Single-arm phase II combination study of low-dose paclitaxel with pembrolizumab in platinum-refractory urothelial carcinoma
Comprehensive Cancer Center of Wake Forest University (CCCWFU)
CCCWFU # 88215

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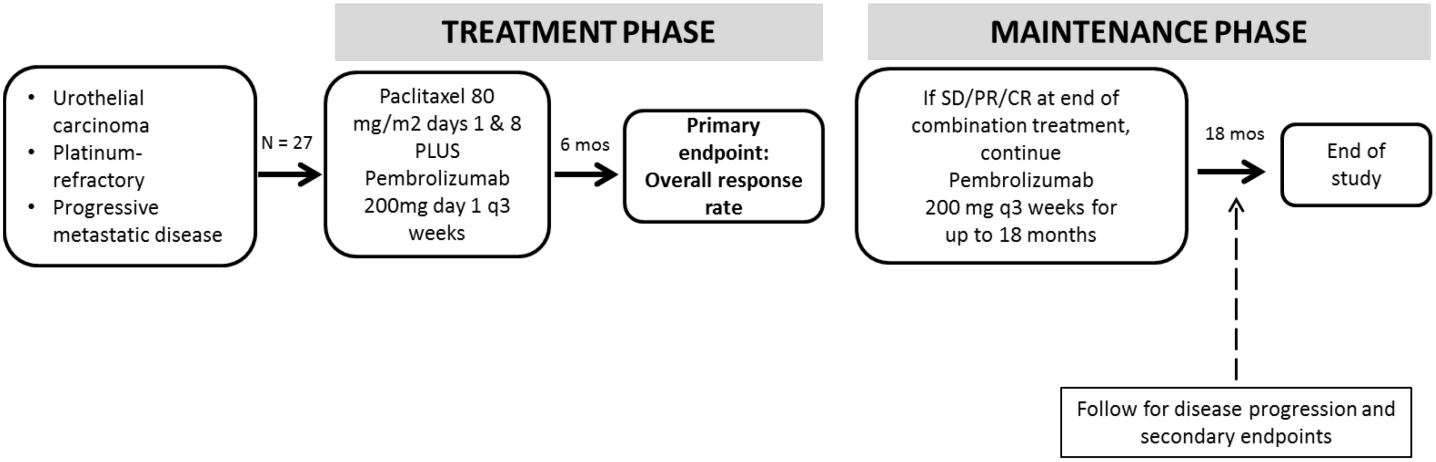
SCHEMA

This will be a single-arm, open label, phase 2 study with the following schema:



1.0 Introduction and Background

In the United States, approximately 74,000 new cases of urothelial cancer (UC) and 16,000 deaths from UC are expected in 2015. Patients with distant metastases at the time of diagnosis have only a 6% likelihood of being alive in 5 years; therefore, improvement in the treatment of advanced UC is urgently needed.[1] The standard-of-care for first-line systemic treatment for patients with metastatic UC is platinum-based combination chemotherapy.[2] Response rates are about 50%, with durable responses seen in a small fraction of patients. However, many patients are not eligible for cisplatin-based regimens due to renal insufficiency or suboptimal clinical status. For patients who are eligible and are treated, nearly all are destined to progress. Second-line therapy using a variety of cytotoxic agents can be given, but response rates are low and there is no accepted standard.

Therapies that target the programmed death-1 (PD-1) and the PD-1 ligand (PD-L1) interaction are promising treatments for a variety of solid tumors. The PD-1 receptor is normally expressed on activated T-cells, and when it encounters its ligand, PD-L1, the T-cell is inactivated. Both tumor cells and tumor-associated lymphocytes may express PD-L1 and therefore evade host immune surveillance. Disruption of the PD-1/PD-L1 interaction maintains and enhances effector T cell responses, thereby leading to tumor regression.[3,4] This is now possible due to the development of agents that interact with one of the two molecules. Among these is pembrolizumab, a monoclonal antibody that binds the PD-1 receptor.

Pembrolizumab treatment can induce tumor regression, including in patients with metastatic urothelial cancer. In KEYNOTE-012, a phase 1b study of pembrolizumab in patients with PD-L1-positive solid tumors, almost 10% of patients with advanced UC had a complete response to therapy and nearly a quarter of patients had no evidence of disease progression at 6 months. The overall response rate in the study for patients with UC was seven of 29 (24%); therefore, while pembrolizumab shows promise as a monotherapy, there is need for improvement.[5]

In general, immunotherapeutic approaches for advanced UC have had limited success due to profound inflammation-associated immune suppression. Myeloid derived suppressor cells (MDSC) with potent T-cell suppressive activities are increased in UC.[6,7] UC is also dominated by T-regulatory (Treg) cells and immune inhibitory cytokines.[8] Antitumor T-cell responses in UC are inhibited by MDSC and Treg cells, which increase with cytotoxic chemotherapy.[9] PD-1 blockade only partially overcomes this MDSC and Treg cell suppression in tumor models,[10] and the effect of treatment with immune checkpoint inhibitors is maximized when MDSCs are fully eradicated.[11] Preclinical studies in UC models similarly highlight the need to abrogate immune suppression to maximize the antitumor efficacy of PD-1 blockade.[12] Therefore, the efficacy of pembrolizumab may be enhanced when given in combination with agents that augment antitumor immune responses.

Single-agent taxanes are commonly used to treat patients with platinum-refractory UC, however response rates are modest at 5-15%, with no known survival benefit.[13-15] Although the antitumor effects of taxanes are generally attributed to effects on microtubules and cell division, there is increasing evidence that taxanes are also immunomodulatory. Several studies have shown that treatment with low-dose taxanes reduces MDSC and Treg cells and modifies the tumor microenvironment to promote immunogenic tumor death.[16,17] Paclitaxel can inhibit MDSC and restore CD8 T-cell effector function, and low-dose cytotoxic therapy enhances the antitumor activity of anti-PD-1 antibody in mouse model systems.[18-20] Overall, the role of chemotherapy to target immunosuppressive cells and improve treatment of advanced cancer is increasingly recognized.[21] **The use of taxanes at non-cytotoxic doses to block the immunosuppressive potential of MDSC and Treg cells is a new therapeutic strategy for enhancing the efficacy of anti-PD-1 immunotherapy with pembrolizumab**.

1.1 Rationale for current study

The effects of pembrolizumab with chemotherapy on immune regulatory mechanisms in cancer patients, in general, and in patients with the highly inflammatory UC, specifically, are not known. Furthermore, biomarkers predictive of pembrolizumab response are needed. Assessment of tumor expression of PD-1 ligands, which can be technically challenging, has not been consistently informative.[22,23] Of note, PD-L1 is widely expressed by UC tumor cells but is not prognostic; PD-L1 expression in UC tumor infiltrating mononuclear cells, in contrast, is associated with longer survival.[24] Antigen-specific T cells, T cell effector and suppressor cells, and MDSC populations have also been assessed to predict PD-1 blockade response, but results have been inconclusive.[25,26] microRNAs (miRs), small non-coding RNAs that regulate multiple processes at the

post-transcriptional level, are emerging as important biomarkers. miRs are easily measureable by polymerase chain reaction (PCR) techniques in most biofluids, and the diagnostic and prognostic utility of measuring blood and urine miRs in patients with UC are under investigation.[27-29] Epigenetic mechanisms of immune response are increasingly being recognized, and several miRs with immune regulatory activities have been identified. For example, in melanoma and in prostate cancer, changes in specific plasma miRs are associated with changes in circulating natural killer, dendritic, and T, MDSC, and Treg cells.[30,31]

To evaluate the potential synergy of paclitaxel and pembrolizumab, we propose a single-arm combination study of pembrolizumab and paclitaxel in patients with platinum-refractory metastatic UC. We hypothesize that combination therapy will double the overall response rate as compared to single-agent pembrolizumab alone. We also incorporate multiple novel biomarker studies. This trial may lead to improved therapy for advanced UC and may also suggest specific interventions to improve antitumor immunologic activity.

1.2 Rationale for Dose Selection/Regimen/Modification

The 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). Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

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

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

The rationale for combination therapy is supported by Merck's preclinical work, in which a murine immunocompetent cancer model was treated with the anti-mouse PD-1 antibody in combination with 4 different chemotherapy regimens, including dexamethasone premedication at dose levels 0.5, 1, or 5 mg/kg. The results revealed that none of the combinations had a negative impact on the efficacy of anti–PD-1 treatment. Several treatment regimens, including those in combination with paclitaxel, resulted in a greater antitumor effect, including some complete responses, than treatment with either chemotherapy or PD-1 inhibition alone.

There are multiple ongoing clinical studies of pembrolizumab in combination with chemotherapy. For example, Merck 021 is U.S.-based a phase I/II study of pembrolizumab in combination with multiple chemotherapy regimens, including paclitaxel, for patients with NSCLC. The chemotherapy in this and other studies is given in cytotoxic doses, and thus far there have been no significant safety issues reported.

Paclitaxel is commonly used to treat patients with platinum-refractory UC. Multiple dosing regimens have been studied. One small study gave paclitaxel 175 to 250 mg/m^2 by 24-hour infusion every 3 weeks[32] and another gave paclitaxel 200 mg/m^2 by 3-hour infusion[33] to pretreated patients with advanced urothelial cancer. Both reported some efficacy with manageable toxicity. Weekly administration of paclitaxel at doses ranging from 80-100 mg/m^2 in patients with breast cancer and other solid tumors has shown better tolerance and minimal immunosuppression.[34] As such, weekly paclitaxel at 80 mg/m^2 given over 1 hour was studied in advanced urothelial carcinoma. 30 patients were treated, and a partial response was seen in 10% of patients. Time to progression was 2.2 months and overall survival 7.2 months. Treatment was well-tolerated, with anemia, neuropathy, and asthenia the most common toxicities reported.[14] Weekly paclitaxel (135mg/m^2) and carboplatin (AUC 2) has also been studied in advanced UC, but significant treatment-related toxicity was noted. [35]

Here we are giving pembrolizumab in combination with weekly paclitaxel at 80 mg/m^2, 2 out of every 3 weeks. This dosing regimen of paclitaxel was chosen based on clinical studies showing this dose to be safe and preclinical studies suggesting that taxanes are immunomodulatory, as described above. Paclitaxel will be given 2 out of every 3 weeks in order to limit myelosuppression and steroid exposure. The use of paclitaxel at non-cytotoxic doses, to block the immunosuppressive potential of MDSC and Treg cells, is a new therapeutic strategy for enhancing the efficacy of anti-PD-1 immunotherapy with pembrolizumab.

2.0 Hypothesis and Objectives

This study hypothesizes that: 1) Combination therapy with low-dose paclitaxel and pembrolizumab will improve the ORR and PFS compared to single-agent pembrolizumab; 2) Combination of low-dose paclitaxel with pembrolizumab will be safe and adequately tolerated; 3) Combination therapy will result in: a) Increased number and proportion of circulating functional CD8+ T-cells, and b) Decreased number and proportion of circulating MDSC and Treg cells; and 4) Response will be associated with increased CD8+ T-cells and/or decreased MDSC and Treg cells.

2.1 Primary Objective

2.1.1 To estimate the overall response rate (ORR) of pembrolizumab combined with paclitaxel

2.2 Secondary Objectives

2.2.1 To determine the safety and tolerability of pembrolizumab combined with paclitaxel
2.2.2 To calculate the progression-free survival (PFS) rate at 6 months

2.3 Correlative Objectives

2.3.1 To determine the immune effects of pembrolizumab combined with paclitaxel
2.3.2 To associate immune effects with tumor response
2.3.3 To explore changes in immune-regulatory microRNAs as biomarkers of response

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients diagnosed with platinum-refractory metastatic urothelial cancer that is measureable based on Response Evaluation Criteria in Solid

Tumors (RECIST) criteria 1.1.[36] Platinum-refractory disease is defined as progressive disease on cisplatin or carboplatin therapy or within 12 months of prior platinum treatment (last dose.)

3.1.2 At least 1 prior chemotherapy regimen containing cisplatin or carboplatin.

3.1.3 Patient must be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 months (168 days) prior to initiation of treatment on Day 1. Archived specimen can be used for subjects, if available.*

3.1.4 Age ≥18 years.

3.1.5 Performance status of 0 or 1 on the ECOG Performance Scale.

3.1.6 Adequate organ function as defined below:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥80,000 / mcL
Hemoglobin	≥9 g/dL without transfusion dependency
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥35 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 > 1.5X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL

3.1.7 Female subject 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.

3.1.8 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. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

3.1.9 Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

3.1.10 Ability to understand and the willingness to sign an IRB-approved informed consent document.

3.2 Exclusion Criteria

3.2.1 Currently receiving or has had treatment with an investigational agent or used an investigational device within 4 weeks of study Day 1.

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

3.2.3 Chemotherapy, targeted small molecule therapy, or radiation therapy within 2 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: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

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

3.2.4 Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. Prior therapy with paclitaxel or docetaxel.

3.2.5 Hypersensitivity to pembrolizumab, any of its excipients, paclitaxel, or any of its excipients.

3.2.6 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.

3.2.7 Known history of active TB (Bacillus Tuberculosis).

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

3.2.9 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. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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

3.2.11 Known history of, or any evidence of active, non-infectious pneumonitis.

3.2.12 Active infection requiring systemic therapy.

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

3.2.14 Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.2.15 Pregnancy or breastfeeding, or expecting to conceive or father 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.

3.2.16 Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

3.2.18 Received a live vaccine within 30 days of planned start of study therapy.
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

The study consent form will also be provided in Spanish for Spanish-speaking participants. We do not expect the percentage of Hispanic/Latino or racial minority cancer patients eligible for this study to be higher than the percentage of Hispanic or racial minority new cancer patients seen at CCCWFU (1.7% and 14.4%, respectively); therefore, we plan to enroll at least 1 Hispanic/Latino and at least 4 racial minority patients.

Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into ORIS Screening Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

   Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The primary outcome measure will be overall response rate.

5.2 Secondary Outcomes

5.2.1 Safety, as assessed by adverse events and serious adverse events
5.2.2 Progression-free survival at 6 months

5.3 Correlative Outcomes

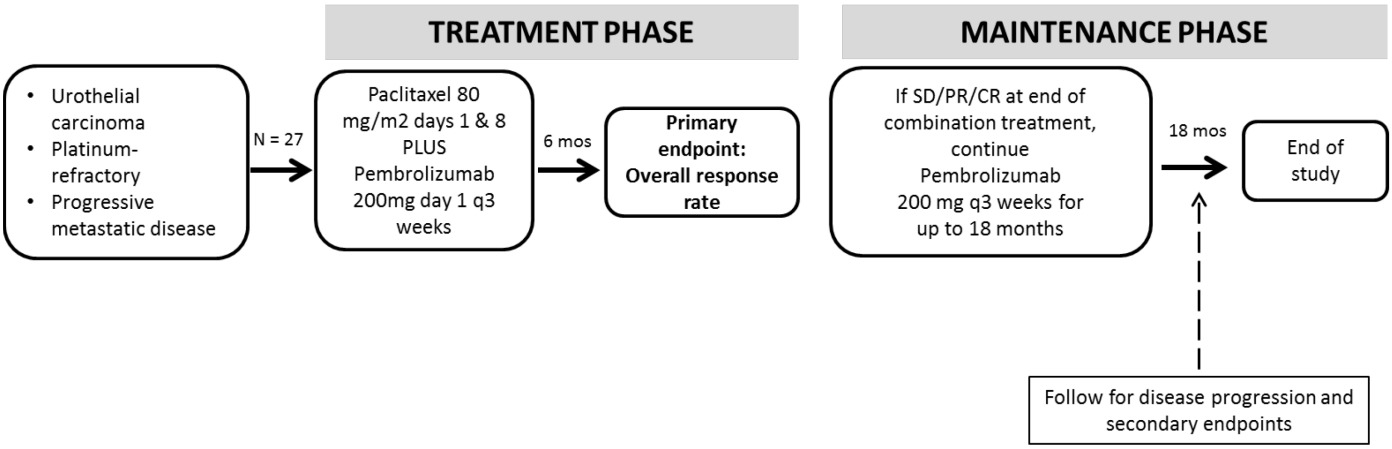
5.3.1 Immune effects, as assessed by changes in the number and proportion of functional CD8+ T-cells, MDSCs, Tregs, and circulating immune-regulatory microRNAs in peripheral blood

5.3.2 Quantify cytotoxic T-cells, MDSCs, and Tregs and determine the correlation of PD-L1 expression in tumor tissue

5.3.3 Changes in serum and urine immune-regulatory microRNAs

6.0 Treatment Plan

6.1 Study schema



6.2 Study-Related Activities

The Trial Flow Chart below summarizes the trial procedures to be performed at each visit. 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.

TRIAL FLOW CHART

Procedure	**Screening[a]**	**TREATMENT PHASE** (UP TO 6 MONTHS) **21 day cycle (+/- 3 days)**	**MAINTENANCE PHASE** (UP TO 18 MONTHS)

	Within 14 days of dosing	Day 1	Day 8	End of Treatment Visit[b]	Treatment 21 day cycle[c] (+/- 10 days)	Follow-up only[d] (+/- 10 days)
Informed consent	X					
Eligibility criteria	X					
Demographic data	X					
Concomitant medications[e]	X	X		X		
Medical history and physical exam	X	X		X	X	X
AE assessment[f]	X	X		X		
Vital signs, height, and weight[g]	X	X		X		
ECOG performance status	X	X		X		
Pembrolizumab dosing		X			X	
Paclitaxel dosing		X	X			
CT chest, abdomen, pelvis[h]	X	X		X	X	X
Standard-of-care laboratory assessments[i]						
CBC with differential	X	X	X	X	X	X
Serum chemistries	X	X	X	X	X	X
LDH		X		X		
Complete urinalysis		X		X		
Thyroid studies		X		X	X	
Urine pregnancy test[j]	X					
Correlative/research studies						
Metastatic tumor site biopsy[k]	X					
Archival tumor tissue[l]	X					
Blood correlates[m]		X		X		
Urinary correlates[m]		X		X		
MicroRNA blood & urine correlates[n]		X		X		

Footnotes to Study Flow Chart:

a. Screening evaluations must be completed within 14 days of first dose of medication and DO NOT need to be repeated on cycle 1 day 1 of treatment, except for the labs (CBC/CMP) which need to be performed within 72 hours of first dose. CT scan of chest/abdomen/pelvis can be within 30 days of cycle 1 day 1. Contrast scans preferred but noncontrasted studies acceptable if renal insufficiency, contrast allergy, or other medical condition prohibits the use of contrast.

b. The End of Treatment Visit is to occur no more than 30 days after the last dose of study agent. At the End of Treatment Visit, if progressive disease, patient will be followed for survival status. If stable disease or partial or complete response, patient will have the option of remaining on pembrolizumab alone for an additional 18 months or until disease progression.

c. Patients who remain on pembrolizumab in the maintenance phase will be seen every 21 days, with imaging every 3 months (+/- 10 days) for up to 18 months.

d. Patients who do not have progressive disease but who decline maintenance pembrolizumab will be followed every 3 months (+/- 10 days) for up to 18 months after the End of Treatment Visit. These patients will have scans every 3 months (+/- 10 days). All patients will continue to be followed for survival status.

e. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the treatment phase should be recorded, including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids.

f. Medical history, physical examination and AE assessments will be performed prior to study agent administration, on day 1 of each cycle. An end-of-study medical history, physical exam, and AE assessment will be performed at the end of treatment phase.

g. Vital signs and weight will be recorded at each visit during the treatment phase. Height will be measured at screening only.

h. Contrast scans preferred but noncontrasted studies acceptable if renal insufficiency, contrast allergy, or other medical condition prohibits the use of contrast. CT scan of chest/abdomen/pelvis can be within 30 days of cycle 1 day 1.

   TREATMENT PHASE: CT scan of chest/abdomen/pelvis to be performed on day 1 of cycle 4, day 1 of cycle 7, and at the end-of-treatment visit (+/-7 days) as part of routine tumor assessment.

   MAINTENANCE PHASE: CT scan of chest/abdomen/pelvis to be performed every 3 months (+/- 10 days) as part of routine tumor assessment.

   These tumor assessments will be performed locally, in accordance with the RECIST 1.1 guidelines.

i. Standard-of-care laboratory assessments at the times indicated include:

   Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.

   Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, carbon dioxide or bicarbonate, calcium, protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase. *Note: During maintenance phase, order BMP except on visits where thyroid testing is included (order CMP.)*

   LDH

   Urinalysis: Including pH, specific gravity, protein, microscopy, hemoglobin, cell count, crystal evaluation, leukocyte esterase, and nitrite without culture will be collected on day 1 of cycles 1, 4, 8, and at the end of treatment visit.

   Thyroid studies: TSH, free T4, and T3 will be performed on day 1 of cycles 1, 4, 8, and at the end of treatment visit due to the potential for thyroid abnormalities while on pembrolizumab. *Note: In the maintenance phase, thyroid studies will be performed every 3 cycles.*

   Note: Day 1 lab tests do not have to be repeated if screening labs are obtained within 3 days prior to the first dose of study drug.

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

k. If safely able to be performed, a metastatic (bone, soft tissue, visceral metastasis permitted) or recurrent bladder tumor biopsy under radiologic or cystoscopic guidance will be performed prior to treatment initiation. Biopsies obtained up to 6 months (168 days) prior to treatment initiation are acceptable.

l. Previously archived formalin-fixed or frozen tumor blocks will be collected on this study and linked to subject outcomes if available. Frozen primary tumor samples will be collected if available.

m. Blood and urine correlates will be collected prior to treatment administration on day 1 of cycle 1, day 1 of cycle 4, day 1 of cycle 8, and at the end of treatment visit.

n. Blood and urine for microRNA analysis will be collected prior to treatment administration on day 1 of cycle 1, day 1 of cycle 4, day 1 of cycle 8, and at the end of treatment visit.

6.2.1 Informed Consent

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

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.

6.2.2 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.

6.2.3 Medical History

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

6.2.4 Prior and Concomitant Medications Review

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.

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 9.0.

6.2.5 Disease Details and Treatments

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

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

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.

6.2.6 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the treatment phase of the study according to NCI CTCAE Version 4.0 (see Section 9.0). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document regarding the identification, evaluation and management of potential irAEs.

Please refer to section 9.0 for detailed information regarding the assessment and recording of AEs.

6.2.7 Physical Exam

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

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

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.

Eastern Cooperative Oncology Group (ECOG) Performance Scale
The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.2.8 Laboratory Procedures/Assessments

Laboratory tests for screening should be performed within 14 days prior to the first dose of treatment and will need to be repeated if not within 72 hours of first dose. After cycle 1 day 1, all 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.

Blood and urine correlates will be collected prior to treatment administration on day 1 of cycles 1, 4, 8, and at the end of treatment visit. A total of six (6) 10 mL EDTA tubes of blood will be collected at each time point. The samples will be kept at room temperature and transported to Dr. Triozzi's lab within 2 hours of collection for further processing.

6.3 Treatment Administration

REGIMEN DESCRIPTION

Agent	Premedications	Dose	Route	Schedule	Cycle Length
Pembrolizumab		200 mg	30-minute IV infusion	Day 1	21 days
Paclitaxel	Premedicate with ondansetron 8 mg IV or po , dexamethasone 10 mg IV or po, diphenhydramine	80 mg/m^2	60-minute IV infusion	Days 1 and 8	

	25 mg IV or po, and ranitidine 50mg IV or po (or equivalent H2 blocker) 30-60 minutes pre-treatment.*				

*Premedications may be substituted according to institutional guidelines.

On day 1 of each cycle, pembrolizumab is to be given first, prior to the premedications and then followed by paclitaxel.

Patients will be observed for 60 minutes after completion of chemotherapy, while in the treatment phase. Patients receiving pembrolizumab alone in the maintenance phase need not have extended monitoring unless clinically indicated. Vitals signs (blood pressure, heart rate, respiratory rate, oxygenation, and temperature) will be checked every hour while receiving treatment and prior to discharge from the treatment area.

Trial treatment should be administered per the schedule above after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.1). 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.

6.4 General Concomitant Medication and Supportive Care Guidelines

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

6.4.1 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 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 9.0.

6.4.2 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:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use

of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

6.4.3 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 Section 7.1. 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 7.0 for dose modification.

- **Pneumonitis**:

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Pneumonitis
– Interstitial lung disease
– Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered. All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for**

a therapeutic trial of antibiotics. If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

- For **Grade 2 events:**

– Hold pembrolizumab.
– Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
– Consider ID consult.
– Conduct an in person evaluation approximately twice per week.
– Consider frequent Chest X-ray as part of monitoring.
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

- For **Grade 3-4 events**:

– Discontinue pembrolizumab.
– Hospitalize patient.
– Bronchoscopy with biopsy and/or BAL is recommended.
– Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
– Add prophylactic antibiotics for opportunistic infections.

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- **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).

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Colitis
– Colitis microscopic
– Enterocolitis
– Enterocolitis hemorrhagic

– Gastrointestinal perforation
– Intestinal obstruction
– Necrotizing colitis
– Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

- For **Grade 2 events:**

– Hold pembrolizumab.
– Symptomatic Treatment
– For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus, consider GI consultation and endoscopy to confirm or rule out colitis
– Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If symptoms worsen or persist > 3 days treat as Grade 3

- For **Grade 3-4 events**:

– Hold pembrolizumab (if grade 3) or discontinue (if grade 4)
– Rule out bowel perforation. Imaging with plain films or CT can be useful.
– Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
– Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

- **Endocrine**:

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Adrenal insufficiency
– Hyperthyroidism
– Hypophysitis
– Hypopituitarism
– Hypothyroidism
– Thyroid disorder
– Thyroiditis

- **Hypophysitis**:

Grade 2-4 events:
– 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.
– 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 2-4** hypothyroidism):
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
– Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
– In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
– In hypothyroidism, thyroid hormone replacement therapy is indicated per standard of care.
– Consultation with an endocrinologist may be considered.

Grade 3/4 hyperthyroidism events:

– Hold pembrolizumab (grade 3) or discontinue (grade 4).
– Rule out infection and sepsis with appropriate cultures and imaging.
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg 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.

- **Type 1 diabetes mellitus (new onset) and ≥ Grade 3 Hyperglycemia**

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
– Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of preexisting diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

T1DM should be immediately treated with insulin.
T1DM or Grade 3-4 Hyperglycemia events:
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- 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.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

- **Hepatic**:

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Autoimmune hepatitis
– Hepatitis
– Transaminase elevations
All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:
- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

- **Grade 2** events:
– Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
– Monitor liver function tests more frequently until returned to baseline values (consider weekly).
– Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

- **Grade 3** events:
– Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
– Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
– Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
– If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

- **Grade 4** events:
– Permanently discontinue pembrolizumab
– Manage patient as per Grade 3 above

- **<u>Renal</u>:**

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Nephritis
– Nephritis autoimmune
– Renal failure
– Renal failure acute

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

- **Grade 2** events:
– Hold pembrolizumab
– Treatment with prednisone 1-2 mg/kg p.o. daily.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

- **Grade 3-4** events:
– Discontinue pembrolizumab
– Renal consultation with consideration of ultrasound and/or biopsy as appropriate
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **<u>Hematologic</u>:**

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:
– Autoimmune hemolytic anemia
– Aplastic anemia
– Disseminated Intravascular Coagulation (DIC)
– Haemolytic Uraemic Syndrome (HUS)
– Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
– Thrombotic Thrombocytopenic Purpura (TTP)
– Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear,

reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

- **Grade 2** events:

– Hold pembrolizumab
– Prednisone 1-2 mg/kg daily may be indicated
– Consider Hematology consultation.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

- **Grade 3** events:

– Hematology consultation
– Hold pembrolizumab. Discontinuation should be considered as per specific protocol guidance.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

- **Grade 4** events:

– Hematology consultation
– Discontinue pembrolizumab .
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

- **<u>Neurologic</u>**:

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Autoimmune neuropathy
– Demyelinating polyneuropathy
– Guillain-Barre syndrome
– Myasthenic syndrome
All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

- **Grade 2** events:

– Consider withholding pembrolizumab.
– Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
– Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

- **Grade 3 and 4** events:

– Discontinue pembrolizumab
– Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other

immunosuppressive therapies as per local guidelines. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Skin**:

Rash and Pruritus
The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:
– Pruritus
– Rash
– In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
- rash with a duration >2 weeks; OR
- rash that is >10% body surface area; OR
- rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs
The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:
– Dermatitis exfoliative
– Erythema multiforme
– Steven's Johnson syndrome
– Toxic epidermal necrolysis

- **Grade 2** events:
– Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
– Treatment with oral steroids is at physician's discretion.
- **Grade 3** events:
– Hold pembrolizumab.
– Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
– Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less,
steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- **Grade 4** events:
– Permanently discontinue pembrolizumab.
– Dermatology consultation and consideration of biopsy and clinical dermatology photograph.

– Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks

- **Ocular**:

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:
– Uveitis
– Iritis
All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

- **Grade 2** events:
– Evaluation by an ophthalmologist is strongly recommended.
– Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
– Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.
- **Grade 3** events:
– Evaluation by an ophthalmologist is strongly recommended
– Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
– Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- **Grade 4** events:
– Evaluation by an ophthalmologist is strongly recommended
– Permanently discontinue pembrolizumab.
– Treat with corticosteroids as per Grade 3 above

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1	Increase monitoring of vital signs as medically indicated	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Mild reaction; infusion interruption not indicated; intervention not indicated	until the subject is deemed medically stable in the opinion of the investigator.	
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.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.5 Other Considerations

6.5.1 Contraception

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

6.5.2 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

6.5.3 Use in Nursing Women

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

6.6 Duration of Therapy

TREATMENT PHASE:

In the absence of treatment delays due to adverse events, treatment with the combination of paclitaxel and pembrolizumab may continue for 8 cycles or until one of the following criteria applies:

- Confirmed radiographic disease progression (a subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Confirmed positive serum pregnancy test,
- Noncompliance with trial treatment or procedure requirements,
- The patient is lost to follow-up,

- Patient/legal representative withdraws consent, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating physician.

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 9.0.

MAINTENANCE PHASE:

In the absence of treatment delays due to adverse events, treatment with pembrolizumab may continue for 18 months or until one of the following criteria applies:

- Confirmed radiographic disease progression (a subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Confirmed positive serum pregnancy test,
- Noncompliance with trial treatment or procedure requirements,
- The patient is lost to follow-up,
- Patient/legal representative withdraws consent, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating physician.

Patients who remain on pembrolizumab in the maintenance phase will be seen every 21 days, with imaging every 3 months (+/- 10 days) for up to 18 months.

6.7 Post-treatment Visits

6.7.1 Safety Follow-up Visit (End-of-treatment visit)

The mandatory Safety Follow-Up Visit should be conducted within 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.

If stable disease or partial or complete response noted at this visit, the patient will have the option of remaining on pembrolizumab alone for an additional 18 months, in the maintenance phase as described above.

6.7.2 Follow Up

Patients who do not have progressive disease but who decline maintenance pembrolizumab will be followed every 3 months (+/- 10 days) for up to 18 months after the end of treatment. These patients will have scans every 3 months (+/- 10 days). All patients will be continued to followed for survival status.

. Patients who discontinue treatment for reasons other than progressive disease should be assessed every 3 months (± 10 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, end of the study or lost to follow up. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

All patients will have survival status assessed every 3 months until death or withdrawal of consent. .

7.0 Dosing Delays/Dose Modifications

7.1 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 the table below. Toxicity must return to Grade 0-1 by day 1 of each cycle. 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.

Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		

	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

7.2 **Paclitaxel**

On day of treatment	Paclitaxel Modification
ANC < 1000	Hold paclitaxel for one week. If ANC >1000 the following week, treat at 80 mg/m2. If ANC still <1000, hold for another week and reduce all subsequent doses to 60 mg/m2.
Platelet < 100,000	Hold paclitaxel for one week. If platelet > 100K at the following week, reduce paclitaxel to 60mg/m2 on next and all subsequent doses. If platelets remain <100K, drop paclitaxel and continue with pembrolizumab alone.
Febrile neutropenia	Hold paclitaxel until episode resolves to grade 1 or below. For next cycle, reduce paclitaxel to 60 mg/m2. If recurs, drop paclitaxel and continue with pembrolizumab alone.
Neurotoxicity (including peripheral neuropathy)	Hold paclitaxel until resolution to Grade 1 or below. If recurs, or not resolved to < Grade 2 after having dose held for two weeks, then continue with pembrolizumab alone.
Other Possibly-Related Grade 3 AEs	If probably or possibly related to paclitaxel, hold paclitaxel until resolution to Grade ≤ 1. If it recurs to Grade 3 or greater, discontinue paclitaxel and continue with pembrolizumab alone.
All Grade 4 AEs	All Grade 4 AEs possibly related to paclitaxel should result in discontinuation of paclitaxel

Management of acute hypersensitivity will be as per local institutional guidelines.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

8.0 Measurement of Effect

8.1 Antitumor Effect

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.[36] While in the treatment phase, the patients will be reevaluated for response prior to cycle 4, prior to cycle 7, and at the end-of-treatment. In addition to a baseline scan, confirmatory scans should also be obtained as per RECIST criteria following initial documentation of objective response.

8.1.1 Definitions

- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with pembrolizumab
- Inevaluable for objective response: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.
    - If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.
- Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness);
    - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
    - 20 mm by chest X-ray.
- Measurable lesions:
    - Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
    - Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by crosssectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
    - ‘Cystic lesions’ thought to represent cystic metastases can be considered measurable if they meet the definition of measurability

described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Non-measurable lesions: Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
    - Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- Target lesions: All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
    - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
    - All measurements should be recorded in metric notation using calipers if clinically assessed.
    - A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.
    - Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
    - Target lesions that become ‘too small to measure’: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’, in which case a default value of 5 mm should be assigned.
    - Lesions that split or coalesce on treatment: When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each

individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

- Non-target lesions: All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

8.1.2 Methods for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

8.1.3 Response Criteria

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

8.1.4 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
    - When patient has measurable disease: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A

modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
    - When patient has only non-measurable disease: There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.
- New lesions: The appearance of new malignant lesions denotes disease progression.
    - The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).
    - If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
    - A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.
    - It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
        - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.
        - No FDG-PET at baseline and a positive FDG-PET at follow-up:
            - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
            - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
            - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

8.1.5 Evaluation of Best Overall Response

Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1. Overall response for patients with target (± non-target) disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluate	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Inevaluable			

When patients have non-measurable (therefore non-target) disease only, Table 2 should be used.

Table 2. Overall response for patients with non-target disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = Complete Response, PD = Progressive Disease, NE = Inevaluable [1] Non-CR / non-PD is preferred over 'Stable Disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials. To assign this category when no lesions can be measured is not advised.		

8.1.6 Duration of Response

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

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

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

8.1.7 Survival Outcomes

Progression-Free Survival is defined as the duration of time from the start of treatment to the time of progression, death, or date of last contact.

Overall Survival is defined as the duration of time from the start of treatment to date of death or date of last contact.

8.1.8 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

9.0 Adverse Events List and Reporting Requirements

9.1 Assessing and Recording Adverse Events

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

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

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

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 9.5.

Adverse reactions considered expected for pembrolizumab include:

System Organ Class	Adverse Event Term
Blood and lymphatic system disorders	Anemia
Endocrine disorders	Hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, secondary adrenal insufficiency, thyroid disorder
Eye disorders	Uveitis
Gastrointestinal disorders	Abdominal pain, colitis, constipation, diarrhea, nausea, pancreatitis, vomiting
General disorders and administration site conditions	Asthenia, fatigue, peripheral edema, pyrexia
Hepatobiliary disorders	Hepatitis
Injury, poisoning and procedural complications	Infusion related reaction
Metabolism and nutrition complications	Decreased appetite, diabetic ketoacidosis, hyponatremia, Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, myositis
Renal and urinary disorders	Nephritis
Respiratory, thoracic and mediastinal disorders	Cough, dyspnea, pneumonitis
Skin and subcutaneous tissue disorders	Pruritus, rash, severe skin reactions

9.1.1 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

Refer to the table in section 9.1.4 below for additional details regarding each of the above criteria.

In the pembrolizumab monotherapy trials, the most commonly reported DRSAEs (those that occurred in 3 or more subjects overall in at least 1 study) were pneumonitis (range of 0.7% to 1.3% of subjects); colitis (range of 0.3% to 1.1% of subjects), pyrexia (range of 0.3% to 0.5% of subjects); diarrhea (range of 0.2% to 0.4%); hepatitis (0.7% of subjects); nausea, adrenal insufficiency, hyponatremia, hyperthyroidism, hypophysitis, vomiting, and dyspnea (0.3% of subjects each); and dehydration, generalized edema, hypothyroidism, renal failure acute, and pericardial effusion (0.2% of subjects each). The remaining DRSAEs occurred in 1 or 2 subjects each per study.

In the combination therapy trials, all DRSAEs were reported in 1 subject each. In P021, 8 subjects experienced DRSAEs; the DRSAEs were as follows: anemia, febrile neutropenia, atrial fibrillation, colitis, pyrexia, hypersensitivity, alanine aminotransferase increased, aspartate aminotransferase increased, drug eruption, rash, and urticaria. In P023, 2 subjects experienced DRSAEs; 1 subject had an event of pneumonia and the other had an event of tumor lysis syndrome.

9.1.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor 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 9.1.3, 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).

Additional adverse events:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document." This document can be found in the Investigator Trial File Binder (or equivalent) and provides guidance regarding identification, evaluation and management of ECIs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to 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), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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.

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

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

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

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest

(ECI), using the terminology "accidental or intentional overdose without adverse effect."

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

9.1.4 Merck Requirements for 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.

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.)

9.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A

copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

9.3 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All CCCWFU Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9.5 Merck Reporting Requirements

9.5.1 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), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male 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)

9.5.2 Reporting of SAEs and Events of Clinical Interest

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

10.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 9.0.

10.1 Pharmaceutical Accountability

Drug accountability logs will be maintained for all investigative agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

10.2 Pembrolizumab

Clinical Supplies will be provided by Merck as summarized below.

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

Packaging and Labeling Information
Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

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.

Marketed Packs: When Study Drug is provided in the marketed package, Merck will not supply any Chemistry, Manufacturing, Control (CMC) information. Institution's regulatory submission should reference the Merck Marketing Authorization. If any additional labelling of containers is required, e.g. to add Study Protocol number, and it has not been agreed for Merck to perform the additional labelling, it is Institution's responsibility to arrange for this action to be done in accordance with U.S. regulations.

Storage and Handling Requirements
The lyophilized drug product after reconstitution with sterile water for injection, and the liquid drug product are a clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted MK-3475 solutions in the IV bags.

Clinical supplies must be stored in a secure, limited-access location. The drug product is to be stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2 to 8°C).

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.

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.

10.3 Paclitaxel

Product description: Supplied as:

NDC 0015-3475-30	30 mg/5 mL multidose vial individually packaged in a carton
NDC 0015-3476-30	100 mg/16.7 mL multidose vial individually packaged in a carton
NDC 0015-3479-11	300 mg/50 mL multidose vial individually packaged in a carton

Solution preparation: Paclitaxel Injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride 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 1.2 mg/mL. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Storage requirements: Store the vials in original cartons between 20°–25° C (68°–77° F). Retain in the original package to protect from light.

Stability: Unopened vials of paclitaxel injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Prepared solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions.

Route of administration: Paclitaxel should be administered as an intravenous infusion through an in-line filter with a microporous membrane not greater than 0.22 microns. Monitor infusion site for possible infiltration during drug administration.

Disposal: To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel Injection. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed

thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported.

11.0 Correlative/Special Studies

11.1 Laboratory Correlative Studies

Peripheral blood will be obtained from each patient prior to initiation of treatment, on cycle 4 day 1, cycle 8 day 1, and at the end-of-treatment visit. A total of six (6)
10mL EDTA tubes will be drawn at each time point.

Changes from baseline and in responding versus nonresponding patients will be assessed.

(1) **Activated T-cells:** The goal is to calculate the number and percentage of IFNγ+CD8+ T cells in peripheral blood pre-, on-, and post-treatment.
   i. *Sample collection.* Peripheral blood will be obtained from each patient prior to initiation of treatment, on cycle 4 day 1, cycle 8 day 1, and at the end-of-treatment visit. The lymphocyte fraction will be isolated on a Percoll gradient.
   ii. *T-cell processing.* Cells will be stimulated overnight with plate-bound anti-CD3 (1ug/mL) and soluble anti-CD28 (1ug/mL) in the presence of protein transport inhibitors Brefeldin A and monensin. Following stimulation, cells will be stained with anti-CD8-FITC antibody, fixed and permeabilized using the BD Cytofix/Cytoperm staining kit. Following permeabilization the cells will be stained with anti-IFNg, anti-IL-12, anti-IL2. Stained cells will be run on a FACS Canto and analyzed using manufacturer provided software. The proportion of IFNg+CD8+ T cells will be quantified, with expression of IL-12 considered further evidence of activated effector function.

(2) **MDSC and Tregs:** The goal is to determine whether combination treatment changes the number and proportion of MDSC and Tregs in peripheral blood.
   i. *Sample collection.* Peripheral blood will be obtained from each patient prior to initiation of treatment, on cycle 4 day 1, cycle 8 day 1, and at the end-of-treatment visit. The lymphocyte fraction will be isolated on a Percoll gradient.
   ii. *MDSC and T-reg processing*. Tregs will be quantified using the human Treg staining kit (eBioscience) and established methods.

(3) **MicroRNAs:** The goal is to explore changes in circulating and urinary immune-regulatory microRNAs during treatment, using quantitative real time PCR.
   i. *Sample collection.* Blood and urine will be collected each patient prior to initiation of treatment, on cycle 4 day 1, cycle 8 day 1, and at the end-of-treatment visit. 10 mL of blood will be drawn into EDTA tubes. Peripheral blood mononuclear cells (PBMC) and plasma will be separated by gradient

centrifugation. Urine is centrifuged at 1000 *g* for 10 minutes to pellet cellular debris. All samples are aliquoted and stored at −80°C until further use.

ii. *miRs processing.* Total RNA will be isolated from plasma and urine using the miRNeasy Mini Kit (Qiagen) collected pre-, on-, and post-therapy. Pools of plasma samples collected from healthy donors will be tested as controls. Plasma levels of selected miRs will be measured with qRT-PCR, normalized to spiked-in synthetic miR, in all patients pre- and post-therapy. Reverse transcription reactions are performed using a TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's instructions. qRT-PCR will be performed using the reverse transcription reaction product, TaqMan MicroRNA Assay kits, and TaqMan Universal PCR Master Mix (Applied Biosystems. The $\Delta\Delta C_T$ method is used to determine relative levels (RQ). Data are normalized to a *C. elegans* synthetic miR sequence, cel-miR-39 (Qiagen), which is spiked in as a control during RNA isolation.

11.2 Pathology Correlative Studies

When feasible, a metastatic biopsy will be performed. Archived tumor TURBT and cystectomy specimens will also be accessed. The goal will be to determine PD-L1 expression and to analyze cytotoxic T-cell number and function, MDSC, and Treg cells in tumor tissue.

(1) **Tumor PD-L1 expression**: Biopsy samples will be stored and batched for PD-L1 immunohistochemistry. This will be done with QualTek per Merck's guidelines. Five (5) unstained slides per patient, cut from a formalin-fixed, paraffin-embedded (FFPE) tissue block, will be sent to QualTek for PD-L1 staining. Positively charged ProbeOn Plus slides must be used for tissue sections. Samples may be held as blocks indefinitely at the site and then cut in batches. Slides must be shipped to QualTek immediately after sectioning to comply with the protocol's testing requirements. Sectioned slides must be shipped cold (2-8°C) and in the dark using the shipping materials provided by QualTek. Sectioned slides provided should contain tumor specimen sufficient for pathology review and analysis of tumor sample. If available, greater than 50% tumor content is preferred. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, lavage specimen, frozen sample, plastic embedded sample, or formalin fixed sample that was frozen at any point **will not be accepted** for IHC analysis. Needle core biopsies that are formalin-fixed and paraffin-embedded are acceptable. The slides will be evaluated by a Qualtek-associated pathologist for review of biomarker staining expression levels.

(2) **Tumor immune cells**: Cytotoxic T-cell number and function, MDSC, and Treg cells in tumor tissue will be evaluated in both archival tissue and in fresh biopsy specimens. Tumor tissue will be digested with DNase and Collagenase using standard protocols, and CD8+ T cells will be isolated by flow sorting. Sorted T cells will be stimulated with

anti-CD3/anti-CD28, and expression of IFNg and IL-12 will be quantified by flow cytometry to determine proportion of functional T-cells. For detection of Tregs in biopsy samples, CD4+CD25+ T cells will be isolated by flow sorting, and post-stained for FoxP3. To detect MDSC, Gr+ and CD11b+ cells will be sorted and confirmed by Wright-Giemsa staining of sorted cells. Concordance of immune cell frequency between archival and fresh specimens and the peripheral blood from the same patient will be informative.

12.0 Data Management

Informed consent document	ORIS
Protocol registration form	ORIS
Adverse Events	ORIS
Baseline Data Collection Form	REDCap
Follow-Up Data Collection Form	REDCap
Treatment Evaluation Response Form	REDCap

13.0 Statistical Considerations

13.1 Power, Sample Size and Accrual Rate

Simon's minimax two-stage design[37] will be used. The null hypothesis that the true response rate is 24% will be tested against a one-sided alternative. In the first stage, 15 patients will be accrued. If there are 3 or fewer responses in these 15 patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 10 or more responses are observed in 27 patients. This design yields a type I error rate of .09 and power of 90% when the true response rate is 48%. We anticipate an accrual rate of 1-2 patients per month or 12-24 patients per year.

13.2 Analysis of Primary Objective

The primary endpoint will be overall response rate. The analysis will be performed in all patients that are evaluable for efficacy and will have one interim analysis. In this phase 2 trial, we will calculate the overall response rate (primary outcome) and 6-month PFS. For the overall response rate, if 10 or more responses are observed in the 27 patients, we will reject the null hypothesis that the response rate is 24% or less.

13.3 Analysis of Secondary Objectives

The secondary endpoints include PFS and safety. We will estimate PFS at 6-months using the Kaplan-Meier method on all evaluable patients. All AEs will be

tabulated and presented by preferred term and/or system organ class and grade. All deaths and SAEs will be tabulated. The 6-month PFS will be compared to historical rates using a chi-square test.

13.4 Analysis of Correlative Objectives

The correlative endpoints include immune effects. They will be analyzed in exploratory analyses to associate their levels with tumor response. Categorical endpoints will be analyzed using chi-square or Fisher's exact tests, and continuous measures will be compared using t-tests to compare response groups.

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37. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled clinical trials.* Mar 1989;10(1):1-10.

Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

ECOG Performance Status: ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO
(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

IRB Protocol No.	**CCCWFU Protocol No.**
Study Title: Single-arm phase II combination study of low-dose paclitaxel with pembrolizumab in platinum-refractory urothelial carcinoma	
Principal Investigator: Rhonda Bitting, MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Patients diagnosed with platinum-refractory metastatic urothelial cancer that is measureable based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. Platinum-refractory disease is defined as progressive disease on cisplatin or carboplatin therapy or within 12 months of prior platinum treatment (last dose.)	☐	☐	
At least 1 prior chemotherapy regimen containing cisplatin or carboplatin.	☐	☐	
Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 months (168 days) prior to initiation of treatment on Day 1. Archived specimen can be used for subjects, if available.*	☐	☐	
Age ≥18 years.	☐	☐	
Performance status of 0 or 1 on the ECOG Performance Scale.	☐	☐	
Adequate organ function as defined below: ANC ≥ 1,500/mcL Platelets ≥ 80,000/mcL Hemoglobin ≥9 g/dL without transfusion dependency. Serum Creatinine **OR** Measured or Calculated Creatinine Clearance (GFR can also be used in place of creatinine or CrCl) ≤1.5x upper limit of normal (ULN) **OR** ≥35 mL/min for subject with creatinine levels >1.5x institutional ULN Serum Total bilirubin ≤ 1.5x ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5x ULN AST (SGOT) and ALT (SGPT) ≤ 2.5x ULN **OR ≤** 5x ULN for subjects with liver metastases Albumin ≥2.5 mg/dL	☐	☐	
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.	☐	☐	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
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. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.	☐	☐	
Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document.	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Currently receiving or has had treatment with an investigational agent or used an investigational device within 4 weeks of study Day 1.	☐	☐	
Anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.	☐	☐	
Chemotherapy, targeted small molecule therapy, or radiation therapy within 2 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: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.	☐	☐	
Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. Prior therapy with paclitaxel or docitaxel.	☐	☐	
Hypersensitivity to pembrolizumab, any of its excipients, paclitaxel, or any of its excipients.	☐	☐	
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.	☐	☐	
Known history of active TB (Bacillus Tuberculosis).	☐	☐	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.	☐	☐	
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. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.	☐	☐	
Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.	☐	☐	
Known history of, or any evidence of active, non-infectious pneumonitis.	☐	☐	
Active infection requiring systemic therapy.	☐	☐	
History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.	☐	☐	
Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.	☐	☐	
Pregnancy or breastfeeding, or expecting to conceive or father 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.	☐	☐	
Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).	☐	☐	
Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).	☐	☐	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Received a live vaccine within 30 days of planned start of study therapy. *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

ORIS Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Treating Physician**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix C – Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?

☐ **Yes** ☐ **No**

Was a discrepancy found? ☐ **Yes** ☐ **No**

If yes, please provide what is currently indicated in the EMR:

Ethnicity: _____ Race: _____

Additional comments: _____

_____

_____

Appendix D – Mandatory STRC SAE Reporting Guidelines

Safety and Toxicity Review Committee (STRC) Serious Adverse Event (SAE) Notification SOP	**Date: 07/10/2019**

Mandatory STRC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Safety and Toxicity Review Committee (STRC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1. The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2. WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3. The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1. Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2. Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.

   There are three types of trials that are included in this category:

   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.

   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites.

AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the STRC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the STRC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the STRC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the STRC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire STRC committee will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the STRC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to STRC.

STRC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the STRC members will not be notified until a date is entered into the STRC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the STRC has been contacted. Indicate the name of the STRC clinician that was contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the STRC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the STRC clinician who was notified and Date/Time notified. In addition, state attribution by STRC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. STRC clinician name and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with STRC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification *This is required in order for the email notification to be sent*
13. Adverse Event Details – Enter all details for each AE associated with the SAE.

a. Course start date
b. Category
c. AE Detail
d. Comments
e. Grade/Severity
f. Unexpected Y/N
g. DLT Y/N
h. Attributions
i. Action
j. Therapy
k. Click ADD to attach the AE Detail to the SAE.

14. Enter Date Notified STRC -- *This is required for the email notification to be sent*

15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified STRC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the STRC members immediately so that their assessment can be obtained within the 24 hour time frame requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD – Director-at-Large, WFBCCC; Section Head, Hematology/Oncology 6-
Glenn Lesser, MD – Hematology Oncology 6-
Stefan Grant, MD, JD-Hematology Oncology 3-
Jimmy Ruiz, MD-Hematology Oncology 6-
Mercedes Porosnicu, MD- Hematology Oncology 6-
Michael Farris, MD – Radiation Oncology 3-

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with a different STRC clinician. Allow up to 30 minutes for the new STRC clinician to respond to a phone call or page before contacting another member. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the STRC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right to disagree with the Investigator's assessment. If STRC does not agree with the Investigator, STRC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the STRC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click update. This will allow additional informatio n to be added

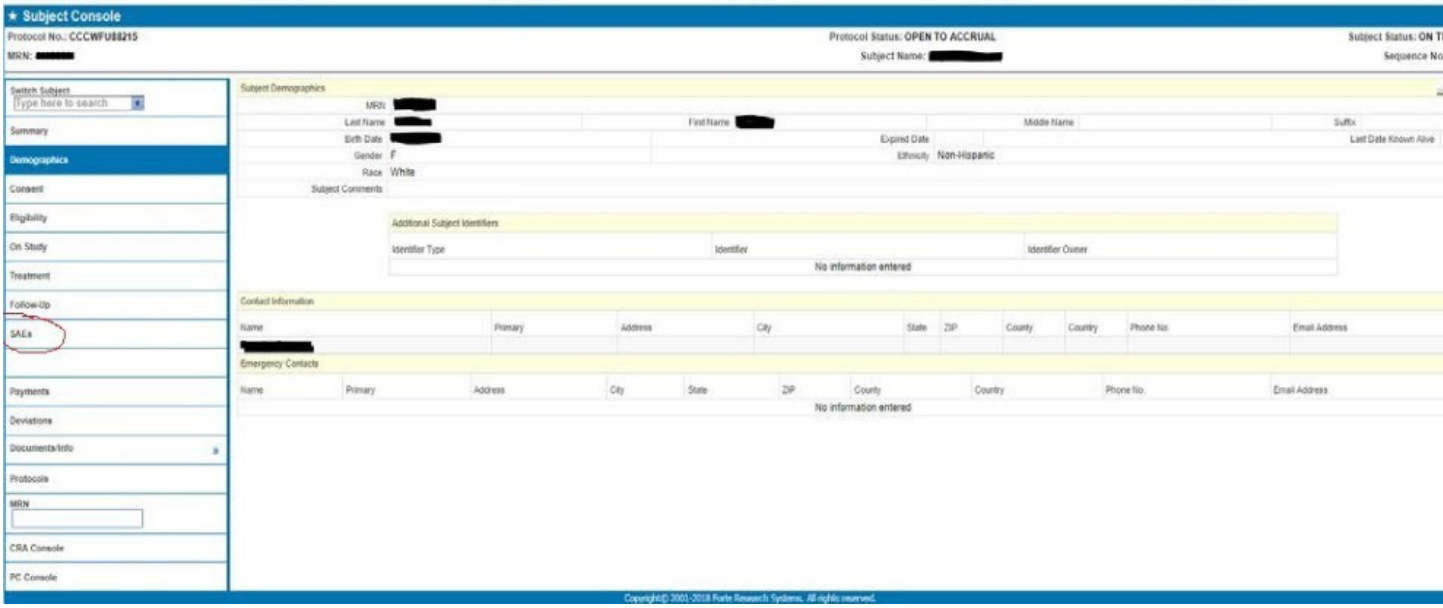
Acronyms

AE – Adverse Event
STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

Screen Shots:

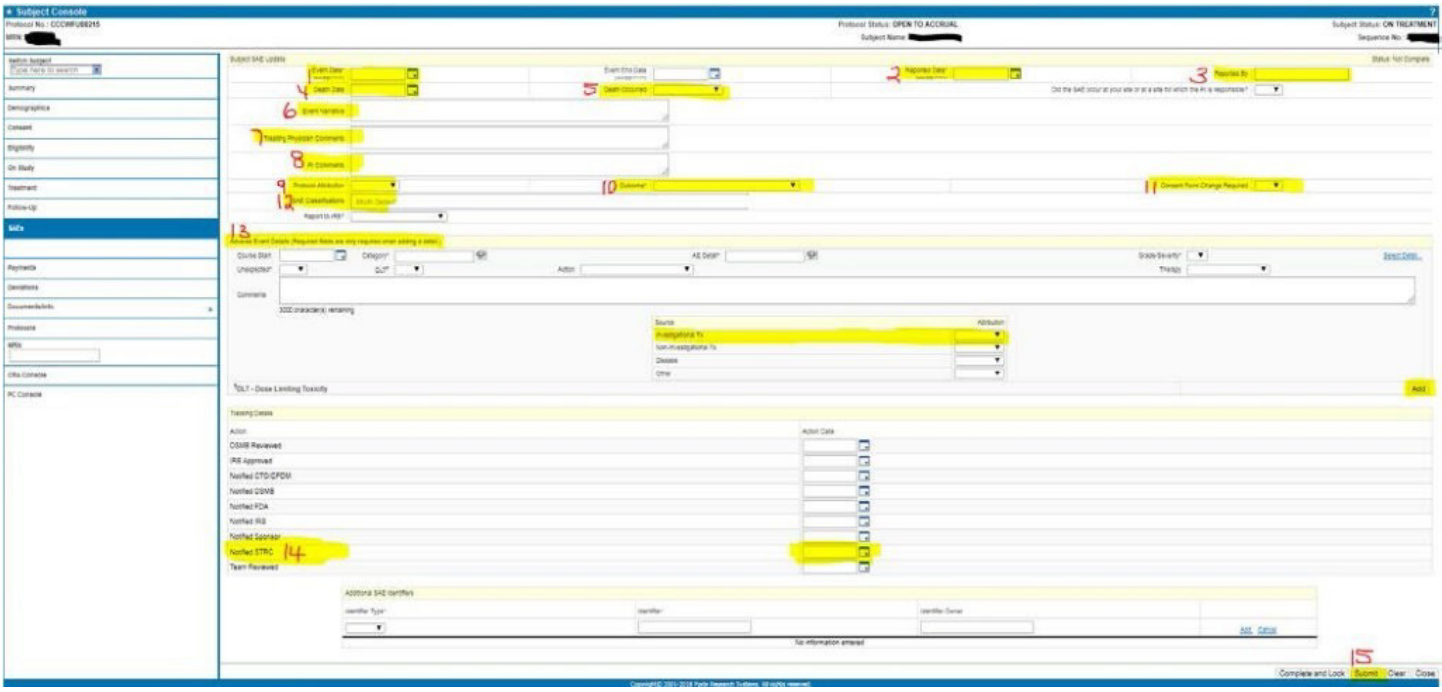
The following screen shots come from the SAE Console within the Subject Console in WISER.

Screen Shot 1:

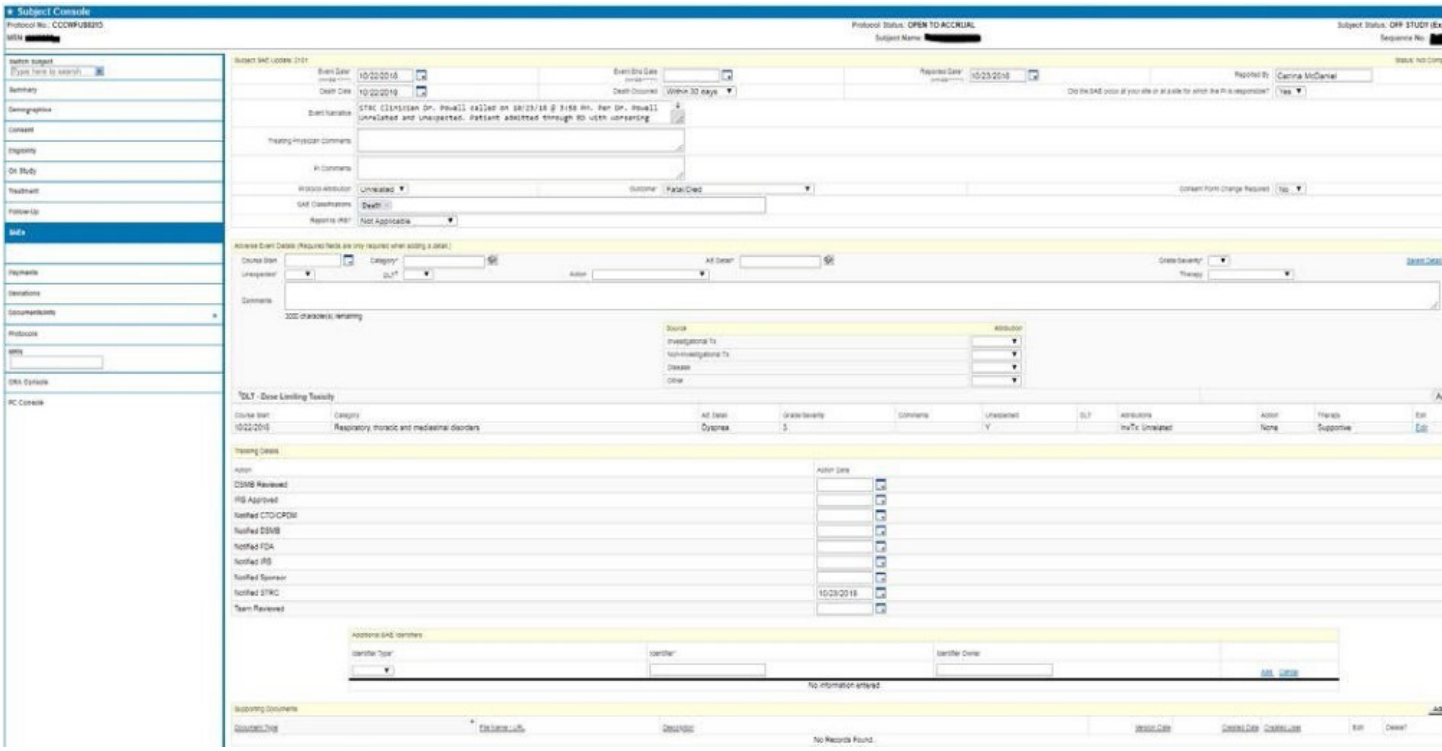


Screen Shot 2:

Screen Shot 3:



Screen Shot 4



Appendix E – TUMOR RESPONSE WORKSHEET (RECIST v1.1)

Target Lesions

TARGET Lesions	Lesion	Site	Nodal/Non-nodal *(measure shortest diameter for nodal)*	Imaging *(ie,CT, MRI)*	Baseline Date:	Cycle_____ Date:	Cycle_____ Date:	Cycle_____ Date:	Cycle_____ Date:	Cycle_____ Date:
	01				mm	mm	mm	mm	mm	mm
	02				mm	mm	mm	mm	mm	mm
	03				mm	mm	mm	mm	mm	mm
	04				mm	mm	mm	mm	mm	mm
	05				mm	mm	mm	mm	mm	mm
	Sum of Diameters				mm	mm	mm	mm	mm	mm
	% Change (% Δ) from Baseline or Nadir* & absolute value (AbV)				NA / NA	% Δ / AbV				
	Target Lesion Response				**N/A**					

Non-Target Lesions

NON-TARGET Lesions	Lesion	Site	Nodal/Non-nodal	Imaging	Baseline	Cycle_____	Cycle_____	Cycle_____	Cycle_____	Cycle_____
	01									
	02									
	03									
	04									
	05									
	06									
	07									
	08									
	09									
	10									
	Non-Target Lesion Response				**N/A**					

New Lesions

New										
	1				**N/A**					
	2				**N/A**					
	3				**N/A**					

Overall Tumor Response		Cycle___	Cycle___	Cycle___	Cycle___	Cycle___
Radiologist Signature:						
Treating Physician Signature:						
PI Signature:						

***Terms & Calculations**

Baseline: *The set of data collected prior to randomization*

Nadir: *The lowest point*

$$\frac{\text{Current SLD} - \text{Baseline or Nadir SLD}}{\text{Baseline or Nadir SLD}} \times 100\%$$

WEEK / CYCLE #	INVESTIGATOR PRINTED NAME	INVESTIGATOR SIGNATURE	DATE

TARGET AND NON-TARGET LESIONS

TARGET LESION	NON-TARGET LESION	NEW LESION	OVERALL RESPONSE
CR	CR	NO	CR
CR	NON-CR/NON-PD	NO	PR
CR	NOT EVALUATED	NO	PR
PR	NON-PD OR NOT ALL EVALUATED	NO	PR
SD	NON-PD OR NOT ALL EVALUATED	NO	SD
NOT ALL EVALUATED	NON-PD	NO	NE
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD

ANY	**ANY**	**YES**	**PD**

Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	**No**	**CR**
Non-CR/Non-PD	**No**	**Non-Cr/Non-PD**
Not All Evaluated	**No**	**NE**
Unequivocal PD	**Yes or No**	**PD**
Any	**Any**	**PD**

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evluated

Target Lesion Timepoint Assessment

Target Lesion Response	Definition
Complete Response (CR)	**Disappearance of all target lesions. Pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm**
Partial Response (PR)	**At least a 30% decrease in sum of diameters, taking as reference the baseline sum diameters**
Progressive Disease (PD)	**At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study based on all target lesions recorded since the treatment started. The sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)**
Stable Disease (SD)	**Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference smallest sum diameters while on study**
Not Evaluated (NE)	**Any target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point**
Not Applicable (NA)	**No target lesions were identified at baseline**

Non-Target Lesions Timepoint Assessment

Non-Target Lesion Response	Definition
Complete Response (CR)	**Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)**
Non-Complete Response/Non-	**Persistence of one or more non-target lesions not qualifying for**

Progressive Disease	**either CR or PD**
Progressive Disease (PD)	**Unequivocal progression of existing non-target lesions.** • **subjects with measurable non-target disease – Substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** • **subjects with non-measurable disease – Increase in overall tumor burden comparable in magnitude to the increase required to declare PD for measurable disease.**
Not Evaluable (NE)	**Any non-target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine status**
Not Applicable (NA)	**No non-target lesions identified at baseline**

Appendix F – Baseline Data Collection Form

Date of visit _ _/_ _/_ _

1. Oncologic history

   a. Most immediate prior cancer therapy (select one):
   ☐ chemotherapy ☐ radiation ☐ surgery ☐ hormone ☐ other: _____

   b. Specify most immediate prior cancer therapy: _____

   Dates of administration: Started: __ __ / __ __ / __ __ Stopped: __ __ / __ __ / __ __

   Dose _____ & total # of treatments _____

   c. Other prior cancer therapies (excluding 1b.) for most recent cancer. Mark all that apply:
   ☐ None ☐ Chemotherapy ☐ Radiation ☐ Surgery ☐ Hormone therapy ☐ Other: _____

Regimen Name	Total # of Treatments	Date of Last Treatment
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

Site of RT	Total Dose in Gy	Date of Last Treatment
1.		
2.		
3.		
4.		
5.		

Type of surgery	Date of surgery
1.	
2.	

Hormone Therapy Name	Dose	Date of Last Treatment
1.		
2.		

Other	Dose	Date of Last Treatment
1.		
2.		

2. Date of baseline imaging: __ __ / __ __ / __ __

   Sites of disease: _____

   Imaging modality: ☐ CT scan ☐ PET scan ☐MRI scan ☐ Bone scan ☐Other, specify _____

3. Medical history (check all that apply):
   - ☐ Myocardial infarction
   - ☐ Congestive heart failure
   - ☐ Peripheral vascular disease (claudication, arterial bypass, untreated aneurysm (≥6cm)
   - ☐ Cerebrovascular disease (history of TIA or CVA)
   - ☐ Dementia
   - ☐ Chronic pulmonary disease (with symptomatic dyspnea)
   - ☐ Connective tissue disease (SLE, polymyositis, mixed CTD, polymyalgia rueumatic, moterate to severe RA)
   - ☐ Peptic ulcer disease (bleeding ulcer)
   - ☐ Liver disease (on treatment, cirrhosis without portal hypertension, chronic hepatitis); check here if mild ☐
   - ☐ Diabetes
     end organ damage? Yes ☐ No ☐
   - ☐ Hemiplegia
   - ☐ Leukemia
   - ☐ Lymphoma
   - ☐ AIDS
   - ☐ Other major medical condition; specify _____

4. Concurrent medications and supplements

a. List all prescription and over-the-counter medications (includes prescription supplements)

Medication Name	Is it PRN?	Medication Name	Is it PRN?
1.	yes no	11.	yes no
2.	yes no	12.	yes no
3.	yes no	13.	yes no
4.	yes no	14.	yes no
5.	yes no	15.	yes no
6.	yes no	16.	yes no
7.	yes no	17.	yes no
8.	yes no	18.	yes no
9.	yes no	19.	yes no
10.	yes no	20.	yes no

b. List all supplements (excludes prescription supplements)

Supplement Name	Is it PRN?	Supplement Name	Is it PRN?
1.	yes no	11.	yes no
2.	yes no	12.	yes no
3.	yes no	13.	yes no
4.	yes no	14.	yes no
5.	yes no	15.	yes no
6.	yes no	16.	yes no
7.	yes no	17.	yes no
8.	yes no	18.	yes no
9.	yes no	19.	yes no
10.	yes no	20.	yes no

5. Physical exam:
   - Derm – ☐ WNL ☐ Abnormal, specify _____
   - HEENT – ☐ WNL ☐ Abnormal, specify _____
   - CV – ☐ WNL ☐ Abnormal, specify _____
   - Pulm – ☐ WNL ☐ Abnormal, specify _____
   - GI – ☐ WNL ☐ Abnormal, specify _____
   - Other – ☐ Abnormal, specify _____

6. Vital signs:
   - a. HR_____
   - b. BP____ /____
   - c. RR_____
   - d. Temp _____(°F)

e. Weight _____(kg) f. Height _____(cm)

7. ECOG Performance Status (check one):

GRADE	Description
☐ **0**	Fully active, able to carry on all pre-disease performance without restriction
☐ **1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
☐ **2**	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**	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
☐ **4**	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
☐ **5**	Dead

8. Documentation of negative pregnancy test for women of child-bearing potential?
   Yes ☐ No ☐, reason _____ Not applicable ☐

9. Blood Draws:

   a. CBC with Differential, Date drawn __ __ /__ __ / __ __

   b. Serum Chemistry, Date drawn __ __ /__ __ / __ __

   c. Urinalysis Date __ __ /__ __ / __ __

10. Metastatic tumor biopsy:
    a. Date __ __ /__ __ / __ __
    b. Site of biopsy:_____
11. Archival tumor tissue:
    a. Date __ __ /__ __ / __ __
    b. Site from which tissue obtained:_____

Appendix G – Follow-up Data Collection Forms

Follow-Up Visit: ☐Cycle 1 ☐Cycle 2 ☐Cycle 3 ☐Cycle 4 ☐Cycle 5 ☐Cycle 6 ☐Cycle 7 ☐Cycle 8 ☐End of Treatment ☐Follow-up

Date of Visit: __ __ / __ __ / __ __

1. Medical History ☐Medical Conditions, new from baseline (specify)_____
☐Hospitalizations since last visit (specify)_____

2. Concurrent medications and supplements
a. List all prescription and over-the-counter medications (includes prescription supplements).

Medication Name	Is it PRN?	Medication Name	Is it PRN?
1.	yes no	11.	yes no
2.	yes no	12.	yes no
3.	yes no	13.	yes no
4.	yes no	14.	yes no
5.	yes no	15.	yes no
6.	yes no	16.	yes no
7.	yes no	17.	yes no
8.	yes no	18.	yes no
9.	yes no	19.	yes no
10.	yes no	20.	yes no

b. List all supplements (excludes prescription supplements).

Supplement Name	Is it PRN?	Supplement Name	Is it PRN?
1.	yes no	11.	yes no
2.	yes no	12.	yes no
3.	yes no	13.	yes no
4.	yes no	14.	yes no
5.	yes no	15.	yes no
6.	yes no	16.	yes no
7.	yes no	17.	yes no
8.	yes no	18.	yes no
9.	yes no	19.	yes no
10.	yes no	20.	yes no

3. Physical exam:
Derm – ☐ WNL ☐ Abnormal, specify _____
HEENT – ☐ WNL ☐ Abnormal, specify _____
CV – ☐ WNL ☐ Abnormal, specify _____
Pulm – ☐ WNL ☐ Abnormal, specify _____
GI – ☐ WNL ☐ Abnormal, specify _____
Other – ☐ Abnormal, specify _____

4. Vital signs:
g. HR_____
h. BP____ /____
i. RR _____
j. Temp _____(°F)
k. Weight _____(kg)
l. Height _____(cm)

5. ECOG Performance Status (check one):

GRADE	Description
☐ **0**	Fully active, able to carry on all pre-disease performance without restriction
☐ **1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
☐ **2**	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**	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
☐ **4**	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
☐ **5**	Dead

6. Documentation of negative pregnancy test for women of child-bearing potential?
   Yes ☐ No ☐, reason _____ Not applicable ☐

7. Blood Draws

   a. CBC with Differential, Date drawn __ __ /__ __ / __ __

   b. Serum Chemistry, Date drawn __ __ /__ __ / __ __

   c. Urinalysis Date __ __ /__ __ / __ __

Appendix H – Treatment Response Evaluation

Overall Response Rate is the primary objective for this study. Patients will be evaluated with imaging at baseline, every 9 weeks (+/-7days), and end of treatment. At the end of treatment, if no progression, patients will be evaluated with imaging every 3 months (+/-10 days) for 1 year.
Study Visit:

- ☐ Week 9 (± 7 days)
- ☐ Week 18 (± 7 days)
- ☐ Week 27 (± 7 days)
- ☐ Week 36 (± 14 days)
- ☐ End of Treatment
- ☐ 3 months (± 10 days) post Treatment
- ☐ 6 months (± 10 days) post Treatment
- ☐ 9 months (± 10 days) post Treatment
- ☐ 12 months (± 10 days) post Treatment
- ☐ Other visit: (please specify) _____

Date of Scan: ___ ___ /___ ___ /___ ___

Imaging Modality: ☐ CT ☐ PET/CT ☐ MRI ☐ Other_____

Evaluation of imaging per clinical review– measurable disease

☐ Complete Response (CR)

☐ Partial Response (PR)

☐ Progressive Disease (PD): Date of progression ___ ___ /___ ___ /___ ___

☐ Stable Disease (SD)

☐ N/A

Evaluation of non-measurable disease (e.g., pleural effusion)

☐ Complete Response (CR)

☐ Non-CR/Non-PD

☐ Progressive Disease (PD): Date of progression ___ ___ /___ ___ /___ ___

☐ N/A

Treating Physician Signature: _____ Date: ___ ___ /___ ___ /___ ___

PI Signature: _____ Date: ___ ___ /___ ___ /___ ___

Appendix I – Adverse Event Log

WFBCCC Adverse Event (AE) Log

PI: _____ Subject PID: _____ MRN: _____
Cycle #: Cycle Start Date: Cycle Start Time: Cycle End Date: Cycle End Time:

Adverse Event CTC Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**Attribution** DEF= Definite PROB= Probable POSS= Possible UNLK= Unlikely UNRL= Unrelated	**Treating MD Initials + Date**	**End Date**	**Expected** N= No Y= Yes	***Serious Adverse Event Detail:** NO= No LT= Life Threatening DTH= Death DIS= Disability HOS= Hospitalization CA= Caused congenital anomaly RI= Required intervention to prevent impairment	**Dose Limiting Toxicity (DLT)** N= No Y= Yes	**Action Taken** NO= None DR= Dose Reduced RI= Regimen Interrupted TD= Therapy discontinued INTR= Interrupted then reduced	**Therapy Given** NO= None SYM= Symptomatic SUP= Supportive VSUP= Vigorous Supportive	**Reportable?** IRB= IRB STRC= STRC FDA= FDA SPON= Sponsor (Mark all that apply)	**Adverse Event Report (AER) filed?** N= No Y= Yes	**Outcome** R= Recovered TX= Still under treatment or observation A= Alive with Sequalae D= Died

*Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

STRC = Safety and Toxicity Review Committee

Version 10/30/17