**Protocol Title**

Phase II Study of Pembrolizumab in Combination with Carboplatin and Paclitaxel for Advanced or Recurrent Endometrial Adenocarcinoma
Big Ten Cancer Research Consortium BTCRC-GYN15-013

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**Trial Supported by**
Merck Sharp & Dohme Corp.
(MISP 52552)

**Trial Management by**
BTCRC Administrative Headquarters at Hoosier Cancer Research Network
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Indianapolis, IN 46204

**Investigational New Drug (IND) Application Number**
131231

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13OCT2016

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27FEB2017
17APR2017
31MAY2017
**08JUN2018** (current)

## PROTOCOL SIGNATURE PAGE

Phase II Study of Pembrolizumab in Combination with Carboplatin and Paclitaxel for Advanced or Recurrent Endometrial Adenocarcinoma

**VERSION DATE: 08JUN2018**

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the site investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to BTCRC Administrative Headquarters and keep a record for your files.

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

**PLEASE COMPLETE AND EMAIL TO BTCRC ADMINISTRATIVE HEADQUARTERS**

**STUDY SYNOPSIS**

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| **TITLE** | Phase II study of pembrolizumab in combination with carboplatin and paclitaxel for advanced or recurrent endometrial adenocarcinoma |
| **SHORT TITLE** | Phase II pembro/carbo/Taxol in endometrial cancer |
| **PHASE** | II |
| **OBJECTIVES** | **Primary Objective:**<br>To estimate the objective response rate of pembrolizumab in combination with standard carboplatin/paclitaxel in subjects with measurable advanced or recurrent endometrial cancer.<br>**Secondary Objectives:**<br>To determine the toxicities of pembrolizumab in combination with standard carboplatin/paclitaxel in subjects with advanced or recurrent endometrial cancer.<br>**Correlative Objectives:**<br>To evaluate potential biomarkers or prognostic factors for those who may respond to pembrolizumab. |
| **OUTCOME MEASURES** | **Primary Endpoint**<br>Objective response rate is defined as the proportion of subjects with a partial response or complete response according to immune-related RECIST criteria.<br><br>**Secondary Endpoints**<br>Toxicity is defined as the proportion of subjects who experience ≥ Grade 3 toxicity according to CTCAE v4.<br><br>**Correlative/ Exploratory Endpoints**<br>Immunohistochemical evaluation of expression of PD-L1; Treg, Tumor Infiltrating Lymphocytes, and Myeloid Derived Suppressor Cell abundance in formalin-fixed, paraffin-embedded endometrial tumor and fresh frozen biopsy specimen, if available.<br><br>Characterization of circulating immune cell populations ($TIM3^+/PD\text{-}1^+/CD8^+$, $PD\text{-}1^+$/Treg) will be evaluated on samples collected prior to the start of and upon completion of combination pembrolizumab/cytotoxic chemotherapy.<br><br>Determination of the mutational landscape of endometrial cancer and its influence in the response to pembrolizumab. Exome sequencing and targeted next generation sequencing, targeting all exons of approximately 300 cancer related genes will be performed from FFPE tissue from participants' tumors. |
| **STUDY DESIGN** | This is a single-arm, open-label, multi-center phase II study for subjects with measurable advanced or recurrent endometrial cancer using pembrolizumab in combination with carboplatin and paclitaxel chemotherapy. As this combination of agents has not been tested in this subject population, the first six subjects enrolled will constitute a safety run-in cohort (see Section 5.2). |

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| **ELIGIBILITY CRITERIA** | **Inclusion Criteria**<br>Subjects must meet all of the following applicable inclusion criteria to participate in this study:<br><br>**1.** Written informed consent and HIPAA authorization for release of personal health information prior to registration for protocol therapy.<br>**NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.<br><br>**2.** Age ≥ 18 years at the time of consent.<br><br>**3.** ECOG Performance Status of 0 or 1 within 28 days prior to registration for protocol therapy.<br><br>**4.** Histological evidence of newly diagnosed Stage III or IV or recurrent endometrial carcinoma who have had definitive surgery for endometrial cancer (at least hysterectomy and bilateral salpingo-oophorectomy). Pathologic documentation of the recurrence (i.e., biopsy) will be performed per standard of care, at the treating physician's discretion. If a subject with recurrence is undergoing a biopsy for clinical indications and is willing and able, an optional collection of 3 frozen tissue cores of the recurrence site is requested for correlative analysis.<br><br>**5.** Measurable disease according to RECIST v1.1 and obtained by imaging within 28 days prior to registration for protocol therapy. Disease in an irradiated field as the only site of measurable disease is acceptable only if there has been clear progression since completion of radiation treatment.<br><br>**6.** The subject must have recovered (≤ grade 1) from the acute toxic effects of prior therapy.<br>**7.** Prior treatment: Subjects may have received none or one platinum-based chemotherapy regimen and none or one non-platinum regimen. Subjects having received prior platinum-based chemotherapy must have a disease-free interval > 6 months (be platinum sensitive).<br>**8.** Prior therapy with hormones or biologic agents is allowed. These treatments must be discontinued at least 28 days prior to registration for protocol therapy.<br>**9.** The subject must have completed prior radiation therapy at least 28 days prior to registration for protocol therapy, provided that toxicity has resolved to ≤ grade 1.<br>**NOTES**: Subjects may have received prior radiation therapy for treatment of endometrial carcinoma. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para-aortic radiation therapy, and/or intravaginal brachytherapy. Chemotherapy used for radiation sensitization is allowed. Chemotherapy used for radiation sensitization will not count as second chemotherapy regimen.<br><br>Palliative radiation given primarily for symptom relief, without the intent to treat or cure the patient's endometrial cancer is excluded from the above criteria. Treatment-directed radiation will be defined as more than 30 Gy of radiation. |

**10.** No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the subject has been disease-free for at least 5 years.

**11.** Female subjects must be of non-childbearing potential. Women of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥1 year.

**12.** Laboratory values must be obtained within 14 days prior to registration for protocol therapy. Note: Institutional/laboratory upper limit of normal (ULN)

- Hemoglobin (Hgb) > 9 g/dL (without transfusion or EPO dependency within 7 days of assessment)
- Platelets > 100 K/mm$^3$
- Absolute neutrophil count (ANC) ≥ 1.5 K/mm$^3$
- Creatinine or measured/calculated creatinine clearance (as calculated by institutional standard) ≤ 1.5 X institutional ULN OR ≥ 60mL/min for subjects with creatinine levels > 1.5 x institutional ULN
- Serum total bilirubin ≤ 1.5 × ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
- AST, ALT or alkaline phosphatase < 2.5 × ULN OR ≤ 5 x ULN for subjects with liver metastases
- Albumin ≥ 2.5 mg/dL
- International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless subject is receiving anti-coagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants
- Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 x ULN unless subject is receiving anti-coagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

**Exclusion Criteria**

**1.** Subjects with carcinosarcoma.

**2.** Subjects who have a solitary central pelvic recurrence which can be curatively resected.

**3.** Hypersensitivity to pembrolizumab or any of its excipients.

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

**5.** Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to registration for protocol therapy and

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| | 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 registration for protocol therapy. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. *Note: Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis.*<br>**6.** Treatment with any investigational agent within 28 days prior to registration for protocol therapy.<br>**7.** Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).<br>**8.** Active autoimmune disease that has required systemic treatment in 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.<br>**9.** Has received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to registration for protocol therapy. (Prednisone (or equivalent) < 10mg/ day is allowed).<br>**10.** Has a known history of active TB (Bacillus Tuberculosis)<br>**11.** Pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or hypersensitivity pneumonitis.<br>**12.** Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.<br>**13.** Evidence of interstitial lung disease<br>**14.** Has an active infection requiring systemic therapy with the exception of an uncomplicated urinary tract infection.<br>**15.** Pre-existing peripheral neuropathy that is ≥ Grade 2 by CTCAE v 4 criteria.<br>**16.** Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.<br>**17.** Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. **Note**: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.<br>**18.** Has received a live vaccine within 30 days of registration for protocol therapy.<br>*Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*<br>**19.** History of solid organ or stem cell transplant requiring immunosuppressive medications |

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| **STATISTICAL CONSIDERATIONS** | **Analysis Plan for Primary Objective**<br>The principal parameter employed to evaluate efficacy of the addition of pembrolizumab to the combination of carboplatin and paclitaxel is the frequency of objective response. The response rates will be compared with actual data from the historical control using Fisher's exact test.<br><br>**Analysis Plan for Secondary Objective**<br>All adverse events and safety monitoring measures will be described longitudinally using descriptive statistics such as frequencies, proportions, and ranges. Individual data will be reported for values out of normal range.<br><br>For the primary outcome, response rate (RR), a single stage, single arm design will assume a historical control response rate of 50%. A meaningful clinical response would be an improvement in RR of 15% given the potential risks and increased cost for the additional immunotherapy; for our purposes, we will target a 65% response rate. The proposed sample size will be 46 subjects total. A single group of 46 subjects will give us a 77% power to detect a higher overall response rate (65%) than the historical control (50%), assuming a one-tailed test and a Type I error rate of 10%. All subjects who receive pembrolizumab will be evaluated for treatment efficacy and toxicity.<br><br>Statistical analysis will be done by the Biostatistics Core Facility of the Robert H. Lurie Comprehensive Cancer Center. |
| **TOTAL NUMBER OF SUBJECTS** | 46 subjects |
| **ESTIMATED ENROLLMENT PERIOD** | Estimated 18 months |
| **ESTIMATED STUDY DURATION** | Estimated 36 months |

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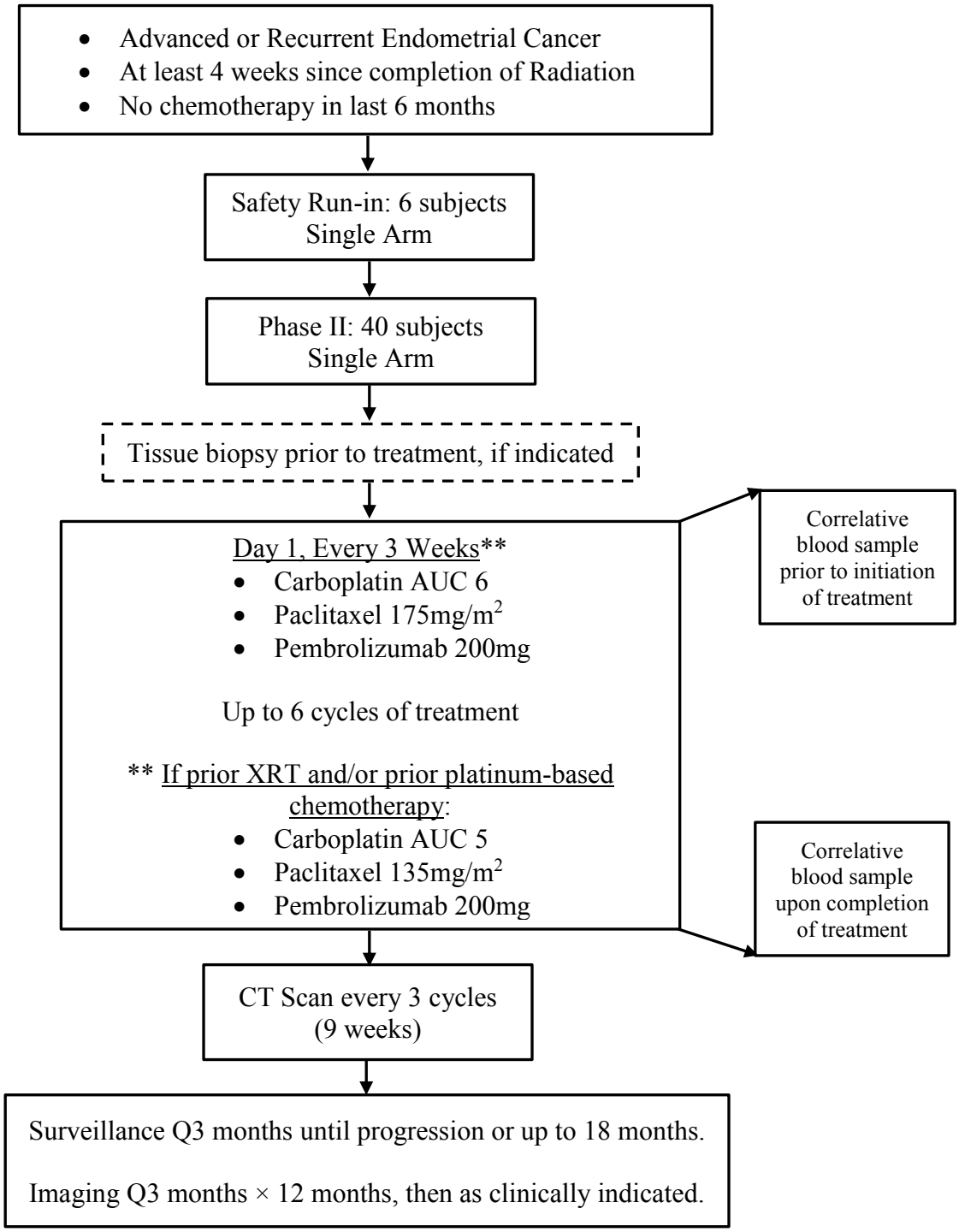
**SCHEMA**


• Advanced or Recurrent Endometrial Cancer
• At least 4 weeks since completion of Radiation
• No chemotherapy in last 6 months
Safety Run-in: 6 subjects
Single Arm
Phase II: 40 subjects
Single Arm
Tissue biopsy prior to treatment, if indicated
Day 1, Every 3 Weeks**
• Carboplatin AUC 6
• Paclitaxel 175mg/m2
• Pembrolizumab 200mg
Up to 6 cycles of treatment
** If prior XRT and/or prior platinum-based chemotherapy:
• Carboplatin AUC 5
• Paclitaxel 135mg/m2
• Pembrolizumab 200mg
Correlative blood sample prior to initiation of treatment
Correlative blood sample upon completion of treatment
CT Scan every 3 cycles
(9 weeks)
Surveillance Q3 months until progression or up to 18 months.
Imaging Q3 months × 12 months, then as clinically indicated.

# 1. BACKGROUND & RATIONALE

The hypothesis of this study is that the addition of pembrolizumab, an anti-PD-1 antibody, to carboplatin/paclitaxel for the treatment of patients with advanced and recurrent endometrial adenocarcinoma will improve the objective response rate by 15% (from 50% to 65%) when compared to historical controls of patients treated with carboplatin/paclitaxel alone.

## 1.1 Endometrial Adenocarcinoma

Endometrial cancer is the most common cancer of the female reproductive tract and the fourth most common cancer in the United States. It is estimated that more than 60,000 new endometrial cancer diagnoses will have been made in 2016. For many women initial therapy is curative. However, 20-25% of patients with endometrial cancers are initially detected at an advanced stage; these women have a guarded prognosis, poor overall response to chemotherapy and an increased risk of recurrence compared to patients with early-stage disease. In women with advanced endometrial cancer response rates to the most active single agent chemotherapies range from 20-35%. The most recently reported large randomized clinical trial in this patient population compared two active combination regimens (doxorubicin/cisplatin with and without paclitaxel). The objective response rates were 57% v 34%, respectively, and overall survival intervals were 15.3 v 12.3 months, respectively [1].

In the advanced and recurrent setting chemotherapeutic interventions are limited (NCCN Guidelines Uterine Neoplasms V 1.2015). There is a desperate need to identify additional active therapies for this patient population. In a retrospective analysis of patients with histologically confirmed endometrial carcinoma or uterine carcinosarcoma who received second-line platinum-based chemotherapy, the response rate for the entire cohort was 50% (129 CR+PR out of 262 total evaluable patients). All patients had received primary platinum-based chemotherapy with or without concurrent chemoradiation therapy[2]. A similarly designed, but significantly smaller, trial examined 22 patients with uterine papillary serous carcinoma who were treated with a platinum-based chemotherapy for recurrent disease[3]. Most of these patients (18) had received platinum-based chemotherapy as part of their definitive upfront treatment. The overall response rate was 50%.

## 1.2 Carboplatin/Paclitaxel

The combination of carboplatin/paclitaxel every three weeks has become the clinical standard of care chemotherapy for advanced and recurrent endometrial cancer. This is based upon the recently reported widespread clinical experience with this regimen and an interim analysis of a randomized phase III, non-inferiority trial demonstrating that the commonly used doublet carboplatin/paclitaxel is not inferior to the most active regimen previously identified: doxorubicin, cisplatin, and paclitaxel[4,5].

## 1.3 Immune Checkpoints

T cell-mediated immunity is a sequential multistep process that is regulated by complex counterbalancing co-stimulatory and inhibitory signals termed immune checkpoints. These checkpoints are important for maintenance of self-tolerance and to protect healthy tissues from the immune system from damage from the immune response to pathogenic infection[6]. T cells are activated when their cognate antigens are presented by antigen presenting cells (APC) to the T cell receptor. This activation is amplified by a co-stimulatory signal triggered by CD80 (also known as B7) on the APC binding to the T cell-expressed CD28. After activation of the T-cell, cytotoxic

T-lymphocyte antigen 4 (CTLA-4), a receptor expressed on T cells, is upregulated and also binds to CD80. CTLA-4 counteracts the stimulatory activity of CD28. The programmed cell death protein 1 (PD-1) is another inhibitory signaling pathway functioning to limit the activity of activated effector T cells in the peripheral tissues at the time of an inflammatory response to infection/tissue injury and to limit autoimmunity[7,8]. 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[9,10]. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. P D-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 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[11]. 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 and in various tumors[12,13].

### 1.4 PD-1 Pathway and Cancer

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformations has been well recognized. The presence of tumor-infiltrating lymphocytes in cancer tissue correlates with favorable prognosis in various malignancies. In particular, the presence of $CD8^+$ T cells and the ratio of $CD8^+$ effector T cells/$FoxP3^+$ regulatory T cells (Tregs) correlate with improved prognosis and long-term survival in multiple solid malignancies including ovarian carcinoma. PD-1 is expressed on activated lymphocytes including peripheral $CD4^+$ and $CD8^+$ T cells, B cells, Tregs and Natural Killer cells[6]. High expression of PD-L1 on tumor cells has been found to correlate with poor prognosis and survival in various solid tumors[14-16]. On the other hand, a higher mutation burden in tumors may be associated with improved and durable objective responses and progression-free survival in patients receiving anti- PD-1 therapy.[17] Deleterious mutations in genes such as POLE, and POLD1, specifically if the mutations are in the proofreading, exonuclease domain of the polymerase, are likely to exhibit a hypermutated tumor phenotype. Although most of these mutations are likely 'passenger mutations' that do not drive tumor growth, they may lead to protein alterations that can serve as neo-antigens that in turn will stimulate T-cell immunity. Additionally, POLE mutations are seen in ~ 10% of endometrial cancers and are associated with high mutation burden, increased expression of immune checkpoint ligands PD-L1 and T-cell markers.[18-23] This leads to the hypothesis that tumors with high mutational burdens, due to underlying DNA repair defects, may be more "immunogenic" and thus vulnerable to immune checkpoint disruption. Additionally, high expression of the programmed death receptor 1 ligand (PD-L1) is under investigation as a potential predictor of response to therapy. However, while patients with higher PD-L1 expression may indeed sustain greater benefit, there are a subset of patients with PD-L1 negative cancers who sustain important responses.[18] Thus use of PD-L1 expression alone to select patients for anti-PD-1 therapy may not be optimal for every patient and the discovery of additional predictive markers may complement its utility.

Therefore, we hypothesize that endometrial cancers with high mutation burden will respond better to anti-PD-1 therapy and that specific mutations in DNA polymerases and DNA repair genes, as well as high mutational burden, will predict response to anti-PD-1 treatment.

### 1.5 Pembrolizumab

The PD-1 pathway represents a major pathway hijacked by tumors to suppress immune control. Pembrolizumab (also known as Keytruda® and MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Pembrolizumab potently blocks binding to both ligands with half maximal inhibitory concentration (IC50) values below 1 nM. Pembrolizumab enhances T cell responses in human donor blood cell cultures with an EC50 of ~0.1 to 0.3 nM. Pembrolizumab binds to cynomolgus PD-1 with similar affinity, blocking activity, and demonstrates equivalent enhancement of cynomolgus T cell responses. It does not cross-react with rodent PD-1 (Merck, pembrolizumab Investigator's Brochure).

Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells. Using an anti-mouse PD-1 analog antibody, PD-1 blockade is demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-FU and combination therapy results in increased efficacy and increased complete regression rates *in vivo*. In addition, there has been significant clinical experience with pembrolizumab (Merck pembrolizumab Investigator's Brochure).

### 1.6 Study Rationale

The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers 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. Data remains limited for the role of anti-PD-1 treatment in gynecologic malignancies and additional investigation is warranted to determine if pembrolizumab is an effective addition to a cytotoxic backbone in the treatment of endometrial cancer. A recent publication reported greater than 90% of endometrial cancers evaluated expressed the PD-1 ligand, PD-L1[24]; this suggests that PD-1 blockade may be a common and targetable mechanism for endometrial cancer immune evasion.

This phase II trial will study the effects of pembrolizumab in combination with carboplatin/ paclitaxel for the treatment of subjects with advanced or recurrent endometrial cancer.

## 2. OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

#### 2.1.1. Primary Objective

To estimate the objective response rate of pembrolizumab in combination with standard carboplatin/paclitaxel in subjects with measurable advanced or recurrent endometrial cancer.

#### 2.1.2. Secondary Objectives

To determine the toxicities of pembrolizumab in combination with standard carboplatin/paclitaxel in subjects with advanced or recurrent endometrial cancer.

### 2.1.3. Correlative/ Exploratory Objectives

To evaluate potential biomarkers or prognostic factors for those who may respond to pembrolizumab.

## 2.2. Endpoints

### 2.2.1. Primary Endpoint

Objective response rate is defined as the proportion of subjects with a partial response or complete response according to immune-related RECIST criteria.

### 2.2.2. Secondary Endpoints

Toxicity is defined as the proportion of subjects who experience ≥ Grade 3 toxicity according to CTCAE v4.

### 2.2.3. Correlative/ Exploratory Endpoints

**2.2.3.1** Immunohistochemical evaluation of expression of PD-L1; Treg, Tumor Infiltrating Lymphocytes, and Myeloid Derived Suppressor Cell abundance in formalin-fixed, paraffin-embedded endometrial tumor and fresh frozen biopsy specimen, if available.

**2.2.3.2** Characterization of circulating immune cell populations ($TIM3^+/PD\text{-}1^+/CD8^+$, $PD\text{-}1^+/Treg$) will be evaluated on samples collected prior the start of and upon completion of combination pembrolizumab/cytotoxic chemotherapy.

**2.2.3.3** Determination of the mutational landscape of endometrial cancer and its influence in the response to pembrolizumab. Exome sequencing and targeted next generation sequencing, targeting all exons of approximately 300 cancer related genes will be performed from FFPE tissue from participants' tumors.

# 3. ELIGIBILITY CRITERIA

## 3.1. Inclusion Criteria

Subjects must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration for protocol therapy.
   **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status of 0 or 1 within 28 days prior to registration for protocol therapy.
4. Histological evidence of newly diagnosed Stage III or IV or recurrent endometrial carcinoma who have had definitive surgery for endometrial cancer (at least hysterectomy and bilateral salpingo-oophorectomy). Pathologic documentation of the recurrence (i.e., biopsy) will be performed per standard of care, at the treating physician's discretion. If a subject with recurrence is undergoing a biopsy for clinical indications and is willing and

able, an optional collection of 3 frozen tissue cores of the recurrence site is requested for correlative analysis.

5. Measurable disease according to RECIST v1.1 and obtained by imaging within 28 days prior to registration for protocol therapy. Disease in an irradiated field as the only site of measurable disease is acceptable only if there has been clear progression since completion of radiation treatment.
6. The subject must have recovered (≤ grade 1) from the acute toxic effects of prior therapy.
7. Prior treatment: Subjects may have received none or one platinum-based chemotherapy regimen and none or one non-platinum regimen. Subjects having received prior platinum-based chemotherapy must have a disease-free interval > 6 months (be platinum sensitive).
8. Prior therapy with hormones or biologic agents is allowed. These treatments must be discontinued at least 28 days prior to registration for protocol therapy.
9. The subject must have completed radiation therapy at least 28 days prior to registration for protocol therapy, provided that toxicity has resolved to ≤ grade 1.

   **NOTES**: Subjects may have received prior radiation therapy for treatment of endometrial carcinoma. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para-aortic radiation therapy, and/or intravaginal brachytherapy. Chemotherapy used for radiation sensitization is allowed. Chemotherapy used for radiation sensitization will not count as second chemotherapy regimen.

   Palliative radiation given primarily for symptom relief, without the intent to treat or cure the patient's endometrial cancer is excluded from the above criteria. Treatment-directed radiation will be defined as more than 30 Gy of radiation.
10. No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the subject has been disease-free for at least 5 years.
11. Female subjects must be of non-childbearing potential. Women of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥1 year.
12. Laboratory values must be obtained within 14 days prior to registration for protocol therapy. Note: Institutional/laboratory upper limit of normal (ULN)
    - Hemoglobin (Hgb) > 9 g/dL (without transfusion or EPO dependency within 7 days of assessment)
    - Platelets > 100 K/$mm^3$
    - Absolute neutrophil count (ANC) ≥ 1.5 K/$mm^3$
    - Creatinine or measured/calculated creatinine clearance (as calculated by institutional standard) ≤ 1.5 X institutional ULN OR ≥60mL/min for subjects with creatinine levels > 1.5 x institutional ULN
    - Serum total bilirubin ≤ 1.5 × ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN

- AST, ALT or alkaline phosphatase < 2.5 × ULN OR ≤ 5 x ULN for subjects with liver metastases
- Albumin ≥ 2.5 mg/dL
- International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless subject is receiving anti-coagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants
- Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 x ULN unless subject is receiving anti-coagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

### 3.2. Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Subjects with carcinosarcoma.
2. Subjects who have a solitary central pelvic recurrence, which can be curatively resected.
3. Hypersensitivity to pembrolizumab or any of its excipients.
4. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to registration for protocol therapy or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
5. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to registration for protocol therapy 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 registration for protocol therapy. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

   **NOTE**: Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis.
6. Treatment with any investigational agent within 28 days prior to registration for protocol therapy.
7. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
8. Active autoimmune disease that has required systemic treatment in 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.
9. Has received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to registration for protocol therapy. (Prednisone (or equivalent) < 10mg/ day is allowed).
10. Has a known history of active TB (Bacillus Tuberculosis).

11. Pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or hypersensitivity pneumonitis.
12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
13. Evidence of interstitial lung disease.
14. Has an active infection requiring systemic therapy with the exception of an uncomplicated urinary tract infection.
15. Pre-existing peripheral neuropathy that is ≥ Grade 2 by CTCAE v4 criteria.
16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
17. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. **Note**: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
18. Has received a live vaccine within 30 days prior to registration for protocol therapy. **NOTE**: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
19. History of solid organ or stem cell transplant requiring immunosuppressive medications.

## 4. SUBJECT REGISTRATION

All subjects must be registered through BTCRC Administrative Headquarters' electronic data capture (eDC) system. A subject is considered registered when an 'On Study' date is entered into the eDC system.

Detailed guidelines for subject registration can be found in the electronic case report form (eCRF) guidelines associated with this protocol.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within 5 business days of registration.

# 5. TREATMENT PLAN

## 5.1. Rationale for Pembrolizumab Dose Selection/Regimen/Modification

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

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (Merck pembrolizumab Investigator's Brochure). 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 subjects. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the alternate 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 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 subject exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual subject 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.

## 5.2. Safety run-in

To ensure the safety of this combination treatment, an initial safety run-in will be conducted for the first 6 subjects. This initial cohort of 6 subjects will be enrolled and treated with standard doses as described below. Upon the sixth subject's completion of the first two cycles of treatment, the toxicity data will be reviewed by the investigators in partnership with the Data Monitoring Committee at Northwestern University to determine if further subjects could be treated at the current dose level. Based on the experience with the initial 6 subjects, it will be determined if an extended safety run-in period would be beneficial. **The decision will be based on the following criteria:**

- If 0 or 1 of the 6 subjects experience DLT (see definition below), the study will proceed to enroll and treat the rest of the subjects on the current dose level to reach the enrollment goal.
- If 2 or more subjects experience DLT, the safety run-in will be repeated with an additional 6-subject cohort. The dose of carboplatin will be reduced to AUC of 5, the dose of paclitaxel will be reduced to 135mg/m$^2$ and pembrolizumab will be held for the first cycle. Toxicity data will again be reviewed following completion of first two cycles of treatment for the additional cohort.
    - If >33% of subjects in the additional cohort experience DLT at the reduced levels of carboplatin (AUC of 5)/paclitaxel (135mg/m$^2$) per dose (dose level -1), then the study will be suspended for further review. Next steps will be determined following DMC review of toxicity data, which will be formally communicated to site investigators and the industry supporter Merck.

The dose determination rules listed above only apply to subjects who have received at least 1 dose of pembrolizumab. If one or more of the first 6 subjects terminate treatment without receiving at least 1 dose of pembrolizumab, additional subjects will be accrued during the safety run-in period to achieve an initial cohort of 6 subjects, each with at least 1 dose of pembrolizumab.

### 5.2.1. Definition of Dose-limiting Toxicity (DLT)

A DLT is defined as any adverse event observed during the first two cycles which is judged to be possibly, probably, or definitely related to any study drug (pembrolizumab, carboplatin or paclitaxel) and fulfilling one of the criteria below. Fatigue and alopecia will be excluded from the DLT definitions.

- Dose modifications of more than one missed dose of pembrolizumab
- Grade 4 non-hematologic toxicity (not laboratory)
- Sepsis requiring intravenous antibiotics
- Grade 3 non-hematologic toxicity related to treatment lasting ≥ 3 days despite optimal supportive care
- Any Grade 3 or Grade 4 laboratory value if:
    - Medical intervention, including granulocyte colony-stimulating factors, is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for ≥ 7 days (other than as noted for thrombocytopenia)
- Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as ANC < 1000/mm$^3$ with a single temperature of > 38.3°C

(101°F) or a sustained temperature of ≥ 38°C (100.4°F) for > 1 hour.
    - Grade 4 is defined as ANC < 1000/mm$^3$ with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38 degrees C (100.4° F) for more > 1 hour, with life-threatening consequences and urgent intervention indicated
- Thrombocytopenia < 25,000/mm$^3$ if associated with:
    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
    - Prolonged delay (> 14 days) in initiating Cycle 2 due to treatment-related toxicity
- Missing > 10 % of carboplatin or paclitaxel doses as a result of AE(s) during a cycle
- Grade 5 toxicity

### 5.3. Pre-medication

Pembrolizumab does not require any pre-medications unless indicated for an infusion reaction (section 6.1.3 and Table 4).

Paclitaxel will be administered as a 3-hour infusion on this study. For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), antihistamine H1 (such as diphenhydramine), and antihistamine H2 (such as cimetidine, ranitidine, or famotidine). Institutional standards should be followed for hydration and pre-medications.

Carboplatin does not require any pre-medications.

### 5.4. Drug Administration

All subjects will be treated in cycles lasting 21 days (3 weeks). The drugs being used in this study include pembrolizumab, paclitaxel, and carboplatin. Pembrolizumab will be administered first, followed sequentially by paclitaxel and carboplatin.

Table 1: Drug dosing in the absence of prior therapy

| Drug | Administration sequence | Dose | Frequency of administration | Route of administration | Number of cycles |
|---|---|---|---|---|---|
| Pembrolizumab | 1$^{st}$ | 200mg | Day 1<br>Every 21 days | IV | 6 |
| Paclitaxel | 2$^{nd}$ | 175mg/m$^2$ | Day 1<br>Every 21 days | IV | |
| Carboplatin | 3$^{rd}$ | AUC 6 | Day 1<br>Every 21 days | IV | |

**NOTE:** Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. This should be clearly documented in the subject's chart and case report forms.

### 5.4.1. Dosing and Route of Administration

#### 5.4.1.1. Pembrolizumab

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

Please refer to the separate Pharmacy Manual for specific instructions regarding the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

#### 5.4.1.2. Paclitaxel

Paclitaxel will be dosed at 175mg/$m^2$ and be administered as a 3-hour continuous IV infusion. Paclitaxel dose should be completely administered before initiating carboplatin dose. A window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 3 hours: -5 min/+10 min).

#### 5.4.1.3. Carboplatin

Carboplatin will be dosed at an AUC of 6 and given as an IV infusion according to institutional standards. A window of -5 minutes and +10 minutes is permitted.

#### 5.4.1.4. Dosing in Subjects with Prior Radiotherapy/Platinum-based Chemotherapy

Subjects must initiate paclitaxel and carboplatin at a reduced dose if they have had:

- prior external radiotherapy involving the whole pelvis or abdomen or over 50% of their spine,
- prior platinum-based chemotherapy for this, or any other cancer (see below and Section 6.1.1.).

The subsequent doses of paclitaxel and carboplatin may be escalated (to dosing given in Table 1 above), provided these subjects do not exhibit hematologic or non-hematologic toxicity > Grade 1, except alopecia.

**Table 2: Drug Dosing in subjects with prior radiotherapy involving the whole pelvis or abdomen or over 50% of their spine or prior platinum-based chemotherapy**

| Drug | Administration sequence | Dose | Frequency of administration | Route of administration | Number of cycles |
|---|---|---|---|---|---|
| Pembrolizumab | 1st | 200mg | Day 1<br>Every 21 days | IV | 6 |
| Paclitaxel | 2nd | 135mg/$m^2$ | Day 1<br>Every 21 days | IV | |
| Carboplatin | 3rd | AUC 5 | Day 1<br>Every 21 days | IV | |

**NOTE:** Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms.

#### 5.4.1.5. Dose Calculations

The body surface area and drug dose should be recalculated only if the subject's weight changes by ≥ 10% during the course of the study.

Body Surface Area (BSA)
BSA calculations will be used for dosing of paclitaxel. BSA should be calculated on Day 1 of each cycle based on the subject's current height and weight using the DuBois formula.

Area Under the Curve (AUC)
Dosing of carboplatin will be calculated using the Calvert formula, using the target AUC and glomerular filtration rate (GFR) on Day 1 of each cycle. This formula is as follows: mg = AUC x (GFR +25). GFR should be calculated using the Cockcroft & Gault method using the subject's actual body weight. For the dosing calculation, the maximum GFR should be capped at 125 mL/min.

### 5.4.2. Missed doses

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, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor-investigator in collaboration with the BTCRC AHQ project manager. The reason for interruption should be documented in the subject's study record.

## 5.5. Supportive Care

### 5.5.1. Antiemetics

Carboplatin, paclitaxel, and pembrolizumab:
Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Anti-emetic prophylaxis should follow pembrolizumab infusion, but otherwise timing and rate of administration are per institutional standard. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below (see Section 6).

## 5.6. Concurrent Therapy

### 5.6.1. Concomitant Medications/Vaccinations (allowed and prohibited)

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

### 5.6.2. Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 11.3.

### 5.6.3. Prohibited Concomitant Medications and Therapies

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Radiation therapy
- Systemic glucocorticoids for any purpose other than to treat symptoms from an event of clinical interest of suspected immunologic etiology or as premedication for paclitaxel or imaging studies. The use of physiologic doses of corticosteroids for other indications may be approved after consultation with the Sponsor-investigator

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

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

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

## 6. DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 will be used to grade adverse events. These can be located on the CTEP website at http://ctep.cancer.gov.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in the Study Calendar and Evaluations section.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

## 6.1. Dose Modifications

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the Table 5 below.

### 6.1.1. Dose Levels and Toxicity Management

Table 3 should be used for all dosing adjustments based on the toxicities described in this section. There will be no dose escalations except those specified for subjects with prior radiotherapy/ platinum-based chemotherapy (in Section 5.4.1.4).

**Table 3: Dose levels for carboplatin, paclitaxel, pembrolizumab**

| Dose level | Carboplatin | Paclitaxel | Pembrolizumab |
|---|---|---|---|
| Starting dose (no prior therapy) | AUC 6 | 175 mg/m$^2$ | 200 mg |
| Starting dose (for prior therapy) | AUC 5 | 135 mg/m$^2$ | 200 mg |
| First dose reduction | AUC 5 (AUC 4, prior therapy) | 135 mg/m$^2$ (110 mg/m$^2$, prior therapy) | See Table 5 |
| Second dose reduction | AUC 4 (Discontinue, prior therapy) | 110 mg/m$^2$ (Discontinue, prior therapy) | See Table 5 |
| Discontinuation | Toxicity resulting in dose delay >21 days | Toxicity resulting in dose delay >21 days | See Table 5 |

### 6.1.3. Dose Modifications for Treatment Related Hematological Toxicity:

Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC). Subsequent cycles of therapy will not begin until the ANC is > 1,500/mm$^3$ and the platelet count is > 100,000/mm$^3$. Therapy will be delayed on a week-by-week basis until these values are achieved.

- Treatment modifications will be employed in a sequential manner using cycle delay and dose reduction.
- There will be no dose modifications based on uncomplicated nadirs.
- Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor (GM CSF) should follow national standards (see ASCO guidelines). Prophylactic use of colony-stimulating factors in patients who have received prior pelvic radiotherapy is allowed, according to ASCO guidelines.
- Subjects who experience dose-limiting neutropenia, defined as febrile neutropenia or Grade 4 neutropenia lasting ≥7 days, or sepsis requiring intravenous antibiotics will receive a dose reduction of one level using the table above, without addition of G-CSF.
- Carboplatin and/or paclitaxel will be discontinued in subjects who require a delay of > 21 days for toxicities associated with carboplatin and/or paclitaxel (See Table 3). Single-agent pembrolizumab may continue per protocol.
- Subjects who experience grade 4 thrombocytopenia (<25,000/mm$^3$) will have a dose reduction of carboplatin one level, without a change in paclitaxel dosage. Transfusion of platelets may be used if clinically indicated.
- Transfusions may be utilized as clinically indicated for the treatment of anemia.

### 6.1.4. Guidelines for Infusion Reactions

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

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

**Table 4 Pembrolizumab Infusion Reaction Treatment Guidelines**

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | None |
| Grade 2<br>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.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:<br><br>Diphenhydramine 50 mg po (or equivalent |

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>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.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further pembrolizumab administration.** | dose of antihistamine).<br><br>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |
| Grades 3 or 4<br>**Grade 3:**<br>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)<br>**Grade 4:**<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**Subject is permanently discontinued from further pembrolizumab administration.** | No subsequent dosing |
| An appropriate resuscitation plan must be in place and a physician readily available during drug administration. | | |

### 6.1.5. Dose Modifications for Other Treatment-Related Non-Hematological Toxicity

#### 6.1.5.1. Paclitaxel Hypersensitivity Reaction

If hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur, it will usually be during the first few minutes of infusion. Appropriate symptomatic therapy should be given. Continued treatment may be considered if the reaction is not life threatening; however, subjects must be cautioned about potential recurrences of the reaction. Should the subject decide to continue with treatment, it is preferable that this be done on the same day of the occurrence. A suggested procedure would be to administer the drug first with 1 cc of the original IV solution diluted in 100 ml over one hour, then 5 cc in 100 ml over one hour, then 10 cc in 100 ml over one hour, and finally, the original solution at the original speed. Subjects who elect not to have continued treatment with paclitaxel after experiencing a hypersensitivity reaction may continue on protocol therapy with pembrolizumab and carboplatin only.

#### 6.1.5.2. Renal Toxicity

If creatinine rises to > 2.0 mg/dL, a calculated creatinine clearance ($CalC_{cr}$) should be obtained (calculated per institutional standard). If $CalC_{cr}$ is less than 50 cc/min, hold treatment and check weekly $CalC_{cr}$. Resume therapy when $CalC_{cr}$ is ≥50 cc/min. Carboplatin may be resumed at one dose level lower (See Table 3) once the $CalC_{cr}$ returns to ≥ 50 cc/min or returns to Grade 1 toxicity level. If $CalC_{cr}$ is < 50 cc/min or serum creatinine is >2 mg/dL after treatment has been held for 2 weeks, carboplatin will be discontinued and the BTCRC AHQ project manager notified. Paclitaxel and pembrolizumab can be continued, based on discussion with the Sponsor Investigator.

#### 6.1.5.3. Myalgias

Myalgias in the several days following paclitaxel treatment may be severe, and should receive aggressive symptomatic treatment, including narcotics or steroids as required. They are not, however, an indication for dose reduction.

#### 6.1.5.4. Neurologic Toxicity

Grade 2 or greater peripheral neuropathy requires discontinuation of protocol therapy until symptoms resolve to ≤ Grade 1. When treatment resumes, the carboplatin dose should be reduced one level and the paclitaxel should be reduced a level (See Table 3). Discontinue protocol regimen in subjects with recurrent Grade 3 or any Grade 4 neurologic toxicity.

#### 6.1.5.5. Hepatic Toxicity

Hepatic function labs should be assessed on Day 1 of each cycle.

See specific recommendations for immune-related hepatic toxicity in section 6.1.4.8 Immune-Related Adverse Events (irAE).

Bilirubin must return to within normal limits prior to further therapy.

#### 6.1.5.6. Other Toxicity

For any Grade 3 or 4 toxicity not mentioned above, protocol treatment should usually be withheld until subjects recover completely or to Grade 1 status. The next dose of the agent believed responsible will be given at a one dose level reduction. In general, any Grade 3 or 4 toxicity not mentioned above should be discussed with the BTCRC AHQ project manager in collaboration with sponsor-investigator. Subjects whose treatment is delayed > 21 days because of toxicity attributable to carboplatin and/or paclitaxel, should discontinue carboplatin and/or paclitaxel (See Table 3). Single-agent pembrolizumab may continue per protocol.

#### 6.1.5.7. Dose Modification Specifically For Pembrolizumab

If a dose of pembrolizumab is withheld for toxicity, subjects may resume dosing with pembrolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described below in Table 5: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab

**Table 5: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab**

**General instructions:**

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤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 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment<br>• 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 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).<br>• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.<br>• 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- 1 mg/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 1-2 mg/kg prednisone or equivalent) followed by taper | |

| | | | | |
|---|---|---|---|---|
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer anti-hyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes. |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated. | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders. |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care | • Monitor for signs and symptoms of thyroid disorders. |
| Nephritis and Renal dysfunction | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Grade 1 or 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| All other immune-related AEs | Intolerable/ persistent Grade 2 | Withhold | • Based on type and severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis | | |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue | | |

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
**NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

If toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, pembrolizumab should be discontinued after consultation with the BTCRC project manager and the sponsor-investigator. With site investigator and sponsor-investigator agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. If a subject has more than 3 delays in pembrolizumab dosing due to other toxicities specific to this medication, they will be discontinued from pembrolizumab.

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

Subjects who permanently discontinue pembrolizumab due to toxicity but who have not progressed may remain on chemotherapy per physician discretion until progression, intolerable toxicity or completion of six cycles of carboplatin and paclitaxel per protocol treatment.

#### 6.1.5.8. Immune-Related Adverse Events (irAE)

Where appropriate, guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the event to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance.

It may be necessary to perform diagnostic procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

#### 6.1.5.9. Anti-infective

Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

## 7. STUDY CALENDAR & EVALUATIONS

| Study Day<br>Cycle= 21 days | Screen | Cycle 1[14] | Cycles 2-6 | 30 Days Post Treatment | Follow up |
|---|---|---|---|---|---|
| | -28 days | Day 1 | Day 1 (±3) | 30 days (±7) after last dose | Every 3 months for 18 mos (±14) |
| **REQUIRED ASSESSMENTS** | | | | | |
| Informed Consent | X | | | | |
| Medical History[1]; Diagnosis and Staging[2] | X | | | | |
| Physical Exam | X | X | X | X | X |
| Vital Signs (as listed in 7.1.1) & ECOG PS | X | X | X | X | X |
| AEs, ECIs & Concomitant Medications | X | X | X | X | X |
| Neuropathy Assessment | X | X | X | X | |
| **LABORATORY TESTS** | | | | | |
| Complete Blood Cell Count (CBC) with diff and platelets | -14 | X | X | X | |
| Comprehensive Metabolic Profile (CMP)[3] | -14 | X | X | Basic profile[3] | |
| Mg, Phos, LDH | -14 | X | X | | |
| PT/INR and aPTT | -14 | X | X | | |
| Thyroid Function Panel (TSH, T3 and free T4)[4] | -14 | | Even cycles | TSH only[4] | |
| Urinalysis[5] | -14 | X | X | X | |
| **DISEASE ASSESSMENT** | | | | | |
| CT Chest | X | | Pre Cycle 4 | X | |
| CT (MR) abdomen/pelvis[6] | X | | Pre Cycle 4 | X | X[15] |
| CT or MRI brain, if indicated[7] | [X] | | | | |
| Biopsy of Recurrence[8] | X | | | | |
| **TREATMENT EXPOSURE** | | | | | |
| Pembrolizumab, Paclitaxel, Carboplatin | | X | X | | |
| **CORRELATIVE STUDIES (SPECIMEN COLLECTION)** | | | | | |
| Whole Blood for Circulating Immune Cell Analysis[9]- Mandatory | | X | | X | |
| Unstained Slides[10]-Mandatory (If Available) | | X | | | |
| Tissue Collection from Biopsy of Recurrence[8] | X | | | | |
| **BANKING SAMPLES (SPECIMEN COLLECTION)** | | | | | |
| Whole Blood[11] | | X | | | |
| Unstained Slides[12] (If Available) | | X | | | |
| Serum and Plasma[13] | | X | | X | |
| **FOLLOW UP** | | | | | |
| Survival | | | | | X |

Footnotes:
1: Medical History to include Lynch Syndrome status, if tested, demographics, tobacco and alcohol use, trial awareness question, prior treatments, radiation and surgical history.
2: Diagnosis and Staging to include pathology report (with mismatch repair protein status, if available) and FIGO staging.
3: Comprehensive Metabolic Profile will include: sodium, potassium, serum creatinine, calcium, albumin, ALT, AST, total bilirubin, alkaline phosphatase, total protein. Basic Metabolic Profile (calcium, sodium, potassium, creatinine) will be performed at 30-Day post-treatment visit.
4: Thyroid Function panel should be obtained at screening, cycle 2, and every other cycle thereafter. Only TSH will be collected at 30-Day post-treatment visit.
5: Urinalysis including blood, glucose, protein, specific gravity, reflex microscopy
6: CT is preferred, MR is acceptable; see Section 8.2.1. Regardless, the same type of scanner and image acquisition should be as consistent as possible throughout the study.
7: Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis.
8: Pathologic documentation of the recurrence (i.e., biopsy) will be performed per standard of care, at the treating physician's discretion. It is preferred that all subjects with recurrence undergo a biopsy for confirmation prior to initiating treatment; in this setting, a collection of 3 frozen tissue cores of the recurrence site is requested for correlative analysis. See Correlative Laboratory Manual (CLM) for collection, labeling, and shipping instructions.
9: Whole blood for circulating immune cell analysis is to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Post Treatment visit. See CLM for collection, labeling, and shipping instructions.
10: Submission of unstained slides from the subject's archived primary tumor block is mandatory (if available) for PD-L1 expressions and other biomarker analyses. See CLM for collection, labeling, and shipping instructions.
11: Submission of whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling, and shipping instructions.
12: Submission of unstained slides for banking from an archived FFPE tumor block is requested (if available). See CLM for collection, labeling, and shipping instructions.
13: Submission of serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Post Treatment visit. See CLM for collection, labeling, processing, and shipping instructions.
14: Cycle 1 Day 1 lab testing need not be repeated if completed within 3 days of starting protocol therapy.
15: Imaging of abdomen and pelvis to be repeated every 3 months for the first 12 months of follow-up.

## 7.1 Screening

### 7.1.1 Within 28 days prior to registration

The screening procedures include the following assessments:

- All eligibility requirements according to Section 3 must be satisfied.
- Pathologic confirmation of advanced or recurrent endometrial adenocarcinoma diagnosis (see Section 3 Pathology Requirements for Enrollment and Calendar footnote #8)
- Document relevant medical history including history of subject's endometrial cancer and prior treatments, other past medical and surgical histories (including Lynch Syndrome status, if available), current medications, allergies, social history (including tobacco and alcohol use), and family history. Trial awareness question will also be collected.
- Physical exam (includes height and weight), vital signs (temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG PS (Study Procedures Manual [SPM])
- Sensory neuropathy assessment by history and graded by CTCAE v4. Subjects with pre-existing peripheral neuropathy ≥ Grade 2 are excluded.
- Screening scans including: CT Chest, CT Abdomen/Pelvis per institutional standards. CT Abd/Pelvis is preferred, MR is acceptable. Regardless, the same type of scanner and image acquisition protocol should be as consistent as possible throughout the study (see Section 8.2.1). Note: Additional other imaging may be used at the discretion of the treating physician to assess other areas based on previously known disease or suspicion of new areas of involvement due to subject complaints. These baseline tests will be used to determine the location(s) of baseline disease that may be used for responses assessment (see Section 8 Criteria for Disease Evaluation) (within 28 days of registration).
- Biopsy of recurrence: Pathologic documentation of the recurrence (i.e., biopsy) will be performed per standard of care, at the treating physician's discretion.
    - Tissue Collection from Biopsy of Recurrence: If a subject with recurrence is undergoing a biopsy for clinical indications and is willing and able, a collection of 3 frozen tissue cores of the recurrence site is requested for correlative analysis (see also Section 3.1.4).

### 7.1.2 Within 14 days prior to registration

- CBC with differential and platelets
- Comprehensive Metabolic Panel (sodium, potassium, serum creatinine, calcium, albumin, ALT, AST, total bilirubin, alkaline phosphatase, total protein)
- Magnesium, Phosphorus, LDH
- Thyroid function test including; TSH, T3, and free T4
- PT/INR, aPTT
- Urinalysis (including blood, glucose, protein, specific gravity, reflex microscopy)

## 7.2 On Treatment

The following assessments will be completed prior to chemotherapy treatment. Lab values will be recorded and checked for toxicity that would necessitate a dose reduction (most notably white blood count and differential to calculate absolute neutrophil count (ANC), platelet count, creatinine, AST, ALT, Alk Phos, and bilirubin). Grading of all toxicities will be according to

CTCAE v4. Only if subject's weight changes by ≥ 10% during the course of the study, the body surface area and drug dose should be recalculated (see Section 5.4.1.5 Dose Calculations).

### 7.2.1 Cycle 1 Day 1:

**Note:** Cycle 1 Day 1 lab testing need not be repeated if completed within 3 days of starting protocol therapy.

- Physical exam (includes weight), vital signs (temperature, blood pressure, heart rate, respiratory rate, and pulse oximetry) and ECOG Performance Status
- Sensory neuropathy assessment.
- AE assessment including ECIs and concomitant medications
- CBC with differential and platelet count
- Comprehensive Metabolic Panel (including sodium, potassium, serum creatinine, calcium, albumin, ALT, AST, total bilirubin, alkaline phosphatase, total protein)
- Magnesium, Phosphorus, Lactate dehydrogenase (LDH)
- PT/INR and aPTT
- Urinalysis (including blood, glucose, protein, specific gravity, reflex microscopy)
- Pembrolizumab, Paclitaxel, and Carboplatin administration (IV)
- Collect unstained slides from an archived primary tumor block. Refer to the Correlative Laboratory Manual (CLM) for the amount of tissue required to be deemed adequate. Note: if an adequate amount of tissue is unavailable, a pre-treatment biopsy of recurrent disease is preferred but not mandatory.
- Correlative and Banking samples. See CLM for specific instructions.
- Pembrolizumab, Paclitaxel, and Carboplatin administration (IV)

### 7.2.2 Cycles 2-6 Day 1 (±3 days):

- Physical exam (includes weight), vital signs (temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG Performance Status
- Sensory neuropathy assessment.
- AE assessment including ECIs and concomitant medications
- CBC with differential and platelet count
- Comprehensive chemistry panel (including sodium, potassium, serum creatinine, calcium, albumin, ALT, AST, total bilirubin, alkaline phosphatase, total protein
- Magnesium, Phosphorus, Lactate dehydrogenase (LDH)
- PT/INR and aPTT
- Thyroid function test including; TSH, T3 and free T4 (Cycle 2 and every other cycle thereafter)
- Urinalysis (including blood, glucose, protein, specific gravity, reflex microscopy)
- Pembrolizumab, Paclitaxel, and Carboplatin administration (IV)

### 7.2.3 Prior to Cycle 4

- A CT of the chest with IV contrast and CT Abd/Pelvis with PO and IV contrast. CT Abd/Pelvis is preferred, MR is acceptable. Regardless, the same type of scanner and image acquisition should be as consistent as possible throughout the study (see Section 8.2.1). Note: Repeat all other imaging studies at these same intervals if disease was identified at baseline. Additional imaging studies may be obtained at these intervals or at any time as

directed in Section 8.3, if clinically indicated and at investigator discretion. Results from all imaging, whether at the scheduled interval or otherwise, should be recorded and used for response assessments (see Section 8.3 Response Assessment)

## 7.3 Off Treatment

### 7.3.1 Protocol therapy discontinuation:

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 11 - Adverse Events.

A subject will be discontinued from the protocol therapy under the following circumstances:

- If there is evidence of disease progression (per immune related RECIST [irRECIST])
- If the treating physician thinks a change of therapy would be in the best interest of the subject
- If the subject requests to discontinue protocol therapy
- If the protocol therapy exhibits unacceptable toxicity
- If carboplatin and/or paclitaxel is interrupted for > 21 days due to a treatment-related adverse event attributable to carboplatin and/or paclitaxel, discontinue carboplatin and/or paclitaxel. Single-agent pembrolizumab may continue per protocol.
- If pembrolizumab therapy is interrupted for >12 weeks due to a treatment-related adverse event attributable to pembrolizumab, discontinue pembrolizumab but continue carboplatin/paclitaxel per protocol.

## 7.4 End of Treatment Assessment/Safety Follow-up: 30 days (±7 days) after final dose of protocol therapy

The Safety Follow-Up Visit should be conducted within 30 days of the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

- Physical exam (includes weight), vital signs (temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG Performance Status
- Sensory neuropathy assessment.
- AE assessment including ECIs and concomitant medications
- CBC with differential and platelet count
- Basic Metabolic Profile (calcium, sodium, potassium, creatinine)
- TSH
- Urinalysis (including blood, glucose, protein, specific gravity, reflex microscopy)
- A CT of the chest with IV contrast and CT Abd/Pelvis with PO and IV contrast. CT Abd/Pelvis is preferred, MR is acceptable; regardless, the same type of scanner and image acquisition protocol should be followed as closely as possible throughout the study (see Section 8.2.1). Note: Additional imaging studies may be obtained if clinically indicated

and at investigator discretion. Results from all imaging should be recorded and used for response assessments (see Section 8 Response Assessment).
- Correlative and Banking samples. See CLM for specific instructions.

### 7.5 Follow-up

- Physical exam (includes weight), vital signs (temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG Performance Status
- AE assessment including ECIs and concomitant medications
- Repeat imaging if clinically indicated and at the discretion of the investigator

Subjects who discontinue treatment without evidence of progression will have repeat imaging every 3 months for the first year off treatment. Follow-up for survival every 3 months thereafter until completion of the study period.

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, or death. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects can stop study participation at any time. However, if they decide to stop, subjects will continue to be followed every 3 months for 18 months from the time of treatment discontinuation (if they have not withdrawn consent).

## 8. CRITERIA FOR DISEASE EVALUATION

In this study, disease parameters (section 8.1) and methods for tumor evaluation (Section 8.2)—but **not** evaluation of tumor response—will be in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1.

RECIST 1.1 response criteria are primarily designed to evaluate the early effects of cytotoxic agents, and depend on tumor shrinkage to demonstrate biologic activity. However, clinical evidence of tumor responses seen with immunotherapeutic agents such as pembrolizumab can take longer to achieve, and may occur after a period of disease stabilization or following an initial increase in tumor burden. In light of the limitations of utilizing RECIST 1.1 to evaluate immunomodulatory agents, immune-related response criteria (irRC) have been proposed to systematically detect the novel response patterns observed with immunologic agents[26]. Therefore, in this study, tumor response will be evaluated with an irRC modification of RECIST v1.1. (See section 8.3).

### 8.1 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[27]

**8.1.1** ***Measurable disease:*** The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion *less than* 2 cm, its neoplastic nature should be confirmed by cytology/histology.

**8.1.1.1** ***Measurable lesions:*** 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).

**8.1.1.2** ***Non-measurable lesions:*** 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 subject, these are preferred for selection as target lesions.

**8.1.1.3** ***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.

**8.1.1.4** ***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.

**8.1.1.5** ***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.

## 8.2 Methods of Measurement

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 28 days before the beginning of the treatment.

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. The same imaging modality must be used throughout the study to measure disease.

### 8.2.1 CT and MRI:

CT and MRI are the best currently available and most reproducible methods for measuring target lesions. 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 that may bias an investigator if it is not routinely or serially performed.

### 8.2.2 Chest X-Ray:

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung (CT is preferable).

### 8.2.3 Clinical Examination:

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

### 8.2.4 Cytology and Histology:

Cytologic and histologic techniques can be used to differentiate between complete and partial responses in rare cases (e.g., after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

## 8.3 Response Assessment: Immune-Related RECIST

As previously noted, this study will assess tumor response with an immune-related modification of RECIST 1.1 (see Table 6 below). Determination of response via irRECIST should take into consideration all target and non-target lesions.

A key distinction between standard RECIST 1.1 criteria and immune-related response criteria is that irRECIST requires early evidence of progressive disease (i.e., a determination of irPD ≤ 12 weeks after starting study treatment) be confirmed by repeat, consecutive imaging ≥ 4 weeks after the initial documentation in the absence of rapid clinical deterioration. During this interim ≥ 4-week period, subjects should continue to be followed per protocol, including continued dosing of the study drug(s).

Additionally, the immune-mediated responses expected from pembrolizumab require activation of the immune system prior to the observation of clinical responses, and such immune activation may take weeks to months to be clinically evident. Some subjects with advanced cancer may have objective volume increase of tumor lesions within 12 weeks following the start of dosing on study. Such subjects may not have had sufficient time to develop the required immune activation or, in some subjects, tumor volume increases may represent infiltration of lymphocytes into the original tumor. In traditional oncology studies, such increases in tumor volume during the first 12 weeks of the study would constitute progressive disease and lead to discontinuation of study treatment and of imaging to detect response, thus disregarding the potential for subsequent immune- mediated clinical response. Therefore, in this study, the first imaging assessment will be performed at Week 9 (prior to Cycle 4). Subsequent imaging will be performed upon completion of the study and every 12 weeks thereafter for the first year.

**Table 6: Tumor Response Evaluation: Comparison between RECIST 1.1 and irRECIST**

| Criteria | RECIST 1.1 | irRECIST |
|---|---|---|
| New measurable lesions (≥10 mm) | Always represents PD | Incorporated into tumor burden |
| New non-measurable lesions (< 10 mm) | Always represents PD | Does not define progression but precludes irCR |
| Non-Target lesions | Changes contribute to defining BOR of CR, PR, SD, and PD | Contribute to defining irCR (complete disappearance required) |
| CR | Disappearance of all lesions | Disappearance of all lesions |
| PR | ≥ 30% decrease in the sum of the longest diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions | ≥ 30% decrease in tumor burden compared with baseline |
| 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 | Neither a 30% decrease in tumor burden compared with baseline nor a 20% increase compared with nadir can be established |
| PD | At least 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression. | At least 20% increase in tumor burden compared with nadir (at any single time point)* |
| ***Subjects with an initial finding of progressive disease (irPD) before or at the 12 week imaging assessment, but without rapid clinical deterioration, require confirmation of irPD with a second, consecutive scan obtained ≥ 4 weeks from the initiation documentation. Subjects will continue to receive study treatment until irPD is confirmed at this later time point. Best overall response (BOR) will therefore include responses occurring at any time before disease progression and after early progression (i.e., within the first 12 weeks of the study.** | | |

### 8.3.1 Response in Measurable Lesions

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (≥ 10 mm [lymph nodes ≥ 15 mm in shortest diameter]; up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB):

TMTB = SumD target lesions + SumD new, measurable lesions

Percentage changes in TMTB per assessment time-point describe the size and growth kinetics of both old and new, measurable lesions as they appear. At each TA, the response in target and new, measurable lesions is defined based on the change in TMTB (after ruling out irPD) as follows:

| Response in Measurable Lesions | |
|---|---|
| Complete Response (irCR): | Complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes, which must decrease to < 10 mm in short axis. |
| Partial Response (irPR): | Decrease in TMTB ≥ 30% relative to baseline (see below). |
| Stable Disease (irSD): | Not meeting criteria for irCR or irPR, in absence of irPD. |
| Progressive Disease (irPD): | Increase in TMTB ≥ 20% relative to nadir. |

### 8.3.2 Response in Non-measurable Lesions

At each TA, the presence of any new, non-measurable lesions is assessed. The presence of such lesions will rule out an overall response of irCR. An increase in the size or number of new, non-measurable lesions does not necessarily imply an overall response of irPD; if these lesions become measurable (≥ 10 mm) at a subsequent TA, their measurement will at that point start to contribute to the TMTB.

In addition, the response in non-target lesions is defined as follows:

| Response in Non-measurable Lesions | |
|---|---|
| Complete Response (irCR): | Complete disappearance of all non-target lesions |
| Stable Disease (irSD): | Non-target lesions are stable |
| Progressive Disease (irPD): | Unequivocal increases in number or size of non-target lesions. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening of non-target disease that is of a magnitude that the treating physician would feel it is important to change therapy. |
| NOTE: Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next scheduled assessment. | |

**8.3.3 Evaluation of Biomarkers:** Serum CA-125, if collected, must be within normal limits for a subject to be considered in complete clinical response.

### 8.3.4 Overall Response (OR):

The OR according to the irRC is derived from the responses in measurable lesions (based on TMTB) as well as the presence of any non-measurable lesions as follows:

| Overall Response | |
|---|---|
| Complete Response (irCR): | Complete disappearance of *all lesions* (whether measurable or not); lymph nodes must decrease to < 10 mm in shortest dimension. Serum CA-125 within normal limits. |
| Partial Response (irPR): | Decrease in TMTB ≥ to 30% relative to baseline. |
| Stable Disease (irSD): | Not meeting criteria for irCR or irPR, in absence of irPD. |
| Progressive Disease (irPD): | Increase in TMTB ≥ 20% relative to nadir. |

The immune-related best overall response (irBOR) is the best irRC OR over the study as a whole, recorded between the date of first dose until the last TA prior to subsequent therapy (including tumor resection surgery) for the individual subject in the study. As with the primary definitions of tumor response, early progression (i.e., irPD occurring prior to Week 12) will not preclude an irBOR of irCR, irPR or irSD resulting from the Week 12 assessment. An assessment of irPD at or after Week 12 will preclude a subsequent irBOR of irCR, irPR or irSD. However, any post-progression clinical activity in subjects with irBOR of irPD may be summarized for exploratory purposes.

**Table 7: Best Overall Response (irBOR)**

| **Target Lesions** Baseline (Index) and New Measurable Lesions | **Non-Target Lesions*** | | **irRC Overall Response** |
|---|---|---|---|
| **Total Measurable Tumor Burden (TMTB)** | **Baseline Lesions** | **Unequivocal New Lesions** | |
| irCR | irCR | No | irCR |
| irCR | irSD | No | irPR |
| irPR | irCR or irSD | No | irPR |
| irSD | irCR or irSD | No | irSD |
| irPD | Any | Yes or No | irPD |
| Any | Unequivocal Progression | Yes or No | irPD |
| Any | Any | Yes | irPD |

***NOTE:** Any increase in the size or number of non-measurable lesions does not necessarily imply an overall response of irPD. If these lesions become measurable (≥ 10 mm) at a subsequent TA, their measurement will at that point start to contribute to the TMTB. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening in non-target disease that is of a magnitude that the treating physician would feel it is important to change therapy. Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next schedule assessment.

### 8.3.5 Objective Response Rate

Objective response rate is defined as the proportion of subjects with a partial response or complete response according to immune-related RECIST criteria.

### 8.3.6 Duration of Response

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

The duration of overall irCR is measured from the time measurement criteria are first met for irCR

until the first date that irPD is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for irPD are met.

### 8.3.7 Progression-Free Survival

Progression-Free Survival: defined as the duration of time from registration to time of progression (irPD) or death, whichever occurs first.

### 8.3.8 Survival

Survival: defined as the duration of time from registration to time of death due to any cause, or the date the subject was last confirmed to be alive.

## 9. BIOLOGICAL CORRELATIVES

### 9.1 Objective: To evaluate potential biomarkers or prognostic factors for those who may respond to pembrolizumab

Please refer to the Correlative Laboratory Manual for all sample collection, processing, labeling, and shipping instructions.

**9.1.1** Immunohistochemical evaluation of PD-L1 expression on formalin-fixed, paraffin-embedded tissue section from primary tumor and/or fresh frozen biopsy of recurrent disease, if available

- PD-L1 staining intensity (-, +/-, +) and percent of tumor positive (<50%, ≥50%) will be correlated with response rate.

**9.1.2** Immunohistochemical evaluation of tumor-infiltrating lymphocytes ($CD8^+$), T regulatory lymphocytes (Treg, $CD4^+/Foxp3^+$) and myeloid derived suppressor cells ([MDSC] $HLADR^{low/-}$, $CD11b^+$, $CD14^+$) on formalin-fixed, paraffin-embedded tissue section from primary tumor and/or biopsy of recurrent disease, if available

- Cell subset total/field will be correlated with response rate.

**9.1.3** Flow cytometric quantification of tumor-infiltrating lymphocytes ($CD8^+$), T regulatory lymphocytes (Treg, $CD4^+/Foxp3^+$) and myeloid derived suppressor cells ($HLADR^{low/-}$, $CD11b^+$, $CD14^+$) on fresh frozen core biopsy of recurrent disease, if available

- Cell subset total/field will be correlated with response rate.

**9.1.4** Characterization of circulating immune cell populations ($TIM3^+/PD\text{-}1^+/CD8^+$, $PD\text{-}1^+/Treg$) will be evaluated on samples collected prior the start of and upon completion of combination pembrolizumab/cytotoxic chemotherapy.

- PD-1 Mean Fluorescence Intensity (MFI) on cell subset analyzed, percent of total lymphocytes (for each cell subset), and absolute number of cell subset will be correlated with response rate. This analysis will be performed on pre-treatment and post-treatment blood sample.

**9.1.5** IFN-γ and CD107a expression in/on circulating $CD8^+$ T cells will be measured to characterize effector function

- Mean Fluorescence Intensity (MFI) of IFN-γ and CD107a expression on cell subset analyzed, percent of total lymphocytes (for each cell subset), and absolute number of cell subset will be correlated with response rate. This analysis will be performed on

pre-treatment and post-treatment blood sample.

**9.1.6** Determination of the mutational landscape of endometrial cancer and its influence in the response to pembrolizumab.

- Exome sequencing and targeted next generation sequencing, targeting all exons of approximately 300 cancer related genes will be performed from FFPE tissue from participants' tumors.

## 9.2 Source of Study Specimens

**9.2.1** Unstained slides from an archived formalin-fixed, paraffin-embedded primary tumor block are required (if available) for each subject enrolled. If unavailable, biopsy of recurrence is required for correlative analysis.

**9.2.2** If a biopsy is performed for histologic documentation of recurrence, 3 frozen cores will be requested and shipped to laboratory for analysis.

**9.2.3** Whole blood will be collected at pre-treatment Cycle 1 Day 1 and at the 30-Day Post Treatment visit as noted in section 7.

## 9.3 Banking Samples for Future Studies

Subject consent will be obtained for additional samples collected for future Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the BTCRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood
  - Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma
  - Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30 Day Post Treatment Visit.
- Pre- and Post-treatment serum
  - Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30 Day Post Treatment Visit.
- Unstained slides (If Available)
  - Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor block.

Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

## 9.4 Pathology Requirements for Study Specimens

A pathology report confirming the diagnosis of advanced stage endometrial cancer must be available at the time of enrollment on study. For subjects with advanced or metastatic disease at the time of diagnosis, the original pathology from this diagnosis is sufficient. For subjects with early stage disease who later developed metastatic disease, biopsy confirmation of the metastatic disease is required. Additionally, pathologic documentation of the recurrence is required if there is only a single site of disease on imaging and that site is less than 2 cm. It is preferred that all subjects with recurrence undergo a biopsy for confirmation; in this setting, an optional collection of 3 frozen tissue cores of the recurrence site is requested for correlative analysis. All

surgeries/biopsies done at referring institutions should be reviewed and confirmed by a pathologist at the local study site.

## 10. DRUG INFORMATION

### 10.1. Pembrolizumab

#### 10.1.1. Other Names
Keytruda® (Pembrolizumab; MK-3475 [Anti-PD-1 Antibody MK-3475])

#### 10.1.2. Chemical Name and Properties
Humanized X PD-1_mAb (H409A11) IgG4

#### 10.1.3. Availability and Distribution

Merck will supply pembrolizumab directly to sites at no charge to subjects participating in this clinical trial.

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

#### 10.1.4. Storage

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

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

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

#### 10.1.5. Preparation and Administration
Please refer to the Pharmacy Manual for a comprehensive description of pembrolizumab preparation.

Pembrolizumab is provided as a white to off-white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2°C - 8°C).

The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution, essentially free of visible particles. The reconstituted product and liquid product are intended for IV administration. The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes

room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags may be stored at 2 to 8 °C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted pembrolizumab solutions in the IV bags.

### 10.1.6. Side Effects

Please refer to the current version of the Investigator's Brochure for a complete list of adverse events.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism), Type I diabetes mellitus, uveitis, myositis, Guillain-Barre syndrome, pancreatitis, myocarditis, severe skin reactions including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and "solid organ transplant rejection following pembrolizumab treatment in donor organ recipients" (risk applicable to post-marketing setting only, as such patients are currently excluded from Merck clinical trials with pembrolizumab).

The majority of immune-mediated adverse events were mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy.

Since the last IB (v13) update, the risk profile for pembrolizumab also includes 2 important potential risks – i.e. myasthenic syndrome and increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Since the last IB (v13) update, Merck received additional information from the clinical trial and post-marketing environments, which resulted in the following changes to the risk profile for pembrolizumab:

1. Two new important identified risks of "encephalitis" and "sarcoidosis".
2. Further characterization of the existing important identified risk of "Thyroid disorders (Hypothyroidism and Hyperthyroidism) to include "thyroiditis".
3. Elevation of "myasthenic syndrome" from an important potential risk to an important identified risk.
4. Addition of 1 new potential risk of GVHD after pembrolizumab administration in patients with a history of allogeneic HSCT.

Further details around frequency, reporting, and management of immune-related adverse events (irAEs) can be found in the current version of the Investigator's Brochure. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

## 10.2. Carboplatin

### 10.2.1. Other Names
CBDCA, Paraplatin®, JM-8, NSC-241240

### 10.2.2. Classification
Second-generation tetravalent organic platinum compound

### 10.2.3. Formulation
Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used in this study.

### 10.2.4. Preparation
Carboplatin will be prepared according to the product label and institutional standards. See also 'Incompatibilities' section below.

### 10.2.5. Availability and Distribution
Commercial supplies of carboplatin will be used in this study and billed to third party payers or the subject.

### 10.2.6. Storage and Stability
Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 10mg/mL with normal saline or 5% dextrose carboplatin is stable for 8 hours at 25 degrees C. Stability with further dilution to 0.5mg/mL has been reported for up to 8 hours. Other stability data indicate that carboplatin is stable for up to 24 hours and may be refrigerated; however, the manufacturer recommends that reconstituted solutions be discarded after 8 hours due to the lack of preservative in drug formulation.

### 10.2.7. Handling and Disposal
Caution should be exercised in handling and preparing carboplatin injection. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing carboplatin injection. If carboplatin injection contacts the skin, immediately wash the skin thoroughly with soap and water. If carboplatin injection contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

### 10.2.8. Incompatibilities
Aluminum displaces platinum from the carboplatin molecule, resulting in the formation of a black precipitate and loss of potency. Carboplatin solutions should not be prepared or administered with needles, syringes, catheters, or IV administration sets containing aluminum parts that might be in contact with the drug.

### 10.2.9. Side Effects

Incidence rates of adverse events associated with carboplatin are provided in the product package insert. Some of the expected adverse events with carboplatin treatment are listed below.

Hematologic: Thrombocytopenia (dose limiting), neutropenia, leukopenia, anemia.

GI: Nausea and vomiting (frequent but less severe than with cisplatin), treatable with appropriate antiemetic prophylaxis. Anorexia, diarrhea, and constipation have also been reported.

Dermatologic: Rash, urticaria. Rarer reactions include alopecia, mucositis, and hypersensitivity reactions.

Hepatic: Abnormal liver function tests, usually reversible with standard doses.

Neurologic: Rarely peripheral neuropathy is seen. May be more common in subjects greater than 65 years of age. May also be cumulative, especially in subjects with prior cisplatin treatment. Ototoxicity (rare).

Renal: Elevations in serum creatinine, BUN; electrolyte loss (Mg, K, Na, Ca).

Miscellaneous: Pain, asthenia, flu-like syndrome.

#### 10.2.10. Drug Interactions
Concomitant myelosuppressive drugs or radiation therapy may potentiate the hematologic toxicity of carboplatin.

Concomitant nephrotoxic drugs may potentiate the nephrotoxicity of carboplatin, particularly when carboplatin is given in high-dose chemotherapy regimens.

### 10.3. Paclitaxel

#### 10.3.1. Other Names
Taxol®

#### 10.3.2. Classification
Antimicrotubule agent

#### 10.3.3. Mode of Action
Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

#### 10.3.4. Availability and Distribution
Commercial supplies of paclitaxel will be used in this study and billed to third party payers or the subject.

#### 10.3.5. Storage and Stability
Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/ml are stable for up to 27 hours when stored at room temperature and normal room light.

#### 10.3.6. Preparation
The concentrated solution must be diluted to a concentration of 0.3 - 1.2 mg/ml according to the

product label and institutional standards. Solutions exhibit a slight haze, common to all products containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency.

Solutions exhibiting excessive particulate formation should not be used.

### 10.3.7. Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole may inhibit paclitaxel metabolism, based on in vitro data.

### 10.3.8. Side Effects

1. Hematologic: Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia).
2. Hypersensitivity: Thought to be caused by the Cremophor vehicle. Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and tachycardia. More severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.
3. Cardiovascular: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication -- Dexamethasone) may also occur.
4. Neurologic: Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).
5. Dermatologic: Alopecia (universal, complete, and often sudden, between days 14-21); injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.
6. Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
7. Hepatic: Increased AST, ALT, bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.
8. Other: Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

# 11. ADVERSE EVENTS

## 11.1. Definitions

### 11.1.1. Adverse Event (AE):

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

Adverse events may occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the site investigator.

### 11.1.2. Serious Adverse Event (SAE):

A serious adverse event is any adverse event that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to,
  - intensive treatment in an emergency room or at home for allergic bronchospasm;
  - blood dyscrasias or convulsions not resulting in hospitalization;
  - the development of drug dependency or drug abuse.
- A new cancer (that is not a condition of the study);
- A pembrolizumab overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest. Both cases must be immediately reported. See section 11.2.2.

### 11.1.3. Unexpected Adverse Event:

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

## 11.2. Reporting

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. A copy of the CTCAE version 4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

### 11.2.1. Adverse Events (AEs)

Adverse events (AEs) will be recorded from the time of consent, at each time point marked on the Study Calendar, and through 30 days following cessation of treatment. All adverse events regardless of CTCAE grade must also be evaluated for seriousness. The reporting timeframe for adverse events meeting any serious criteria is described in Section 11.2.5.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an Event of Clinical Interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

### 11.2.2. Definition and Reporting of a Pembrolizumab Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. 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 1 working day to BTCRC Administrative Headquarters (AHQ). BTCRC AHQ will report the event within 1 working day to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

### 11.2.3. Definition and Reporting of Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 1 working day to BTCRC AHQ.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 11.2.2, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3× the upper limit of normal **and** an elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal **and**, at the same time, an alkaline phosphatase lab value that is less than 2× the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   ***NOTE**: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 1 working day to BTCRC AHQ. BTCRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229).

### 11.2.4. Serious Adverse Events (SAE)

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

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

Additionally, any serious adverse event considered to be related to pembrolizumab that is brought to the attention of the site investigator outside the 90-day time period specified above must also be reported immediately to BTCRC AHQ in collaboration with sponsor-investigator.

All adverse events will be evaluated for:

| | | |
|---|---|---|
| **CTCAE v4.0 Grading** | **Grade 1** | **Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or | |
| | †**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or | |
| | **Is a** new **cancer;** (that is not a condition of the study) **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. | |
| | **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †). | |
| **Duration** | Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units | |
| **Action taken** | Did the adverse event cause the Merck product to be discontinued? | |
| **Relationship to test drug** | Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.<br>**The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE): | |
| | **Exposure** | Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen? |
| | **Time Course** | Did the AE follow in a reasonable temporal sequence from administration of the Merck product?<br>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)? |
| | **Likely Cause** | Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors |

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

**11.2.4.1. Site Requirements for Reporting SAEs to BTCRC Administrative Headquarters:** Investigators and other site personnel must report all SAEs within **one business day** of discovery of the event using the SAE/ECI submission form. This includes events both related and unrelated to the investigational product.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

| | |
|---|---|
| Unrelated | The Adverse Event is *clearly not related* to the investigational agent(s) |
| Unlikely | The Adverse Event is *doubtfully related* to the investigational agent(s) |
| Possible | The Adverse Event *may be related* to the investigational agent(s) |
| Probable | The Adverse Event is *likely related* to the investigational agent(s) |
| Definite | The Adverse Event is *clearly related* to the investigational agent(s) |

**The completed SAE/ECI submission form (see SPM) must be sent electronically to SAFETY@hoosiercancer.org or faxed (317-921-2053) to Big Ten Cancer Research Consortium (BTCRC) Administrative Headquarters (AHQ) within one business day of discovery of the event.** The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE/ECI submission form and the e-mail correspondence or fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information will be sent electronically using the SAE/ECI submission form to SAFETY@hoosiercancer.org or faxed to BTCRC AHQ. Each re-occurrence, complication, or progression of the original event should be reported as a new follow-up to that event regardless of when it occurs.

The follow-up information should describe:

- whether the event has resolved or continues,
- if and how it was treated,
- whether study medication is ongoing, interrupted or stopped,
- whether the blind was broken or not (if applicable), and
- whether the subject continued or withdrew from study participation.

In addition to faxing the SAE/ ECI submission form to BTCRC AHQ, sites will also enter the event in the SAE tab in the BTCRC electronic data capture system.

**11.2.4.2. BTCRC AHQ Requirements for Reporting SAEs:**

**11.2.4.2.1. BTCRC AHQ Reporting to Merck**

BTCRC AHQ will report any SAE that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, to Merck **within one business**

**day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

BTCRC AHQ will submit all SAE reports to Merck and will provide follow-up information as reasonably requested.

**SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229**

#### 11.2.4.2.2. BTCRC AHQ Reporting to the Northwestern QAM/DMC

BTCRC AHQ will submit all SAEs) to the assigned Northwestern Quality Assurance Monitor (QAM)**. The completed SAE Report Form must be emailed to croqualityassurance@northwestern.edu within 1 business day of discovery of the event.**

#### 11.2.4.2.3. BTCRC AHQ Reporting to the Food and Drug Administration (FDA)

BTCRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of Mario Javier Pineda, M.D., sponsor-investigator. BTCRC AHQ is responsible for all communication with the FDA including but not limited to 15 Day Reports and Annual Progress Reports. BTCRC AHQ will cross-reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, BTCRC AHQ will submit a copy of these reports to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

BTCRC AHQ will report to the FDA using MedWatch Report form, regardless of the site of occurrence, any AE that is serious, unexpected and reasonably related (i.e., possible, probably, definite) to the study treatment. The sponsor-investigator will review these reports and determine if any revisions are needed to the protocol or consent.

According to CFR 312.32, unexpected fatal or life-threatening events associated with the use of the study treatment will be reported to the FDA by fax or by phone as soon as possible but in no event later than 7 calendar days after the initial receipt of the information regarding the event. The fax should be sent to the FDA project manager assigned to the IND. A comprehensive written report will be submitted as an amendment to the IND within an additional 8 days (15 calendar days total).

All other serious unexpected events associated with the use of the study treatment will be reported to FDA as an amendment to the IND as soon as possible but in no event later than 15 calendar days after initial receipt of the information regarding the event.

### 11.3. Sponsor-Investigator Responsibilities

BTCRC AHQ will send a SAE summary to the sponsor-investigator (or designated back-up) within 1 business day of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

### 11.4. IND Safety Reports Unrelated to This Trial

Merck will send IND safety reports from external studies that involve the study drug to BTCRC AHQ (SAFETY@hoosiercancer.org). BTCRC AHQ will forward the safety reports to the sponsor-investigator (or designated back-up) who will review these reports and determine if revisions are needed to the protocol or consent. BTCRC AHQ will forward these reports to participating sites every 2 weeks.

Upon receipt from BTCRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

BTCRC AHQ will also submit IND safety reports to the Northwestern DMC for review (croqualityassurance@northwestern.edu).

## 12. STATISTICAL CONSIDERATIONS

### 12.1. Study Design

This is a single-arm, open-label, multi-center phase II study for subjects with measurable advanced or recurrent endometrial cancer using pembrolizumab in combination with carboplatin and paclitaxel chemotherapy. As this combination of agents has not been tested in this subject population, the first six subjects enrolled will constitute a safety run-in cohort (see Section 5.2). The most recently published Gynecologic Oncology Group trial (GOG-177) evaluating chemotherapeutic response rate in advanced and recurrent endometrial cancer was published in 2004. In this trial, the triplet combination therapy, paclitaxel, doxorubicin, cisplatin had a 50-59% response rate (RR) depending upon histologic subtype; the complete response rate was 22% [1]. In a retrospective analysis of patients with histologically confirmed endometrial carcinoma or uterine carcinosarcoma who received second-line platinum-based chemotherapy, the response rate for the entire cohort was 50% (129 CR+PR out of 262 total evaluable patients). All patients had received primary platinum-based chemotherapy with or without concurrent chemoradiation therapy[2]. Taking both studies into account, we estimate a 50% response rate for combination platinum-based chemotherapy in the up-front setting or as salvage therapy following initial response. A meaningful clinical response would be an improvement in RR of 15% given the potential risks and increased cost for the additional immunotherapy; for our purposes we will target a 65% RR. The proposed sample size will be 46 subjects total. A single group of 46 subjects will give us a 77% power to detect a higher overall response rate (65%) than the historical control (50%), assuming a one-tailed test and a Type I error rate of 10%. All subjects who receive pembrolizumab will be evaluated for treatment efficacy and toxicity. The 46 patients will include the six patients in the successful safety run-in period. If one dose reduction is needed during the run-in period, then the final sample size of 46 used for the primary objective will include only the six patients at the successful run-in dose. The total sample size would then be 52.

Statistical analysis will be done by the Biostatistics Core Facility of the Robert H. Lurie Comprehensive Cancer Center.

### 12.2. Definition of Primary Endpoint

Objective response rate is defined as the proportion of evaluable subjects with a partial response or complete response according to irRECIST criteria.

## 12.3. Definitions of Secondary Endpoints

Toxicity is defined as the proportion of evaluable subjects who experience ≥ Grade 3 toxicity according to CTCAE v4.

## 12.4. Definitions of Correlative Endpoints

**12.4.1.** Immunohistochemical evaluation of PD-L1 expression on formalin-fixed, paraffin-embedded tissue section from primary tumor and/or biopsy of recurrent disease, if available.

**12.4.2.** Immunohistochemical evaluation of tumor-infiltrating lymphocytes (TIL, $CD8^+$), T regulatory lymphocytes (Treg, $CD4^+/Foxp3^+$) and myeloid derived suppressor cells (MDSC: $HLADR^{low/-}$, $CD11b^+$, $CD14^+$) on formalin-fixed, paraffin-embedded tissue section from primary tumor and/or biopsy of recurrent disease, if available.

**12.4.3.** Flow cytometric quantification of tumor-infiltrating lymphocytes ($CD8^+$), T regulatory lymphocytes (Treg, $CD4^+/Foxp3^+$) and myeloid derived suppressor cells ([MDSC] $HLADR^{low/-}$, $CD11b^+$, $CD14^+$) on fresh frozen core biopsy of recurrent disease, if available.

**12.4.4.** Characterization of circulating immune cell populations ($TIM3^+/PD\text{-}1^+/CD8^+$, $PD\text{-}1^+$/Treg) will be evaluated on samples collected prior the start of and upon completion of combination pembrolizumab/cytotoxic chemotherapy

**12.4.5.** IFN-γ and CD107a expression in/on circulating $CD8^+$ T cells will be measured by flow cytometry to characterize effector function.

## 12.5. Analysis Plan for Primary Objective

The response rates will be compared with actual data from the historical control using a one sample test for proportions where the null hypothesis is that the rate is 50%.

## 12.6. Analysis Plan for Secondary Objective

All adverse events and safety monitoring measures will be described longitudinally using descriptive statistics such as frequencies, proportions, and ranges. Individual data will be reported for values out of normal range.

## 12.7. Analysis Plan for Exploratory Objectives

**12.7.1.** PD-L1 staining intensity (-, +/-, +), percent of tumor positive (<50%, ≥50%) primary/recurrent tumor and other immunohistochemical markers (TIL, Treg and MDSC will be quantified and reported as total number per field) will be related to response rate either individually or in a multivariate analysis using logistic regression.

**12.7.2.** Characterization of circulating immune cell populations ($TIM3^+/PD\text{-}1^+/CD8^+$, $PD\text{-}1^+$/Treg) will be evaluated on samples collected prior the start of and upon completion of combination pembrolizumab/cytotoxic chemotherapy and will be compared between time points using either McNemar's test (for categorical metrics) or the Wilcoxon signed rank test (for continuous metrics). These markers at each time point will be related to response using logistic regression.

**12.7.3.** Individual genes will be identified as those up- or down-regulated in tumor relative to adjacent normal tissue. False discovery rate adjustment will be used to identify candidate genes. These analyses will define the mutational landscape. A genetic signature for response will be identified using multivariate and data reduction methods such as principal components analysis, logistic regression and random forest analysis.

## 12.8. Criteria for Stopping Study

Study will be suspended pending evaluation of toxicity during the safety lead-in as described in section 5.2. There are no interim analyses planned for primary objective.

## 12.9. Analysis Datasets

**Methods of Statistical Analysis**

| Population | Definition |
|---|---|
| Enrolled | This will comprise all subjects who meet the eligibility criteria and are registered onto the study. |
| Evaluable | This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation. |
| Intention-to-treat (ITT) | This will comprise all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment. (See Intent-To-Treat principle below). |
| Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample) | This will comprise all subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. This population should be specifically defined in the protocol. |
| Safety | This will comprise all subjects who receive at least one dose of pembrolizumab. |
| Treated | This will comprise all subjects who have been exposed to the planned course of treatment to any extent. |

Intention-To-Treat Principle - The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

## 12.10. Accrual/Study Duration

Recruitment of 46 subjects will last approximately 18 months and subjects will be followed for 18 months from enrollment of the last subject. The estimated study duration is 3 years.

## 12.11. Subject Characteristics /Other Baseline Characteristics

Demographic and other baseline data will be summarized descriptively for all subjects in the enrolled set. All protocol deviations will be documented. The Big Ten Cancer Research Consortium participating institutions will not exclude potential subjects from participating in this

or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible subjects into this protocol, thereby addressing the study objectives in a subject population that is representative of the entire endometrial cancer population treated by participating institutions.

### 12.12. Concomitant Medication

Concomitant medications and significant non-drug therapies at the time of registration and after the start of the study drug will be summarized for the treated set.

### 12.13. Disposition

The number of enrolled subjects will be summarized in a flow chart with frequency of completion and discontinuation. The subjects discontinued from study drug and their corresponding information will be listed. Significant protocol violations will be tabulated and/or listed.

## 13. TRIAL MANAGEMENT

### 13.1. Data and Safety Monitoring Plan (DSMP)

The Robert H. Lurie Comprehensive Cancer Center's Data Monitoring Committee (DMC) will provide study oversight activities as outlined in Section 13.2.

BTCRC AHQ oversight activities include:

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution DMC and attend DMC reviews:
  - during the safety run-in portion of the study, semi-monthly to present safety summary reports
  - during the Phase II portion of the study, as applicable: following any reports of protocol deviations or SAEs; and overall study data delinquency that exceeds 10% incomplete forms or sites with data delinquency that are not responding sufficiently to the BTCRC AHQ data delinquency escalation process
  - throughout the study, semi-annual comprehensive DMC review
- During the safety run-in portion of the study there will be weekly safety calls with all participating institutions

### 13.2 Robert H. Lurie Comprehensive Cancer Center's DMC

BTCRC AHQ will provide the following for the Robert H. Lurie Comprehensive Cancer Center's DMC to review:

- Adverse event summary report
- Monitoring reports
- Audit results if applicable
- Study accrual patterns
- Data delinquency
- Protocol deviations

The Robert H. Lurie Comprehensive Cancer Center's DMC will conduct a comprehensive study review semi-annually, based on the date the study was originally opened with NU. Documentation of DMC reviews will be provided to sponsor-investigator and BTCRC AHQ. Issues of immediate concern by the DMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with BTCRC AHQ to address the DMC's concerns.

### 13.3 Data Quality Oversight Activities

Remote validation of data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

There will be at least one routine visit per site per year for sites that have accrued. Additional for cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the eDC. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by BTCRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Merck or their designee as well as inspection by appropriate regulatory agencies.

## 14. DATA HANDLING AND RECORD KEEPING

### 14.1. Case Report Forms and Submission

This study will utilize electronic case report forms (eCRFs) in an electronic data capture (eDC) system. The eDC system will be compliant with Good Clinical Practices and Federal Rules and Regulations.

Generally, clinical data will be electronically captured in the eDC and correlative results will be captured in the eDC or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the eDC, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at BTCRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and BTCRC AHQ. After the initial publication, the complete data set will be available to all BTCRC institutions.

Trials that use the Lurie Cancer's DSMP are not permitted to publish trial data in any capacity until the data has been approved by the DMC. If a PI anticipates that he or she will publish data prior to three months after the Clinicaltrials.gov primary completion date, they must notify the assigned QAM as soon as possible. QAMs can prepare the data summary for DMC approval upon PI request, but must have a minimum six weeks' notification.

### 14.2. Record Retention

To enable evaluations and/or audits from Health Authorities/BTCRC AHQ, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition in compliance with local and federal regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

### 14.3. Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number.

Subjects will be informed in writing that some organizations, including the sponsor-investigator and his/her research associates, BTCRC AHQ, Merck, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

### 14.4. Changes to the Protocol and Informed Consent

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, BTCRC AHQ, and Merck.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by BTCRC AHQ and must be approved by the sponsor-investigator and Merck in addition to each site's IRB, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the informed consent form sites must notify their local IRB. Approval of the revised informed consent form by the local IRB is required before the revised form is used.

The local investigator is responsible for the distribution of amended documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Merck's willingness to supply study drug is predicated upon the review of the protocol. BTCRC AHQ agrees to provide written notice to Merck of any modifications to the protocol.

## 15. ETHICS

### 15.1. Ethics Review

The final study protocol, including the final version of the informed consent form, must be approved or given a favorable opinion in writing by an IRB. The local investigator must submit written approval to the BTCRC AHQ office before he or she can enroll any subject into the study.

The local investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The local investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Merck will provide this information to the sponsor-investigator and BTCRC AHQ. These reports will be reviewed by the sponsor-investigator and will be forwarded to participating sites every 2 weeks for submission to their Institutional Review Boards per their guidelines.

### 15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

### 15.3. Informed Consent Process

The informed consent will adhere to IRB requirements, applicable laws and regulations, and funder requirements. The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion prior to use. The subject or his/her legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

Each site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study prior to participating in the clinical trial. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed written informed consent form. A copy of the signed informed consent form must be given to the subject.

### 15.4. Compliance with Trial Registration and Results Posting Requirements

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

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