Phase 2 Trial of Dose Dense (Weekly) Paclitaxel with Pembrolizumab (MK-3475) in Platinum Resistant Recurrent Ovarian Cancer

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TITLE: Phase 2 Trial of Dose Dense (Weekly) Paclitaxel with Pembrolizumab (MK-3475) in Platinum Resistant Recurrent Ovarian Cancer

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Participating Sites: Moffitt Cancer Center and Affiliate Sites

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1.0 TRIAL SUMMARY

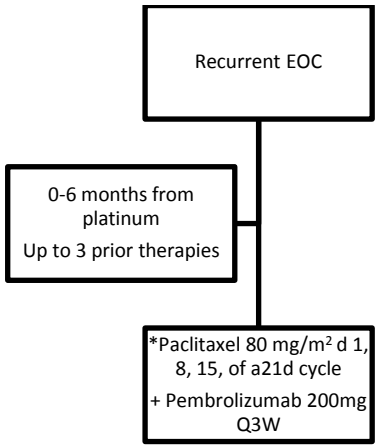
Abbreviated Title	Phase 2 trial of Weekly Paclitaxel and Pembrolizumab in Ovarian Cancer
Trial Phase	2
Clinical Indication	Recurrent Ovarian Cancer
Trial Type	Phase II
Type of control	None
Route of administration	IV
Trial Blinding	No
Treatment Groups	1
Number of trial subjects	50 enrolled patients, 37 evaluable patients
Estimated duration of trial	1.5-year enrollment, 2.5 year total
Duration of Participation	To progression with follow-up

2.0 TRIAL DESIGN

2.1 Trial Design

Single-arm, open-label, phase 2.

2.2 Trial Diagram



- Treatment until PFS. However, paclitaxel may be discontinued (and pembrolizumab continued) if continued administration prohibited by paclitaxel related toxicity, or investigator discretion with CR after 6 cycles. In the case of pembrolizumab toxicity, paclitaxel should be continued alone until progression, unacceptable toxicity, or investigator discretion with CR after 6 cycles. In the case of paclitaxel discontinuation, pembrolizumab should be continued until progression or toxicity.
- *Cycle 1 has no Pembrolizumab given during a lead-in week in first cycle. Only this cycle consists of 4 weeks, with week 2 marking the first dose of Pembrolizumab. Steroids are eliminated starting cycle 1 day 8 if no hypersensitivity reaction (HSR) occurred during Cycle 1day1. The addition of steroids, if needed for subsequent weekly paclitaxel, may diminish the effect of Pembrolizumab.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objectives & Hypotheses

(1) **Objective:** Progression Free Survival

Hypothesis: The addition of Pembrolizumab (MK-3475) to weekly paclitaxel improves the 6-month PFS for patients with recurrent epithelial ovarian, fallopian tube, or peritoneal cancer.

(2) **Objective:** Safety

Hypothesis: The combination of paclitaxel weekly with pembrolizumab Q3W is tolerable without new safety signals.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**:

- To estimate (and compare to historical control) the proportion of patients who respond to the regimen by RECIST v1.1, RECIST based immune-related response criteria (irRC), and exploration of CA125 Rustin Criteria.
- To assess (and compare to historical control) the Disease Control Rate (DCR), and Duration of Response (DOR) in the study population.
- To assess (and compare) Overall Survival (OS) in the study population.

3.3 Exploratory Objective

(1) **Objective:** Biomarkers (4.2.3.2) of response prediction (4.2.3.1)

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-

cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7,8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7,10-12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13,14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15,16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [13,18-20]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475 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.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

In the United States, epithelial ovarian cancer is the second most frequent gynecologic malignancy; however, due to diagnosis at advanced stage and resistance to therapy it is the leading cause of death from gynecologic malignancy. Each year approximately 26,000 women will be diagnosed with ovarian cancer and 15,000 will die from the disease. Most patients will have recurrent disease and receive several lines of chemotherapy. The treatment of recurrent ovarian cancer is difficult due to drug resistance even after initial response. Many compounds and combinations have been evaluated such as liposomal doxorubicin, topotecan, docetaxel, and paclitaxel. It has also been demonstrated that the weekly administration of paclitaxel leads to responses in platinum- and taxane-resistant cancers [22,23].

There is evidence in platinum-resistant ovarian cancer that the weekly administration of paclitaxel leads to better tolerance with decreased myelosuppression (i.e. GOG protocol 126N). Weekly paclitaxel (80 mg/m^2/week) in this setting showed an objective response rate of 20.9% (two CRs, eight PRs) among 48 evaluable patients. Serious adverse events were relatively uncommon with 21% of patients experiencing grade 2 neuropathy and only 4% developing grade 3 neuropathy. In the randomized comparison of weekly paclitaxel to every 3-week paclitaxel, Rosenberg and colleagues showed that (at equivalent dose intensity) the weekly regimen (RR = 19%) was better tolerated without compromising efficacy [24].

Weekly paclitaxel has gained widespread use as a standard treatment of recurrent, platinum resistant ovarian cancer. Many recent and ongoing randomized trials in recurrent ovarian cancer are using weekly paclitaxel in the control arm (i.e. TRINOVA-1, MITO-11, AURELIA, ESP2011-002). There is additional evidence suggesting that dose-dense chemotherapy improves mechanisms of antitumor immune response [25] as well as adding anti-angiogenic properties [26]. Furthermore, there may be synergistic activity between anti-angiogenic therapy and immunotherapy [27].

For platinum resistant disease, the recent AURELIA trial compared three different chemotherapies with or without bevacizumab [28]. This trial allowed patients whose disease had recurred within 6 months of prior platinum therapy, and up to 2 prior therapies, to get one of 3 investigator-preselected chemotherapies (weekly paclitaxel, liposomal doxorubicin, or topotecan) and then randomized the bevacizumab. There was an approximate doubling of the median PFS 3.4 (2.2-3.7) to 6.7 (5.7-7.9). The 6-month PFS, although not reported, can be closely estimated from the PFS graph in the reported manuscript and is approximately 0.25 on the high end of the control confidence interval (CI), and 0.5 on the low end of the experimental arm CI. The statistically significant improvement has led to a pending FDA approval application. Although the chemotherapy was not randomized, the weekly paclitaxel arm had a non-statistically significant trend toward better PFS.

Additionally, some have suggested that this may represent the bar for a new platinum resistant single agent or combination therapy to achieve. However, there may be different

populations that ultimately benefit from bevacizumab versus immunotherapy (e.g. PD1 directed therapy). Weekly paclitaxel may impart new attributes to angiogenic or immunotherapy strategies. It is reasonable to first see if the combination of paclitaxel and Pembrolizumab appears superior to the current standard of paclitaxel alone. If so, and if this doublet is tolerable (and bevacizumab gets approval for this setting), a next consideration may be to look at triplet combination therapy (Bev+Pacl vs Bev+Pembro+Pacl), or even compare doublets (Bev+Pacl vs Pembro+Pacl).

In the platinum resistant ovarian cancer setting, the number of previous therapies does not seem to greatly change the overall response rate or PFS of tumors to therapy. This likely stems from the overall poor response rate in general (approximately 11-21%) (GOG 126 series) and poor PFS. Recognizing this, recent industry randomized phase 2 and phase 3 trials using weekly paclitaxel in this setting have allowed up to 3 prior treatments [29,30]). The authors noted that comparison of activity (PFS) to lines of therapies revealed no differences. Randomized studies with weekly paclitaxel, such as TRINOVA-1, appear to have better PFS compared to others such as AURELIA and MITO-11, despite the fact that TRINOVA-1 allowed up to 25% with 3-prior therapies and the latter trials only allowed up to 2. This is because PFS is primarily a function of recurrence interval from prior platinum, i.e. TRINOVA-1, but not the others, allowed semi-resistant 6-12 month platinum free patients to be included. (Table 11).[28,30,31]

Furthermore, the number of lines of therapy may have even less meaning for an agent that works via activating an immune mechanism, rather than reliance on tumor sensivity/resistance. Therefore, the number of lines of therapy, referring to chemotherapy, may make sense primarily in the context of chemotherapy. It may lose meaning even in platinum sensitive disease, where the number of lines of therapy has more meaning.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab (MK-3475): 200 mg Q3W

In an open-label, solid-tumor, Phase I trial (Protocol 001) to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475), three dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg) were 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 (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, became the dose and schedule utilized in further cohorts. However, some data from other clinical studies within the pembrolizumab (MK-3475) program have shown that a lower dose of pembrolizumab (MK-3475) and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab (MK-3475) administered Q2W and Q3W show slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggest that peripheral target engagement is

durable (>21 days). The early PK and pharmacodynamic data provided scientific rationale for testing both Q2W and Q3W dosing schedule.

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

Further studies have looked at the safety and PK parameters using 200 mg as a single adult dose without adjustment for weight given on an every 3 week schedule. This dose is currently being used in several new and ongoing studies (i.e. MK-3475-012/KEYNOTE-012/NCT01848834, MK-3475-031/NCT02212730, MK-3475-021/KEYNOTE-021/ NCT02039674, (MK-3475-023/KEYNOTE-023/NCT02036502, and (MK-3475-042/KEYNOTE-042/ NCT02220894) and has been the dose recommended for use in future trials of pembrolizumab by Merck.

Paclitaxel: 80 mg/m² days 1, 8, 15 q 21d

Weekly Paclitaxel as a Single Agent:
In patients with platinum-taxane refractory ovarian cancer, retreatment with paclitaxel using a weekly schedule has demonstrated activity, possibly through anti-angiogenic as well as direct cytotoxic mechanisms. GOG-0126N demonstrated a 21% objective response rate (and a 46% rate of stable disease) in this population [32].

Recent and current randomized phase 3 trials [29,31] in recurrent ovarian cancer that have utilized a designated backbone of weekly paclitaxel have used 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. The AURELIA study used continuous weekly dosing at 80 mg/m^2 on a 28-day cycle. This trial will use the same continuous weekly dosing, however, on a 3-week cycle to mirror the Pembrolizumab schedule. Assessments will be at 9-week (3 cycle) intervals, rather than 8-week (2 cycle) intervals in the AURELIA trial. The effect of this should be quite minimal. [28].

*Cycle 1 has no Pembrolizumab given during a lead-in week in first cycle. Only this cycle consists of 4 weeks, with week 2 (cycle 1, day 8) marking the first dose of Pembrolizumab.

Steroids are eliminated starting cycle 1, day 8 if no hypersensitivity reaction (HSR) occurred during Cycle 1, day 1 administration of Paclitaxel. The addition of steroids, if needed for subsequent weekly paclitaxel, may diminish the effect of Pembrolizumab. [33]

4.2.3 Rationale for Primary Endpoints

Primary: Progression Free Survival at 6-months (6-month PFS)

PFS is the appropriate endpoint for this study both in terms of the disease and the agents being studied. Recurrent ovarian cancer is not considered curable. Drugs that provide longer durations of disease and symptom control are generally preferred over drugs that do not, even if the latter drugs might provide temporary reductions in tumor measurements (response). A patient who lacks progression on an agent in this setting is generally better off remaining on treatment despite a lack of response, as subsequent regimens are unlikely to be beneficial. Most recent and current randomized studies in recurrent ovarian cancer use PFS as the primary endpoint. The FDA has provided approval of new regimens based upon this endpoint (i.e. gemcitabine + carboplatin) [34]. In terms of pembrolizumab (MK-3475), the mechanism of this drug may be associated with tumor suppression without measurable disease reduction in some patients, despite a possible long-term disease control rate. Additionally, the relatively small 6-month PFS in this population (GOG 126 series, communication) proposed makes it a feasible endpoint to study.

Safety: Given the relatively well-documented toxicities associated with dose-dense paclitaxel and the lack of anticipated overlapping toxicities with pembrolizumab (MK-3475), it is deemed reasonable to conduct a phase II trial with the combination. It is not anticipated that the safety profile of pembrolizumab will change with the addition of paclitaxel. However, the accurate prospective measurement of toxicities and a descriptive comparison to treatment with dose-dense paclitaxel only is important, particularly if there appears to be an improvement in the PFS hazard ratio.

Immunotherapy has been combined with paclitaxel in cancer patients. In a phase II study in NSCLC, grade 3/4 events were not different between 204 patients receiving ipilimumab or placebo with carboplatin and paclitaxel. A multi-arm phase II study that combines Pembrolizumab with paclitaxel 200mg/m^2 (and carboplatin AUC 6) is currently underway (KEYNOTE-021).

4.2.3.1 Efficacy Endpoints

Primary Objectives:

- Efficacy: To estimate the 6-month progression-free survival of the combination of weekly paclitaxel with pembrolizumab (MK-3475) and to compare to historical weekly paclitaxel alone in patients with persistent or recurrent ovarian, fallopian tube, or primary peritoneal cancer.

- Safety: To determine the frequency and severity of adverse events associated with treatment with weekly paclitaxel with pembrolizumab (MK-3475) in this population of patients as assessed by CTCAE.

Secondary Objectives:

- To estimate the proportion of patients who respond to the regimen by RECIST v1.1, RECIST based immune-related response criteria (irRC), and exploration of CA125 Rustin Criteria.
- To assess the Disease Control Rate (DCR), and Duration of Response (DOR) in the study population.
- To assess median Overall Survival (OS) in the study population.

4.2.3.2 Biomarker Research

There is the potential that certain immune markers may predict response to immunotherapy agents. PD-L1 overexpression correlates with malignancy and immune regulation in ovarian cancer [35]. PD-L1 has been suggested to predict anti-PD-1 responses [35]-[36]. In a phase 1 trial of pembrolizumab (MK-3475), pretreatment tumor PD-L1 expression by immunohistochemistry (IHC) was a statistically significant predictor of response [37]. Therefore, tumor samples must be available from diagnosis to be examined by IHC in all patients (to be analyzed if a significant level of activity is ultimately seen). Also, as mentioned above, a study in patients with ovarian cancer demonstrated the ability to examine peripheral blood mononuclear cells (PBMC) for PD-L1 expression and that it correlates with PD-1 expression in TILs in malignant tumors [35]. Other reports have also noted panels of markers that may be predictive and the data continue to evolve. Therefore, PBMCs will be collected pre and post treatment in participating patients and analyzed if study reaches an endpoint that demonstrates significant clinical activity. Pending additional funding and an amendment to the protocol, pretreatment and post-treatment biopsies may be obtained in a portion of study slots reserved for patients who are willing to participate in these biopsies. These tumors can be examined for TILs and PD-1 expression, and tumor tissue expression of PD-L1 (+/- other markers, i.e., IDO, LAG-3, TIM-3, ICOS, etc.). Separate reporting will be made looking for an association between PFS and RR with PD-L1 positive tumors. Other associations with markers will be explored.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

5.1.2 Subject Inclusion Criteria

1. Be willing and able to provide written informed consent/assent and authorization permitting study-related release of personal health information.

2. Must have confirmation of the histologic diagnosis of high-grade (grade 2-3) epithelial, non-mucinous, non-borderline, ovarian, fallopian tube, or primary peritoneal carcinoma. May be based on original pathology report or review of original slides.

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

4. Disease must have been persistent or have recurred within 6 months (182 days) of a prior platinum therapy. Disease may not have progressed during prior platinum therapy (i.e. refractory).

    a. Evidence of progression and the timing of progression or reoccurrence will be new measurable disease, RECIST defined progression, or first doubling of the CA-125 nadir (however, that will need a confirmatory CA-125 to be done at least 2 weeks or later and the patient will need to have "detectable disease" (see below).

    b. While the disease must have been persistent or progressive within 6 months of a prior platinum therapy, the patient may be enrolled *and* begin treatment up to 12 calendar months (+/- 2 weeks) after the last dose of platinum-based therapy.

5. Have measurable disease or detectable (non-measureable) disease.

    a. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI.

    b. Detectable (non-measurable) disease is defined as not having measurable disease but has:

        i. Baseline values of CA-125 at least 2 x ULN; AND EITHER

            1. Ascites and/or pleural effusion attributed to tumor; OR

            2. Solid and/or cystic abnormalities on radiographic imaging consistent with recurrent disease that do not meet RECIST 1.1 definitions for target lesions.

6. Patients with measurable disease must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1 (Section 7.1.2.5.2.). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

7. Prior Therapy

    a. Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, non-cytotoxic agents (biologic/ targeted) or extended therapy administered after surgical or non-surgical assessment. If patients were treated initially with paclitaxel for their primary disease, this can have been given weekly or every 3 weeks. The most recent therapy and any therapies subsequent to initial therapy, however, cannot have contained weekly paclitaxel. If the immediate prior (most recent therapy) is the initial therapy, it may not have been with weekly paclitaxel.

    b. Patients are allowed to receive, but are not required to receive, two additional cytotoxic regimens for management of recurrent or persistent disease, with no more than 1 non-platinum regimen. Treatment with weekly paclitaxel for recurrent or persistent disease is NOT allowed.

    c. Patients are allowed to receive, but are not required to receive, non-cytotoxic (biologic/targeted) therapy as part of their primary treatment regimen. Patients are allowed to receive, but are not required to receive, non-cytotoxic (biologic/targeted) therapy as part of their treatment for recurrent or persistent disease and/or as treatment for recurrent or persistent disease. If non-cytotoxic (biologic/targeted) therapy is given alone (i.e., not in combination with cytotoxic chemotherapy) it will NOT count as a prior regimen.

8. Have tissue from an archival tissue sample that has been identified and confirmed as available for study, or newly obtained core or excisional biopsy of a tumor lesion.

9. Patients who have received one prior regimen must have an ECOG Performance Status of 0, 1, or 2.

    Patients who have received two or three prior regimens must have an ECOG Performance Status of 0 or 1.

10. Patients must demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	

Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Neurologic Function	
	Neuropathy (sensory and motor) less than or equal to grade 1.
[a]Creatinine clearance should be calculated per institutional standard.	

11. Recovery from effects of recent surgery, radiotherapy, or chemotherapy:
    - Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).
    - Any hormonal therapy directed at the malignant tumor must be discontinued at least two weeks prior to registration. Continuation of hormone replacement therapy is permitted.
    - Any other prior therapy directed at the malignant tumor, including chemotherapy, biologic/targeted and immunologic agents, must be discontinued at least two weeks prior to registration and at least 3 weeks before day 1 on trial.

12. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

13. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

5.1.3 Subject Exclusion Criteria

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

1. Has low-grade or non-epithelial cancers, mucinous cancers, and/or borderline low-malignant potential cancers.

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

3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

4. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to prior therapies.

5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 3 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

6. Has a history of other invasive malignancies (with the exception of non-melanoma skin cancer and or *in situ* cancers that have undergone potentially curative therapy) are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

7. Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

8. Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

9. Patients with a past history of synchronous endometrial cancer are excluded unless all of the following conditions are met: Stage not greater than I-A (FIGO 2010 staging criteria); no more than superficial myometrial invasion (<50%), without vascular or

lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions, and it has been greater than 3 years since diagnosis and there have been no recurrences.

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

11. No 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment..

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

13. Has an active infection requiring systemic therapy.

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

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

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

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

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

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

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

21. Peripheral neuropathy CTCAE grade 2 or higher.

22. Has known hypersensitivity to pembrolizumab or any of its excipients.

23. Has known hypersensitivity to paclitaxel.

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

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q 3 weeks	IV infusion	Until progression or toxicity (or up to 24 months)	Experimental
The pembrolizumab (MK-3475) dosing may be adjusted due to toxicity as described in Section 5.2.1.2. First cycle pembrolizumab will begin on day 8.					
Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Paclitaxel	80 mg/m^2	Q week for 3 weeks	IV infusion	Until progression or toxicity (or complete response if at least 6 cycles, at the discretion of the investigator and patient)	Standard
The Paclitaxel dose may be decreased due to toxicity; see subsequent section on Paclitaxel. Cycle 1 will have an extra lead in week (4 weeks total) with Paclitaxel only on week 1. The inclusion of steroids during treatment with Pembrolizumab may decrease the efficacy of the agent.					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

The dose amount required to prepare the pembrolizumab (MK-3475) infusion solution will not be based on the subject's weight. The dose amount required to prepare Paclitaxel will be based on a calculation of the patient's body surface area (BSA) in mg/m^2. There is no maximum BSA.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

PEMBROLIZUMAB

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids. Refer to EVENT OF CLINICAL INTEREST AND IMMUNE-RELATED ADVERSE EVENT GUIDANCE DOCUMENT, Version 5.0, which takes precedence.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event (grade 3 or 4) at the same grade or greater with re-challenge of pembrolizumab (MK-3475) should be discontinued from trial treatment.

Subjects who must discontinue pembrolizumab, but are without progression and tolerating paclitaxel, should continue to receive paclitaxel. Subjects who must discontinue paclitaxel, but are without progression and tolerating pembrolizumab, should continue to receive pembrolizumab. Treatment continues until progression or subsequent limiting toxicity. In the case of paclitaxel only therapy because of pembrolizumab toxicity, paclitaxel can be discontinued if a CR is achieved and at least 6 cycles have been administered.

PACLITAXEL

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

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

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

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

- NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets. Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

- All patients should be premedicated with diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Please see the specific premedication instructions in section 5.2.2. Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

- Adverse Effects: Consult the package insert for the most current and complete information.

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

DOSE REDUCTIONS:

Study Drug	**Initial dose level**	**1 level reduction**	**2 level reduction**
Pembrolizumab	200 mg Q3W	200 mg Q3W	200 mg Q3W
Paclitaxel	80 mg/m^2	60 mg/m^2	40 mg/m^2

Please note all CTCAE grading below refers to the CTCAE version 4.0.

Hematologic toxicity

- Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:
    - Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.
    - Patients will NOT receive prophylactic thrombopoietic agents. Patients may not receive a platelet transfusion in the 21 days prior to cycle 1. It is not acceptable to transfuse patients who do not have an adequate level of platelets so that they qualify for study. However, patients who are on study and develop thrombocytopenia, may be transfused for any reason felt clinically indicated, including sustained tolerability of therapy, by their treating physicians.
    - Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. Updated package inserts should be consulted.
        - http://www.fda.gov/Medwatch/safety/2007/safety07.htm
    - Patients may NOT receive amifostine or other protective reagents.
- Treatment decisions 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 at least 1500 cells/mcl and the platelet count is at least 100,000/mcl. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two-week delay will have paclitaxel discontinued, but should continue pembrolizumab alone. .
- Uncomplicated granulocyte nadirs (<1500 cells/mcl) that delay the next cycle by 7 or more days may, at the discretion of the treating investigator, receive growth factors (filgrastim) according to institutional standards. Ideally, filgrastim should be discontinued before or when the ANC is approximately 10,000 cells/mcl. Patients must be 24 hours or more from the last dose of filgrastim before receiving treatment.
- The day 8 and 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is as least 50,000/mcl. If not given, these doses are omitted and not made up. For ANC values between 500 to 999 where paclitaxel is administered, the use of filgrastim is permissible following administration if deemed

clinically appropriate.

- For *first occurrence* of **febrile neutropenia**, and/or documented grade 4 neutropenia that requires a paclitaxel dose to be skipped, hold both pembrolizumab and paclitaxel until recovered, and reduce paclitaxel by one dose level on subsequent cycles. Pembrolizumab is not reduced.
- For *recurrent* **febrile neutropenia**, and/or recurrent documented grade 4 neutropenia that requires a paclitaxel dose to be skipped (after initial paclitaxel dose reduction), a second paclitaxel dose reduction will be performed. The investigator may, per their clinical assessment, add prophylactic growth factors (filgrastim) according to institutional standard). In this circumstance, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after paclitaxel chemotherapy. Administration of filgrastim on the same day as chemotherapy is not allowed. Pembrolizumab is not reduced.
- There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days. Patients with *grade 4* **thrombocytopenia** will have a 1 level dose reduction of paclitaxel. Hold treatment up to 3 weeks until resolves to grade 0-1 or baseline. Recurrent grade 4 thrombocytopenia will lead to a second dose reduction of paclitaxel. If not resolved within 3 weeks, patient should be taken off paclitaxel treatment and may continue pembrolizumab. For recurrent grade 4 thrombocytopenia on pembrolizumab alone, discontinue all treatment and go onto study follow-up surveillance until progression.
- Patients with *grade 3* thrombocytopenia, hold up to 3 weeks until resolves to grade 0-1 or baseline. If not resolved within 3 weeks, patient should be taken off paclitaxel treatment and may continue pembrolizumab. For recurrent grade 3 thrombocytopenia on pembrolizumab alone, discontinue all treatment and go onto study follow-up surveillance until progression.
- Patients who are on study and develop thrombocytopenia may be transfused for any reason felt clinically indicated, including sustained tolerability of therapy, by their treating physicians.
- Anemia (red blood cell) will not result in dose reductions. Treatment should be by RBC transfusion only when symptomatic, clinically necessary, and with Hgb < 9.0.
- Patients requiring greater than two dose reductions for any cause will result in removal of the agent that required 2 reductions. If both agents have required >2 reductions, the patient will go off study treatment and on to follow-up.

Non-hematologic toxicity

- Grade 2 (or greater) **peripheral neuropathy** requires reduction of one dose level for paclitaxel and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be removed from study. Reoccurrence of grade 2 or greater requires a second paclitaxel dose reduction and a delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be removed from paclitaxel, but may continue pembrolizumab.
- Grade 2 (or greater) **renal toxicity** requires reduction of one dose level for paclitaxel and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be off study treatment and on to

follow-up. See also section 5.2.1.2, Table 3, on renal toxicity for pembrolizumab.

- Grade 3 (or greater) elevations in **hepatic** related tests: SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level of paclitaxel, discontinuation of pembrolizumab, and a delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be removed from study. Reoccurrence of grade 2 or greater requires a second paclitaxel dose reduction and a delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be taken off study treatment and on to follow-up. See also section 5.2.1.2, Table 3, on hepatic toxicity for pembrolizumab.
- There will be no dose modifications for **alopecia or fatigue**.
- For **nausea, emesis, or diarrhea**, please refer to section 5.6.1.
- Non-hematologic toxicities with an impact on **organ function of grade 2 (or greater)** require reduction of one dose level of paclitaxel and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1, or pre-therapy baseline. If no recovery after 3 weeks, patient should be taken off study treatment and on to follow-up.
- **Heart failure** > grade 2 will result in removal from study. All other **cardiac toxicity** > grade 3 will result in removal from study. All other cardiac toxicity, grade 2, can result in delay of subsequent therapy for a maximum of two weeks and one level dose reduction of paclitaxel. Reoccurrence of any grade cardiac toxicity requires that patient should be removed from study.
- Decrease of left ventricular ejection fraction (LVEF) to < 50 or decrease of LVEF by ≥ 10% from baseline will result in removal from the study (grade 2 or greater, CTCAE v4, Investigations, Ejection fraction decreased).
- Patients requiring greater than two dose reductions of both agents for any cause will result in removal from treatment and on to follow-up.
- For **pneumonitis and reactions that are thought to be immune-related**: please refer to sections 5.6.1.1 and 5.6.1.2.
- Patients with > grade 3 allergic reactions associated with pembrolizumab (MK-3475) will result in permanent discontinuation of pembrolizumab. Paclitaxel may continue and patient followed for efficacy and toxicity.

Infusion reactions

- Table 5 (section 5.6.1) shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).
- For paclitaxel related infusion reactions, please treat per institutional guidelines.

Dose escalations

- There will be no dose escalations or re-escalations on this study.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Patients will given:

- Paclitaxel 80 mg/m^2 IV over 1 hour days 1, 8, 15 every 21 days.
- Pembrolizumab (MK-3475) 200 mg IV over 30 minutes q 21 days (starting day 8 of cycle 1, then on day 1 of subsequent cycles).

One cycle equals 21 days. The first cycle is 28 days with Pembrolizumab given on day 8 in order to determine paclitaxel tolerance. The inclusion of steroids during treatment with Pembrolizumab may decrease the efficacy of the agent.

Pembrolizumab (MK-3475) will be administered as a 200 mg 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). 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). A Procedure Manual contains specific instructions for pembrolizumab (MK-3475) dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Paclitaxel will be administered as a 1 hour IV infusion on days 1, 8, 15 every 21 days, except cycle 1 where it will be administered on days 1, 8, 15, 21 of a 28 day cycle. Sites should make every effort to target infusion timing to be as close to 60 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -10 minutes and +20 minutes is permitted (i.e., infusion time is 60 minutes: -10 min/+20 min).

- Specific Premedication Instructions: Given the immunotherapy mechanism of this trial, there are specific restrictions on the use of steroids. A previous study of weekly paclitaxel examined eliminating steroids on subsequent infusions if no reaction occurred on the initial infusion (when steroids were given) [33]. Subsequent reactions in that setting were rare. Given that many reactions are possibly rate related, investigators should consider rate when considering management of treatment reactions.
    - For all cycles where paclitaxel is to be administered, it is recommended that a preparative regimen be employed, unless contraindicated, to reduce the risk associated with hypersensitivity reactions.
    - This regimen should include:
        i. An anti-histamine H1 blocker such as diphenhydramine 25-50 mg (or an equivalent dose of an alternate H1 blocker such as chlorophineramine, loratadine or fexofenadine) IV or orally 30-60 minutes before paclitaxel administration.

ii. An anti-histamine H2 blocker such as ranitidine 50 mg IV or 150 mg PO (or an equivalent dose of an alternate H2 blocker such as cimetidine, ranitidine, or famotidine) 30-60 minutes before paclitaxel administration.

iii. On the first administration, a steroid such as dexamethasone 10 mg IV or PO should be given 30-60 minutes before paclitaxel. If no hypersensitivity reaction (HSR) to paclitaxel occurs, then subsequent weekly administrations should be attempted without steroids.

iv. All HSRs may be managed with steroids or any other medications deemed medically necessary at the discretion of the investigator. However, given that many reactions are possibly rate related, investigators should consider rate when managing treatment reactions. Infusion times for paclitaxel may be extended up to 150 minutes after a suspected infusion reaction.

v. If a HSR occurs, subsequent cycles may be premedicated with steroids as the investigator deems reasonable (the study chair may be consulted as desired). For pembrolizumab infusion reactions, please refer to 5.6.1, Table 5. The efficacy of pembrolizumab may be decreased in patients who receive steroids.

If side effects are not severe, a patient may remain on study indefinitely until evidence of disease progression or unacceptable toxicity.

5.2.3 Trial Blinding/Masking

This is an open label non-randomized phase 2 trial; therefore, there will be no blinding. All patients will receive paclitaxel and pembrolizumab (MK-3475).

5.3 Registration

Prior to enrollment, there should be documentation that verifies the following:

- _All eligibility criteria have been met.
- _There is a signed appropriate informed consent form and HIPAA authorization form.

Patients registered at Moffitt will be registered by the Moffitt Study Coordinator. Patients placed on trial at affiliate sites will be registered through the Moffitt Clinical Research Network (MCRN). The MCRN Study Coordinator will perform the registration confirmation that will be sent back to the affiliate site.

5.4 Stratification

There is no powered stratification for enrollment. Post hoc trial analyses will be done based upon prior number of treatments, treatment type, platinum free intervals, (0-3, 3-6 months),

whether steroids were given with a majority of cycles where Pembolizumab was given, and exploratory biomarkers (*e.g.* PD-L1 positivity).

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before 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 7.2.

5.5.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab (MK-3475)
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.

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, chicken pox, yellow fever, rabies, BCG, and typhoid

(oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

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

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

- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

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

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

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

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

- **Hypophysitis**:

  - Grade 2-4 events:
    - Report as ECI if appropriate
    - Hold pembrolizumab
    - Rule out infection and sepsis with appropriate cultures and imaging.
    - Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
    - Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).

- Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Consultation with an endocrinologist may be considered.

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

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

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.

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

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
  - Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475)

Table 5. Infusion Reaction Treatment Guidelines (from EVENT OF CLINICAL INTEREST AND IMMUNE-RELATED ADVERSE EVENT GUIDANCE DOCUMENT, Version 5.0)

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- **Nausea/vomiting**: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- **Anti-infectives**: 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.

- **GCSF** – Filgrastim and Pegfilgrastim. Pegfilgrastim is not allowed. The use of filgrastim has limitations (see section 5.2.2) and should be used only when deemed to be absolutely necessary by the treating investigator. See hematologic toxicity section 5.2.1.2.

- **IMMUNE-RELATED ADVERSE EVENTS**: Please see Section 5.6.1.1 below and the separate guidance document (pembrolizumab (MK-3475): EVENT OF CLINICAL INTEREST AND IMMUNE-RELATED ADVERSE EVENT GUIDANCE DOCUMENT, Version 5.0) regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

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

Please reference version 3 of the irAE guidance document "Pembrolizumab Event of Clinical Interest Guidance Document" that will accompany this protocol.

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Immune-related adverse events (irAEs) may be predicted based on the nature of the pembrolizumab (MK-3475) compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document. . Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

The guidelines for handling Pneumonitis are in section 5.6.1.2 below. Others such as Colitis, Endocrine, Hematologic, Hepatic, Neurologic, Ocular, Renal, Skin are listed in the ECI.

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Recommendations to managing irAEs not detailed elsewhere in the protocol or ECI are detailed in Table 6.

Table 6. General Approach to Handling irAEs

irAE	Withhold/Discontinue	Supportive Care

	pembrolizumab (MK-3475)?	
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab (MK-3475)	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold pembrolizumab (MK-3475) Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Also, please refer to pembrolizumab (MK-3475): EVENT OF CLINICAL INTEREST AND IMMUNE-RELATED ADVERSE EVENT GUIDANCE DOCUMENT, Version 5.0.

5.6.1.2 Events of Clinical Interest

Please see the EVENT OF CLINICAL INTEREST AND IMMUNE-RELATED ADVERSE EVENT GUIDANCE DOCUMENT, Version 5.0. For Dermatologic Toxicities, please also refer to and complete Appendicies 2-4 in the ECI, version 5.0

Table 7: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		

Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		

Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (MK-3475) has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab (MK-3475), the subject will immediately be removed from the study. The site will contact the

subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab (MK-3475) is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.

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

- The subject withdraws consent.
- Radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with radiographic progression if clinically stable or clinically improved after consultation with the study PI and consultation with Merck.

- Unacceptable adverse events.
- Intercurrent illness that likely prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab (MK-3475)

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab (MK-3475) after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they have a PS >2, have not had initiation of a new regimen nor had discontinuation due to toxicity. This must be approved by the study PI in consultation with Merck.

- Administrative reasons

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

5.9 Subject Replacement Strategy

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

5.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow

Study Parameter	**Screen**	**Weekly (+/- 1 days)[11]**	**Every Cycle[13] (+/- 2 days)[12]**	**Cycle 2**	**Following Every Third Cycle**	**Cycle 4 Or PD**	**End of Treatment**	**Follow-up Visits[7]**
Paclitaxel 80 mg/m^2 IV		X[14]						
Pembrolizumab (MK-3475) 200 mg IV			X[14]					
Informed consent	X							
History	X		X				X[19]	X
Physical examination	X		X				X	X
Vital signs including Blood pressure	X	X[6]	X				X	X
Height and body weight	X		X[1]				X[1]	
ECOG performance status	X		X				X	X[9]
Survival status								X[10]
Tumor assessment (clinical) [2]	X		X				X	X[4]
Tumor assessment (radiological)	X				X [3,4]		X[3,4]	X[3,4]

CA-125[5]	X[5]		X[5]				X[5]	X[4,5]
Adverse event assessment			X				X	X[9]
CBC with differential	X	X[6]	X					
Serum bilirubin, AST, ALT, alkaline phosphatase, creatinine, creatinine kinase, c-reactive protein	X		X					
Pregnancy test[8]	X		X					
Glucose and Electrolytes (Na, K, BUN, Cl, CO^3)	X		X					
ECG-12 lead	X							
PT/INR and aPTT	X		X					
Urinalysis	X		X					
T3, FT4 and TSH	X		X					
Archival or Newly Obtained Tissue[15]	X							
Correlative Studies Blood Collection	X[16]			X[17]		X[17]		
Biopsy (optional)[18]	X					X		
Post-study anticancer therapy status								X

1 Body weight only after initial height measurement.
2 By physical examination.
3 All assessments obtained should be made using the same type of study (e.g. spiral CT Scan) as was used at baseline. Scans should be done during the 7 days prior to, or on the day of, the next due cycle. For example first scan is during the week before or on day of cycle 4, day 1. Scan must be interpreted for disease response prior to administering cycle. Scan dates should be recorded. If a treatment has to be delayed and patient has already had a scan, it is not necessary to repeat the scan prior to next dosing due to the delay (it will not be out of window).
4 Post-treatment follow-up measurements will be necessary at (approximately 9 week (+/- 5 days) intervals only for patients with CR, PR, or SD who have discontinued treatment and will be performed only until the time they have recurrence, progression, death, or 2.5 years total follow-up.
5 Need 2 levels $\geq$ 70 at least one week apart for evaluable disease progression determination.
6 Not required in weeks with no scheduled treatment.
7 Follow-up visits of every 9 weeks (+/- 5 days) only until progression, initiation of new treatment, or 2.5 years after cycle 1, day 1. Survival data (with or without visits) will continue to be collected every 12 weeks (+/- 4 days) until 2.5 years after cycle 1, day 1.
8 Females of childbearing potential only. Not to include those surgically sterilized or confirmed menopausal.
9 AE and ECOG performance status assessments will continue for the 9 weeks (+/- 5 days) following end of treatment.
10 Survival data will be collected until patient's death or 2.5 years total follow-up
11 Range for +/- 1 day refers to all cycle weeks past cycle week #1.
12 Each cycle may have range of 21 days (28 for cycle 1) +/- 2 days to account for scheduling variability. Labs may be obtained up to 2 days before scheduled day 1 administration of each cycle.
13 Cycle length is 21 days (except cycle 1 of 28 days). The first dose of pembrolizumab is on cycle 1 day 8, then day 1 of subsequent cycles.
14 Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart above (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.All trial treatments will be administered on an outpatient basis. Patients will be given:

- Paclitaxel 80 mg/m^2 IV over 1 hour days 1, 8, 15 every 21 days. First cycle has days 1, 8, 15, 21 of a 28 day cycle.
- Pembrolizumab (MK-3475) 200 mg IV over 30 minutes q 21 days (starting day 8 of cycle 1, then on day 1 of subsequent cycles).

One cycle equals 21 days. The first cycle is 28 days with Pembrolizumab given on day 8 in order to determine paclitaxel tolerance. The inclusion of steroids during treatment with Pembrolizumab may decrease the efficacy of the agent.

15. Verify availability of adequate tissue block or slides, OR willingness to do biopsy prior to drug administration C1Day1
16. Genetic Pax Tube see 7.1.2.6
17. PBMC CPT Tube to be done at screen, Cycle 2 day 1, Cycle 4 day 1 prior to drug administration. May be done as part of screening labs or the pre-chemotherapy treatment labs for that cycle, but no greater than 2 days before day 1 of that cycle. See 7.1.2.6
18. Optional biopsy to be done at screen and cycle 4 day 1 (+/- 5 days – may be done with tumor assessment) OR upon progression see 7.1.2.6
19. End of treatment study visit at 30 days (+/- 5 days). If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur, if possible, before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.0 TRIAL PROCEDURES

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

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

7.1 Administrative Procedures

7.1.1 Informed Consent

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

7.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The study site investigator or qualified designee will provide the subject with an IRB approved Subject Identification Card after the subject provides written informed consent.

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Disease Details and Prior Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.7 Registration Procedures for Affiliate Sites

All subjects at affiliate sites must be registered with the MCRN Coordinating Center to be able to participate in the trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signature page of the informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the MCRN Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the MCRN Research Coordinator will provide the participating site with the study sequence number. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the Oncore database
- Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with supporting documentation to the MCRN via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM (EST).

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

All patients who receive at least 1 dose of study treatment with paclitaxel will be evaluated for safety parameters. AEs will be collected from the start of treatment until off trial.

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab (MK-3475) exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Directed Physical Exams

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening. The investigator or qualified designee will also perform a directed physical exam as clinically indicated prior to each treatment cycle administration.

7.1.2.3 Vital Signs

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

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8, assessment of ECOG status will be performed every other cycle in conjunction with the physical exam.

7.1.2.5 Tumor Imaging and Assessment of Disease

7.1.2.5.1 General requirements regarding imaging and CA-125

All patients with measurable disease will be assessed by RECIST v1.1, and irRC criteria. All patients with elevated CA125 elevated at least 2xULN at baseline and EITHER malignant pleural effusion or ascites OR radiographic evidence of disease that is non-measureable, will be assessed by a combination of radiographic findings (RECIST v1.1) and Rustin criteria.

In ovarian cancer, RECIST v1.1 and CA125 have been used to measure response and document progression. Progression will only be confirmed to occur in the event of RECIST findings of progression. CA-125 will not be used by itself for progression. Notation should be made on tumor assessment (TA) times, however, if the CA-125 has doubled from a nadir value during the course of treatment.

The TA performed during screening will be used as a baseline for efficacy assessments. Contrasted CT (or MRI) imaging of the chest and abdomen and pelvis is required at screening and at each TA, regardless of the location of known metastases. In addition, scans must be obtained of anatomic regions not covered by the chest and abdomen scans in subjects where there is clinical suspicion of metastases. Such additional CT/MRIs will be required at screening when a non-abdominopelvic or chest lesion is known/suspected and must be consistently repeated at all TAs if identified during Screening. The same imaging modality must be used for all TAs, unless contraindicated.

Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest, abdomen, and pelvis are preferred. If not available, conventional (nonhelical, nonspiral CT) may be used; however, a measurable lesion must not have the longest diameter smaller than 20 mm by conventional CT or MRI (10 mm on spiral CT). Oral and IV contrast should be used for all CT scans; if IV contrast is contraindicated, oral contrast alone may be used, or MRI should be used. Subjects who develop oral and IV contrast allergy after study enrollment, or whose tumor is not measurable with the elimination of one form of contrast, must be followed by MRI for subsequent tumor measurements.

A reference measurement ruler must be printed on every image for scale determination. Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (e.g., from 3 to 8 mm, 10 mm cuts are not sufficient). Chest x-rays and ultrasound are not acceptable methods to measure disease.

New fluid findings such as pleural effusion or ascites will not constitute progression by themselves. Skin and soft tissue lesions will be captured as non-measurable lesions through physical examination only.

Any subject who develops an objective tumor response (CR or PR) or progression (PD) is required to undergo confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding. Sites are encouraged to collect additional CT scans after RECIST v1.1 PD has been confirmed, as long as a subsequent line of therapy has not been initiated.

7.1.2.5.2 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (for irRECIST see appendix 12.5)

Response and disease progression will be evaluated using the modified international criteria proposed by the RECIST v1.1 committee. Changes only in the largest diameter (unidirectional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. For tumor lymph nodes, the short axis must be measured. Lesions are measurable or non-measurable using the definitions described below.

Definition of Measurable / Non-Measurable Disease

- Measurable disease is present if the subject has one or more measurable lesions. (Note: If the measurable disease is confined to a solitary lesion, its neoplastic nature should be confirmed by histology or cytology). An exception would be the new appearance of a measurable target lesion and a CA-125 indicative of progression (doubling of the nadir value and with a confirmation of same as per CA-125 criteria (see section 7.1.2.5.1). Disease in a previously irradiated field is acceptable as the only site of measurable disease only if there has been clear progression since completion of radiotherapy.
- Measurable lesions are those that can be accurately measured in at least one dimension, in accordance with the following criteria: if conventional technique CT, MRI, x-ray (for non-spiral or non-helical) the longest diameter of at least one lesion to be recorded must have a diameter ≥ 20 mm. If Spiral (Helical) CT is used at least 1 diameter should be ≥ 10 mm, assuming the images were performed using a 5-mm contiguous reconstruction algorithm (interval). If a 5-mm contiguous reconstruction algorithm (interval) is not used, as a general rule, the lesion diameter should be no less than double the reconstruction algorithm (interval). In all instances, Spiral CT is preferred if available. All tumor measurements must be recorded in millimeters.
- Non-measurable lesions/disease are all other lesions (or sites of disease), including small lesions (those with all measurements < 20 mm when the subject is evaluated with conventional (non-spiral/non-helical CT; MRI or x-ray; or < 10 mm with Spiral CT as described above), and any of the following:
    - Primary breast lesions assessed by physical exam only, bone lesions, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, and lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy.
    -

7.1.2.5.3 Method of Tumor Response Assessment

Baseline measurements should be done within 4 weeks before the beginning of the treatment. For target lesions, largest and/or most reproducible lesions (large or small) must be selected. Tumor lesions situated in previously irradiated areas will not be considered measurable unless disease in a previously irradiated field is the only site of measurable disease and there has been clear progression since completion of

radiotherapy. The same method of assessment should be used to identify and report each lesion at baseline and at re-assessment during treatment. Imaging based evaluation is preferred to clinical examination.

CT and MRI are considered to be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

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

Ultrasound and/or physical exam will not be allowed as the only procedure to evaluate tumor lesions, except for superficial lymph nodes and subcutaneous lesions.

In addition, ultrasound and physical examination together may be used to confirm complete disappearance of superficial lesions (Target or non-target).

7.1.2.5.4 Definition of Target versus Non-Target Lesions

When more than one measurable lesions is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). In addition, target lesions should be selected based on their size (lesions with the largest area and/or longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements.

At baseline, the longest diameters for all non-nodal target lesions and the short axis for all nodal target lesions will be added and considered the baseline sum of diameters. The baseline sum will be used as the reference point to determine the objective tumor response of the target lesions. Lymph nodes with tumor burden will be considered as target lesions if the short axis is ≥ 15 mm. (The short axis is measurement perpendicular to longest measurement of the node assed in plane of measurement). Measurable lesions other than the target lesions, and all sites of non-measurable disease, will be identified as non-target lesions. Lymph nodes will be considered as non-target lesions if the short axis is ≥ 10 mm and < 15 mm and considered as normal if the short axis is < 10 mm. Repeat measurements of non-target lesions is not required but presence or absence of these lesions should be noted throughout the tumor re-assessments. Non-target lesions will be recorded on the CRFs and should be evaluated

at the same assessment time points as all target lesions. All lesions must be followed for response and progression. In subsequent assessments, non-target lesions will be recorded as either:" present," "absent" or "unequivocal progression.

7.1.2.5.5 Definition of Response

Overall tumor response will be based on an integration of the evaluation of target, non-target and new lesions, as described below:

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all clinical and radiological evidence of target lesions. When lymph nodes are included as target and non-target lesions complete response per lymph node will be achieved with short axis of all nodes measuring < 10 mm and the disappearance of all clinical and/or radiological evidence of lymph nodes is not required.
- Partial Response (PR): At least 30% reduction in the sum of longest diameter of all lesions; taking as reference the baseline study measurement.
- Progressive Disease (PD): Requires that there is a 20% or greater increase in the sum of longest diameter of all target lesions AND an absolute increase of at least 5 mm of tumor size, taking as reference the smallest sum of the longest diameter recorded at or following baseline or the appearance of one or more new lesions.
- Stable Disease (SD): Neither PR or PD are met, taking as reference the smallest sum of the longest diameter recorded at baseline.

Evaluation of Non-Target Lesions

All other lesions (or sites of disease) not included in the "target lesions" definition should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent" or "unequivocal progression". Tumor within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
- Non-Complete Response, Non-Progressive Disease (Non-CR, Non-PD): Persistence of one or more non-target lesions and/or maintenance of tumor markers level above the upper limits of normal.
- Progressive Disease (PR): Unequivocal progression of existing non-target lesion(s) (note: the appearance of one or more new lesions is also considered as progression.)

Evaluation of new lesions

- No: There are no new lesions.
- Yes: New lesions are present. If new lesions are present, the subject is

considered to have progressive disease overall.

Notes:

- Unequivocal progression of non-target lesions implies that the subject has progressive disease overall at that time point and must stop study treatment. Increase in radiotracer uptake on bone scan alone is insufficient evidence of progression; additional evidence of progressive disease should be present to declare unequivocal progression. An increase in ascites or effusion alone is insufficient evidence of progression; an additional evidence of progression should be present to declare unequivocal progression. If a scan shows new lesion(s) in an anatomical region which was not included in the baseline scans it is still PD.
- FDG-PET may be used if deemed necessary from an unusual but necessary clinical perspective. The study chair should be consulted when possible. It should not replace standard imaging by RECIST, but may at times complement. Investigators should work with the study chair when interpreting these in the context of response or progression.

7.1.2.5.6 Evaluation of Best Overall Response

Best overall response is the best response recorded from the start of treatment until disease progression or recurrence (taking as reference the smallest measurement recorded since the start of treatment) and will be determined as tabulated below, based on evaluation of target, non-target and new lesions.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

- 5 paraffin 5-micron unstained slides (“TUS”), or equivalent block (tissue block “TB”) to make these, available from initial diagnosis or subsequent recurrence. Notation of relationship to prior treatment should be made (List treatment regimens used prior to acquisition of the tissue in the slides or block, the most recent treatment regimen and number of cycles, last treatment date prior to tissue acquisition, date of tissue acquisition). Directions and kits for processing will be done via Qualtek. An appendix Sample Handling Manual is provided. Confirmation of availability of getting tissue slides or block should be made at screening. Patient may, alternatively, agree to a core biopsy prior to treatment if reviewed and deemed feasible by an interventional radiologist.

- Optional biopsy at Screen. Also optional on or between Cycle 4 day 1 (+/- 5 days), OR upon progression if earlier than Cycle 4 day 1.

- 10 ml tube of whole blood (genomic blood tube “GBT”) at screen (for possible genomic analysis)

- PBMCs (peripheral blood tube "PBT") before treatment on Cycle 1 day 1 (i.e. "screen"), Cycle 2 day 1, Cycle 4 day 1. May be done as part of screening labs or the pre-chemotherapy treatment labs for that cycle, but no greater than 2 days before day 1 of that cycle.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 9. The correlative blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Laboratory Manual and section7.1.2.6.

Table 9. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
	(CO_2 or bicarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		CA-125
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	c-reactive protein		
	Creatinine kinase		

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

‡ If considered standard of care in your region.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab (MK-3475) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.3.3 Blinding/Unblinding

This is an open label study without placebo. No blinding will be performed.

7.1.4 Visit Requirements

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

7.1.4.1 Screening

- Screening will only be done after an initial pre-eligibility determination is made using those requirements that are part of the medical history (disease and treatment history, recent labs or scans, etc.), do not require specific testing, where it appears the patient may be eligible for study, and after an informed consent is made.
- Screening labs and radiology are done in accordance with the sections listed respectively above.
- As part of screening, the requirements for biological samples must be confirmed..

7.1.4.2 Treatment Period

- Patients will remain on treatment until
    - any of the criteria in section 5.8.
    - a patient reaches a CR after 6 cycles and investigator and patient wish to discontinue paclitaxel. Pembrolizumab should continue.

- 24 months of pembrolizumab
- follow-up will be to progression at minimum. Survival may be followed up to 2.5 years per the discretion of the sponsor.

7.1.4.3 Post-Treatment Visits

- Please see study calendar.

7.1.4.3.1 Safety Follow-Up Visit

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

7.1.4.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (± 4 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.4.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (± 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events will be recorded from the start of treatment through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab (MK-3475) by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab (MK-3475). In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

7.2.3.1 Serious Adverse Events

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

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

Progression of the cancer under study is not considered an adverse event (AE) unless it results in hospitalization or death. If the latter are due to progression, it is not a drug-related AE.

Any serious *and* unanticipated toxicities believed at least possibly related to combination treatment should prompt the Primary Investigator to suspend enrollment to the trial and submit an *ad hoc* report and plan to the PMC before continuing enrollment.

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 investigational product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

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

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

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to the sponsor expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in Oncore, the electronic data capture system. The SAE must be reported by email (affiliate.research@moffitt.org) to the MCRN within 2 working days. If applicable, the site should also follow protocol guidelines for additional reporting to government agencies.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) (Please see and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Events of clinical interest for this trial include:

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

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

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

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

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 10. Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Primary Endpoint

Progression free survival at 6 months (6-month PFS) by RECIST 1.1.

Progression-free Survival (PFS) is defined as the time from the date of the first dose to the time of disease progression or death, whichever occurs first. 6-month PFS is defined as the proportion of patients without disease progression or death at 6 months. For comparison purposes, PFS will be assessed separately according to immune-related RECIST criteria (irRC), RECIST v1.1, and CA125 Rustin criteria. If a subject has not experienced disease progression or death at the time of a data lock, the subject will be censored at the last tumor assessment date (for RECIST v1.1 and irRC) or the last CA125 assessment date (for CA125 Rustin criteria). Progression-free Survival will be analyzed on response assessable treated subjects at the time of the analysis of survival endpoints. A separate analysis will be conducted using irRC, but the primary endpoint is based on RECIST 1.1 as in other studies of Pembrolizumab for solid cancers.

Sample Size

There will be 50 enrolled patients, 37 evaluable patients.

Enrollment Period

This trial will have 37 evaluable patients enrolled over a 1.5-year period or less, averaging 2-3 patients per month.

Replacement of Patients

Patients will be considered unevaluable for the primary endpoint of 6-month PFS by RECIST V1.1 if they are not able to complete the first tumor assessment scan at cycle 4. Unevaluable patients will be replaced therefore it is estimated that 50 patients will need to be enrolled to result in 37 evaluable patients.

Sample Size Justification

Under the assumption that the 6-month PFS in the historical control arm (e.g. AURELIA) is 0.25, it is expected that treatment arm will result in a 50% reduction in the risk of progression at 6 months (6-mo PFS =0.5). The enrollment period is approximately 1.5 years and the follow-up time is 1.5 years after the last enrolled patient. We assume a 5-10% drop-out or non-evaluable rate; so estimate total enrollment of 40. With 37 evaluable patients, we will have 90% power at a one-sided 0.05 level of significance to reject the null hypothesis.

The null hypothesis that the true 6-month PFS rate is 0.25 will be tested against a one-sided alternative. The null hypothesis will be rejected if 14 or more with a 6-month PFS are observed in 37 evaluable patients. This design yields a type I error rate of 0.05 and a type II error rate of 0.1 when the true alternative 6-mo PFS rate is 0.5.

Safety will be a descriptive analysis. Other secondary endpoints will be described as point estimates with confidence intervals.

Interim Analysis

Given the short duration of enrollment, the 6-month PFS endpoint, and the relatively small number of patients, there will be no pause in enrollment for an interim analysis.

Table 11. Supporting Weekly Paclitaxel Randomized Studies in Ovarian Cancer

Study **Phase**	**Platinum Res/Sens**	**Prior Tx**	**n**	**RR %**	**PFS (mo.)**	**OS (mo)**	**Dose Schedule**
Karlan et al. RP2	Ref Res Semi-Res Sens Unavail	1-3	4 20 20 10 1	27 (16-41)	4.6 (1.9-6.7)	20.9 (11.3-24.2)	80 mg/m^2 days 1, 8, 15 of 28d
Monk et al. RP3	Ref Res Semi-Res	1-3	1 245 212	29.8 (25.5-34.3)	5.4 (4.3-5.5)	17.3 (15.4-19.1)	80 mg/m^2 days 1, 8, 15 of 28d
MITO-11 RP2	Ref 24 Res 76	1-2	37	21	3.5 (2.0-5.7)	14.8 (9.1-NA)	80 mg/m^2 days 1, 8, 15 of 28d
AURELIA	Res	1-2	361	11.8	3.4 (2.2-3.7)	13.3 (11.9-16.4)	80 mg/m^2 days 1, 8, 15,

RP3							22 of 28d
*AURELIA +BEV	Res	1-2 (2 in ~40%)	361	27.3	6.7 (5.7-7.9) Chemo+BEV	16.6 (13.7-19.0)	Either Paclitaxel, Topotecan, or Doxil
Rosenberg, et al RP3	Res 57 Sens 48	1	105	19	6.1 (5.0-8.0)	13.6 (10.5-18.7)	67 mg/ m^2 days 1, 8, 15 of 21d

RP2 = randomized phase 2, RP3 = randomized phase 3
Ref = refractory (<0), Res = resistant (0-6 months), Semi-sens (6-12 months), Sens (12+months)
*AURELIA reports chemotherapy arm +/- BEV (bevacizumab) without separating the agents.
1. Karlan, B, et al. J Clin Oncol. 2012 Feb 1;30(4):362-71.
2. Pignata, S. MITO-11 Study, J Clin Oncol 32:5s, 2014 (suppl; abstr 5503^)
3. AURELIA JCO May 1, 2014 vol. 32 no. 13, 1302-1308
4. Rosenberg P 2002, Vol. 41, No. 5 , Pages 418-424

Other Analyses

- Response rate
    - Response rate (RR) using the Best Overall Response (BOR) will be determined and reported. RR= CR + PR.
    - Response rate (RR) is defined as the proportion of all response assessable treated subjects whose best response at any time during the study to date following initiation of therapy is a CR or PR. This will be assessed according to irRC, as well as separately by RECIST v1.1 criteria, and by CA125 Rustin criteria. RR will be analyzed at the same time as the analysis of the primary endpoint, as well as at subsequent analysis of the survival endpoints.
- Disease Control Rate (clinical benefit)
    - DCR = CR + PR + (SD x 2mo)
- Duration of response
    - Duration of response is defined as the time that a response was first identified (CR or PR) until the time with a progression was first determined.
- Overall Survival
    - Median OS will be determined.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies, as appropriate, will be provided by Merck.

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

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

10.2 Compliance with Financial Disclosure Requirements

- All PIs and study team members will follow federal and institutional regulatory standards, including compliance with required financial disclosure reporting.

10.3 Compliance with Law, Audit and Debarment

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

- A teleconference will be held between investigational sites no less than every 2 months. Included will be any study clarifications, emerging toxicity or risk information, overall progress, any interval analyses, and other pertinent information. All investigators and/or an investigator designee will be responsible for attending. A copy of the minutes will be distributed to each site PI. These should be signed and filed.

10.6 Data Management and Monitoring/Auditing

- Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/ amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.
- The PMC meets once a month. The PMC reviews and evaluates safety and/or efficacy data for all physician authored clinical intervention trials. The PMC ensures the safety of patients and the validity and integrity of data. PMC reviews SAEs, deviations, Interim analysis, interim and final reports from any external Data Monitoring Committee (DMC) as well as audits both internally and externally. The PMC can make the following determinations, Accepted, Acceptable with Corrective Action and Tabled. Investigators of studies such as this one, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide an interim analysis report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable.
- To obtain access to Oncore, the site research staff must complete an Oncore Access Request Form and a Moffitt Information Systems Confidentiality Agreement (provided in the MCRN Handbook at the site initiation visit) and submit both to the Coordinating Center. Once the completed forms are received, the site coordinator will receive Duo Security remote access, logon/password, and information on how to access Oncore using the Duo Security remote access. The MCRN Coordinating Center will provide Oncore training to the site once initial access is granted and on an ongoing basis, as needed.
- All data analyses will be performed in the department of biostatistics, H. Lee Moffitt Cancer Center. All raw data can be made available to Merck or other appropriate IRB approved study personnel for confirmatory analyses.

10.7 Publications and presentations

- This study may be presented at scientific meetings by any of the study investigators with the approval of the Sponsor and also allowing time for prior review by Merck. Intent to submit should be made no later than 4 weeks before a submission is due, and a copy of any abstract or presentation should be submitted no later than 3 weeks prior to finalization or submission to allow time for review.

- The complete trial will be presented in a peer-reviewed medical journal suitable for an interested audience and deemed of highest impact. Robert M. Wenham is the lead and corresponding author. Last and second authorship will go to the person

designated by the principal investigator at the highest and second highest enrolling external site. Other positions of authorship will be determined by other contributions to trial development, enrollment, analysis, or manuscript preparation as is appropriate to the submitted journal.

- Publications that may emerge and are not directly related to the primary outcomes may be done by investigators after discussion and approval of the study PI. To demonstrate good faith in allowing unbiased reporting, the study PI should have substantial and specific issues regarding the science of a proposal in order to object.

10.8 Affiliate Sites Required Documentation

Before the study can be initiated at any affiliate site, the site will be required to to have the approval of Merck and must provide regulatory documentation to the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center.

Sites must provide a copy of their informed consent to the MCRN coordinating center for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be provided to the MCRN staff for review and approval prior to resubmission to the IRB.

The MCRN Coordinating Center must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Authority Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)
7. Updated Investigator/Personnel documents (CVs, licenses, Conflict of Interest statements, etc.) as needed
8. Updated Laboratory Documents (certifications, normal ranges, etc.) as needed
9. Signed protocol specific Task Order

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff

- Moffitt PI and MCRN research coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The MCRN utilizes the EDC system, Oncore. Training will be scheduled, if indicated, with the appropriate staff from the site.

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12.0 APPENDICES

12.1 ECOG Performance Status

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

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

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

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

12.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan,

D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

12.4

ECI attached

12.5 irRECIST 1.1

As described by Bohnsack, O, et al. ESMO 2014 Abstract 4958 in a modification of Nishino M et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.

1. 0 Baseline: Measurable Lesion
Definitions and Target Lesion
Selection
Follow the definitions from RECIST 1.1.
Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
• 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for nonnodal lesions and ≥15 mm in short axis for nodal lesions
• 10 mm caliper measurement by clinical exam
• 20 mm by chest X-ray

1.1. Baseline: Non-measurable
Lesion Definitions
Follow the definitions from RECIST 1.1
Non-target lesions will include:
• Measurable lesions not selected as target lesions
• All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest per-pendicular diameter is ≥10 and < 15 mm.
• Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner.
These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

1.2 Baseline: Target and Non-Target
Lymph Node Lesion Definitions
Follow the definitions from RECIST 1.1

1.3 Baseline: Non-Target
Lesion Selection
All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

1.4 Baseline: Bone Lesions
Follow the definitions from RECIST 1.1.
Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.

1.5 Baseline: Brain Lesions detected on brain scans can be considered as both target or non-target lesions.

1.6 Baseline: Cystic and Necrotic Lesions as Target Lesions
Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of
all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

1.7 Baseline: Lesions With Prior Local Treatment
During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion

1.8 Baseline: No Disease at Baseline
If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB.

2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements

The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.

2.1 Follow-up: Definition of Measurable New Lesions
In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

2.2 Follow-up: Non-Target Lesion Assessment
The RECIST 1.1 definitions for the assessment of non-target lesions apply.
The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment
All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new nonmeasurable lesions prevent irCR.

2.4 irRC Overall Tumor Assessments
irCR, complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
irPR, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. irSD, failure to meet criteria for irCR or irPR in the absence of irPD. irNN, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
irPD, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions.
Confirmation of progression is recommended minimum 4 weeks after

the first irPD assessment.
irNE, used in exceptional cases where insufficient data exists.
irND, in adjuvant setting when no disease is detected.