[3]
Informed consent	X							
H&P, ECOG PS, wt	X		X	X				
Vital signs (HR, BP, temp)	X		X	X				
CBC	X		X[13]	X[14]				
CMP	X		X[13]	X[14]				
aPTT and PT/INR	X							
Pregnancy test	X[1]							
TSH	X			X[14]			X[8]	
Chest imaging (X-ray or CT)	X				X[2,10]	X[5]		X[9,10]
CT or MRI of abdomen/pelvis	X				X[2,10]	X[5]		X[9,10]
Endometrial biopsy[10]		X			X			
Peripheral blood[10]		X		X	X	X[6]	X[7]	
MK-3475			X	X				
AE assessment		X	Pts will be followed for AEs for 90 days following the last dose of MK-3475. AE assessment at each cycle of MK-3475.					

1. Women of childbearing potential only. To be performed no more than 72 hours prior to start of treatment
2. Within a week of surgery but post-second dose of neoadjuvant MK-3475
3. Follow-up will be performed as per routine care of every 3 months for the first 2 years after surgery and every 6 months for the next 3 years until progression occurs. Data on progression and survival will be recorded.
4. Adjuvant therapy should typically begin between 4 and 6 weeks following surgery. Laboratory assessments will be performed as per routine care and will not be dictated by this research protocol.
5. Radiographic imaging will be considered standard of care after completing chemotherapy +/- radiation therapy
6. Peripheral blood draw at completion of adjuvant therapy
7. Blood draw at Cycles 2 and 4 of MK-3475
8. TSH to be draw in adjuvant setting if elevated in neoadjuvant setting
9. Imaging post completion of MK-3475 Cycle 4 in adjuvant setting. Imaging should be done within 30 days of completing treatment.
10. Research-related assessment
11. Chest imaging and CT or MRI abd/pelvis within 28 days of treatment; all other procedures within 14 days of treatment
12. Within 14 days of enrollment.
13. Screening labs can be used if within 14 days of Day 1.
14. Drawn within 3-5 days of treatment

10.2 Calendar for Participants Who Receive Adjuvant MK-3475

Only patients whose pathology shows high risk features will receive further treatment with MK-3475. This treatment will start 4 to 6 weeks after the end of standard of care adjuvant treatment.

	Dose #1	Dose #2	Dose #3	Dose #4	Post-dose #4
H&P, ECOG PS, wt	X	X	X	X	
CBC[1]	X	X	X	X	
CMP[1]	X	X	X	X	
TSH[1]	X		X		
MK-3475	X	X	X	X	
Blood draw		X		X	
Imaging[2]					X
AE assessment	X ---------- X				

1. Drawn within 3-5 days before treatment
2. Within 30 days of completing dose #4

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Pre-Treatment Summary Form	Prior to starting treatment
MK-3475 Treatment Form	Every dose of MK-3475 (Neoadjuvant and adjuvant)
Surgery Form	Time of surgery
Correlatives Form	Prior to starting treatment Day 22 Surgery Adjuvant therapy Maintenance Dose #2 Maintenance Dose #4
RECIST Form irRECIST Form	Prior to starting treatment Surgery Adjuvant therapy Post-Maintenance Dose #4
Toxicity Form	Continuous
Adjuvant Treatment Summary Form	Adjuvant therapy
Treatment Summary Form	Completion of treatment
Follow Up Form	Q 3 months for first two years and then Q 6 months for additional 3 years until progression occurs
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response per table 10.1 and per the treating physician's discretion if there is a concern of progression sooner In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

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

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

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

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

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

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

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

12.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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

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

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

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

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

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

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

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

12.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

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

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

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.4.4 Duration of Response

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

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

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

12.4.5 Progression-Free Survival

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

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

This single arm, phase I study will investigate the safety of treatment with MK-3475 in women with advanced endometrial adenocarcinoma.

14.2 Study Endpoints

The primary endpoint is safety as measured by treatment related adverse events. Secondary endpoints include 2-year progression-free survival (PFS) for all the endometrial adenocarcinoma patients treated with MK-3475, as well as the anti-endometrial tumor immune response before and after treatment with MK-3475 as measured by PD-L1 IHC expression, immune function in blood and tumor tissue, and immune correlates.

14.3 Data Analysis

Demographic and clinical characteristics will be summarized using descriptive statistics. PFS will be analyzed by Kaplan-Meier (KM) method. Paired t-test and/or paired-sample Wilcoxon Signed Rank test will be used to compare the anti-endometrial tumor immune response before and after treatment with MK-3475.

14.4 Power Analysis and Sample Size

Approximately 9 evaluable patients will be enrolled. The proposed sample size was chosen to allow assessment of safety and was not based on either statistical modeling or methods to obtain adequate power for any endpoint analysis.

14.5 Accrual

The rate of accrual for the study is expected to be about 1 patient per 1-3 month. It is estimated 6-9 patients will be enrolled within one year.

14.6 Toxicity and Plans for Data and Safety Monitoring (Stopping Rule)

Toxicity will be reviewed on a continuous basis. Early stopping of this trial will be based on the excessive MK-3475-related adverse events (AE). Assuming a maximum-tolerated toxicity rate is 30% and a toxicity rate of 25% and or less is acceptable, based on the repeated significance testing (using R function toxbdry) with 80% power and 0.05 overall Type I error, the study will be halted if excessive MK-3475-related adverse events occur in the first patients, or 2 of the first 3 patients, or 3 of the first 5, or 4 of the first 7, or if the 5^{th} unacceptable toxicity is observed before the last evaluable patient has completed the trial.

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APPENDIX A: ECOG Performance Status Scale

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.

APPENDIX B: Carboplatin Dose Calculation Instructions

- The Cockcroft-Gault formula will be used in this trial.
- Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.
- The carboplatin calculation tool is available on the GOG website (Web Menu, Tools).

1) **Dosing of Carboplatin:**

2) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

3) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

4) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

5) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

6) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dl.** For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.
The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

Creatinine Clearance (mL/min) = [140-Age (years)] x Weight (kg) x 0.85
72 x serum creatinine (mg/dl)

Notes:
1) Weight in kilograms (kg):
a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity: If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX C: General Chemotherapy Guidelines

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m^2. For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).