Immune response in patients with recurrent or metastatic non-small cell lung cancer and performance status of 2 treated with a combination of pembrolizumab and low dose weekly carboplatin/paclitaxel

Comprehensive Cancer Center of Wake Forest University (CCCWFU)

CCCWFU # 62415

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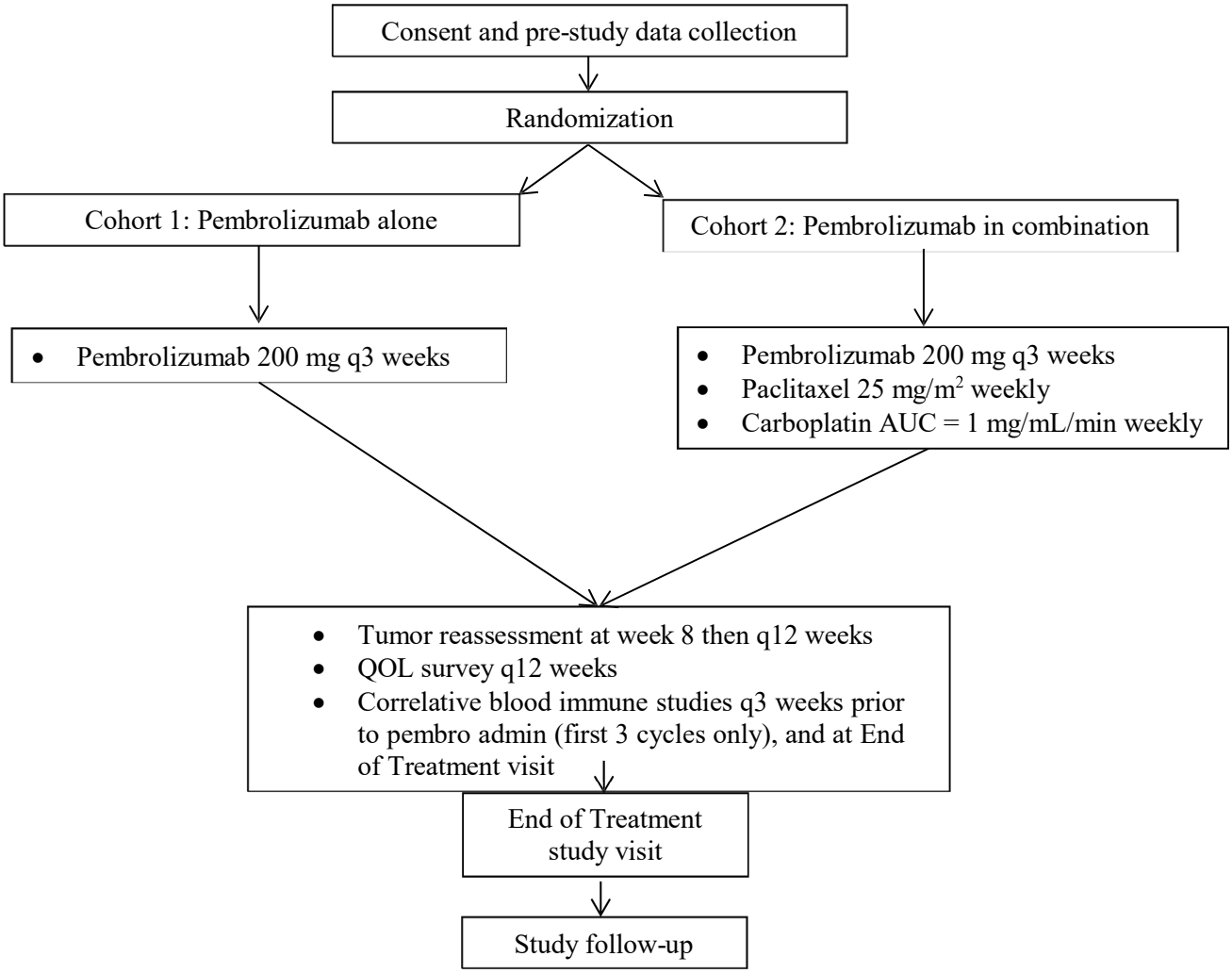
SCHEMA


Consent and pre-study data collection
Randomization
Cohort 1: Pembrolizumab alone
Cohort 2: Pembrolizumab in combination
• Pembrolizumab 200 mg q3 weeks
• Pembrolizumab 200 mg q3 weeks
• Paclitaxel 25 mg/m2 weekly
• Carboplatin AUC = 1 mg/mL/min weekly
• Tumor reassessment at week 8 then q12 weeks
• QOL survey q12 weeks
• Correlative blood immune studies q3 weeks prior to pembro admin (first 3 cycles only), and at End of Treatment visit
End of Treatment study visit
Study follow-up

1.1 Introduction and Background

1.2 Recurrent or metastatic non-small cell lung cancer and performance status of 2

Lung cancer is the leading cause of cancer-related death worldwide. Most patients with advanced non-small cell lung cancer (NSCLC) are candidates for chemotherapy, and first-line platinum-based combination chemotherapy is associated with an overall response rate of 30%, median progression-free survival of 4 months, and median overall survival of 8–11 months for patients with good performance status (PS).[1] The strongest predictor of survival in patients with advanced NSCLC is PS (Appendix Q).[2] It measures the impact of tumor symptoms, together with other preexisting medical problems and comorbidities, on a patient's ability to function daily and for self-care. Although combination chemotherapy has been shown to be beneficial for patients with good PS, PS 0 or 1, there is still debate about its efficacy for patients with a PS of 2, patients who are ambulatory, capable of all self-care, up and about more than 50% of waking hours, but unable to carry out any work.[1,3] PS 2 patients account for up to 30% of patients with advanced NSCLC, and no treatment is widely accepted as standard.[4] Toxicity is the major concern when prescribing chemotherapy in PS 2 patients, but data are conflicting.[5] It was recently shown that in patients with stage IV NSCLC receiving palliative chemotherapy, the median progression free survival was 1.5 to 2.5 months with a median overall survival between 2 to 4 months.[6] These results were not affected by patient age. Interestingly, patients with PS 2 that need to discontinue chemotherapy after first dose due to severe toxicity have a median survival of 2.5 months and a one year survival of only 5%.[7] The overall response rate (RR) on this specific patient population seems to be within the single digits (0 to 10%).[8] In addition to poor response and survival outcomes, many palliative treatments may cause substantial toxicity. In summary, metastatic NSCLC with PS 2 represents a population with a large unmet need for new treatment options in the palliative setting.[9]

1.3 Immunotherapies

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.
The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. As of August, 2016, Keytruda ™ has been approved for the treatment of Head and Neck Cancer, and most recently, as of October 2016, for the treatment of Non-Small Cell Lung Cancer.

1.3.1 Immunotherapies alone

Programmed cell death protein 1, also known as PD-1, is a 288 amino acid cell surface protein molecule. PD-1 has two ligands, PD-L1 and PD-L2, which are members of the B7 family. Several lines of evidence suggest that PD-1 and its ligands negatively regulate immune responses. Different studies have shown that the cancer microenvironment manipulates the PD-L1/PD-1 pathway and that the induction of PD-L1 expression on tumor cells leads to the inhibition of immune responses against cancer, permitting cancer progression and metastasis.[10] In a murine mechanistic experiment, it was shown that the induction of PD-L1 in melanoma microenvironment is mediated by IFN-y produced by the T cells that are antigen experienced and therefore express PD-1.[11]

In tumor cells, PD-L1 expression may range from 45 to 50% in NSCLC biopsies, irrespective of histology.[12] The evidence that PD-L1 is commonly up-regulated in NSCLC and that PD-1 is expressed on the majority of tumor infiltrating lymphocytes, represented the rationale for the development of monoclonal antibodies against PD-L1 or PD-1, and several agents are currently under investigation.[12,13] It has been shown recently, that the anti PD-1 monoclonal antibody nivolumab improves overall survival compared to single agent docetaxel in patients with metastatic NSCLC progressed to platinum-based chemotherapy and squamous histology. It is important to note that only patients with good performance status were allowed to participate in this trial; thus there is no data on the toxicity/efficacy profile of PD-1 check point inhibitors in patients with metastatic lung cancer and poor PS. The overall response rate to the PD-1 inhibitors nivolumab and pembrolizumab in patients with metastatic NSCLC (all comers) is 15 to 20%.[14] The KEYNOTE-001 study that assessed the efficacy and safety of pembrolizumab in patients with advanced NSCLC showed that among all the patients, the objective response rate was 19.4%, and the median duration of response was 12.5 months.[23] The ORR in patients with PS 2 is not known but expected to be lower. Clearly new strategies are needed to improve the RR of patients with metastatic NSCLC and poor PS to the immune checkpoints inhibitors.

1.3.2 Immunotherapies in combination

Immune suppression mediated by myeloid derived suppressor cells (MDSC) and regulatory T (Treg) cells characterizes patients with advanced NSCLC and poor PS. Increases in these immune suppressor cells are also correlated with poor response to chemotherapy. Inhibiting PD-1 receptor/ligand interactions can abrogate the suppressive effects of MDSC and Treg cells but only partially.[15] Several studies have shown that low-dose chemotherapy with taxanes and platinum compounds, alone

and in combination, can reduce MDSC and Treg cells and modify the tumor microenvironment to promote immunogenic tumor death.[16-18] Low-dose carboplatin and paclitaxel have been shown to enhance the antitumor activity of anti-PD-1 antibody in mouse models of ovarian and lung cancer.[19] There is evidence that reductions in MDSC and Treg cells are involved.[20] That antitumor immune responses can be promoted clinically with this approach was suggested by the observation that disease control was associated with increases in interferon-γ and interleukin-2 in patients with refractory ovarian cancer treated with low-dose carboplatin and paclitaxel.[17]

We have examined the combination of weekly low-dose carboplatin and paclitaxel in combination with the anti-EGFR antibody, cetuximab, and have observed remarkable tumor responses and excellent tolerability in patient with advanced head and neck cancer and a PS of 2 (data not published). The ability of taxanes and platinum compounds in non-cytotoxic doses to block the immune-suppressive potential of MDSC and Treg cells represents a new therapeutic strategy for enhancing the efficacy of concomitant anti-PD-1 immunotherapy with pembrolizumab in lung cancer patients.[19] The effects of pembrolizumab, alone or in combination with chemotherapy, on immune regulatory mechanisms in cancer patients with a poor PS, in general, and in patients with the highly immune-suppressive NSCLC, in specific, are not known. A clinical trial will be performed to examine these mechanisms. This trial may lead to improved therapy for patients with NSCLC as well as other advanced cancers with a poor PS. It may also lead to biomarkers of response as well as suggest specific interventions that can be applied to improve antitumor immunologic activity.

1.4 Study Rationale

There remains a significant unmet medical need for additional treatment options for patients with recurrent or metastatic NSCLC and PS of 2. Chang et al., demonstrated on a mice model of ovarian cancer that with the use of dose-dense cisplatin+paclitaxel there is an increase immune response based on an increase number of IFN-γ-secreting CD14+F4/80+ macrophage and subsequent D8+IFN-γ+tumor-infiltrating lymphocytes.(17) We have examined a similar dose dense regimen based on the combination of low dose weekly carboplatin and paclitaxel in combination with the anti-EGFR antibody, cetuximab, and have observed remarkable tumor responses and excellent tolerability in patient with advanced head and neck small cell carcinoma (HNSCC) and poor PS. At our institution, we treated 20 patients with this regimen of weekly cetuximab and carboplatin AUC of 1 and paclitaxel 25 mg m^2. Twelve patients experienced partial response (60%). The median survival was 8 months for the entire cohort and 12 months for the responders (data not published). This preliminary data with a different monoclonal antibody combined with low-dose chemotherapy on a similar tumor model, encouraged us to move forward with the study of the same chemotherapy

combination and the monoclonal antibody pembrolizumab on patient with NSCLC.

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypotheses under evaluation, the treatment proposed for evaluation in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating higher rate and durable clinical responses, thereby improving quality of life (QOL) and potentially extending survival. Therefore, the investigation of the immune-modulatory effects of the combination of pembrolizumab with low dose carboplatin and paclitaxel in this patient population is acceptable and the benefit/risk assessment for this study is favorable per the proposed study design.

2.1 Objectives

2.2 Primary Objectives

2.2.1 Determine the immune effects of single agent pembrolizumab and pembrolizumab combined with low-dose carboplatin and paclitaxel

2.2.2 Estimate the treatment response to single agent pembrolizumab and pembrolizumab combined with low-dose carboplatin and paclitaxel

2.3 Secondary Objectives

2.3.1 Determine the toxicity and tolerability of pembrolizumab and pembrolizumab combined with low-dose carboplatin and paclitaxel

2.3.2 Assess QOL in patients receiving single agent pembrolizumab and pembrolizumab combined with carboplatin and paclitaxel

2.3.3 Assess the association between immune response and clinical response

3.1 Patient Selection

3.2 Inclusion Criteria

3.2.1 Patients must have histologically or cytologically confirmed NSCLC that is advanced/metastatic (stage IIIb/IV) or recurrent (progression after surgery or radiation or chemo-radiation treatment for loco-regional disease). Patients with epidermal growth factor (EGFR) mutation, anaplastic lymphoma kinase

(ALK) gene rearrangement or ROS1 translocation must have received an approved EGFR, ALK, or ROS1-directed therapy and have signs of disease progression prior to receiving pembrolizumab.

3.2.2 Patients 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 12 weeks (84 days) prior to date of signing consent.

Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen (up to 3 years) *only* upon agreement from the Sponsor. At least 4 mm of tumor tissue will be needed for PD-L1 staining.

3.2.3 Patients who have received zero (0) to two (2) previous lines of systemic chemotherapy and are *not currently* receiving chemotherapy treatment (within 2 weeks of randomization).

3.2.4 At least one measurable lesion as defined by RECIST v1.1 on screening computed tomography (CT) or magnetic resonance imaging (MRI)

3.2.5 Age ≥18 years.

3.2.6 ECOG performance status of 2.

3.2.7 Patients must have normal organ and marrow function as defined below:

-	white blood cell count	> 2,500 cells/mcL
-	absolute neutrophil count	≥1,500/mcL
-	platelets	≥100,000/mcL
-	hemoglobin	≥ 9 g/dL
-	total bilirubin	≤ 2.0 x upper limit of normal (ULN)
-	AST(SGOT)/ALT(SGPT)	≤ 2.5 x ULN Or ≤ 5 x ULN in presence of liver metastases
-	creatinine	within normal institutional limits
	OR	
-	creatinine clearance	> 50 mL/min for patients with creatinine levels above institutional normal
-	potassium	≥ lower limit of normal

3.2.8 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for 4 weeks after the final administration of study drugs. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

3.3 Exclusion Criteria

3.3.1 Known active (untreated) central nervous system (CNS) metastases that require steroids. Subjects with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for at least 2 weeks before study entry, defined as:

- No evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases.
- Asymptomatic and receiving either no or stable doses of anticonvulsants and total doses of corticosteroids equivalent to 10 mg of prednisone or less.

3.3.2 Current or previous other malignancy within 2 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy without sponsor approval.

3.3.3 History of previous exposure to an anti PD1/PD-L1 agent

3.3.4 Patients receiving any other investigational agents and or more than two different chemotherapy regimens for treatment of metastatic disease.

3.3.5 Has had prior 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.

3.3.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab, paclitaxel or carboplatin.

3.3.7 Current uncontrolled cardiac disease such as angina or myocardial infarction, congestive heart failure including New York Heart Association functional classification of 3, or arrhythmia requiring treatment.

3.3.8 History of pneumonitis or active lung infection.

3.3.9 Chronic or current active infectious disease requiring systemic antibiotics, antifungals, or antivirals.

3.3.10 Patients receiving chronic steroids and or immunosuppression.

3.3.11 Known HIV infection, Hepatitis B virus (HBV) or hepatitis C virus (HCV) viremia or at risk for HBV reactivation. HBV DNA and testing for HCV RNA must be undetectable. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti-hepatitis B core antibody positive.

3.3.12 History of autoimmune disease(s).

3.3.13 Psychiatric illness/social situations that would limit compliance with study requirements.

3.3.14 Any other condition or circumstance that could interfere with adherence to the study's procedures or requirements, or otherwise compromise the study's objectives such as history of, or any evidence of active, non-infectious pneumonitis.

3.3.15 Has an active infection requiring systemic therapy.

3.3.16 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants, breastfeeding should be discontinued prior to study entry.

3.4 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. Based on CCCWFU population estimates, we expect approximately 40% of participants to be women. Translating this to our sample size estimate of 40, we plan to enroll at least 16 women. We do not expect the percentage of Hispanic/Latino or racial minority lung cancer patients to be higher than the percentage of Hispanic or racial minority new cancer patients seen at CCCWFU (1.7% and 14.4%, respectively); similar to the percentage of newly diagnosed cancer patients, we plan to enroll at least 14% (5) racial minority patients. While we do not expect higher percentages than that of Hispanic/Latino newly diagnosed cancer patients (1.7%), we plan to enroll at least one Hispanic/Latino patient.

4.1 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
- randomize the patient
- register the patient on the study

5.1 Study Outcomes and Study Measures

5.2 Primary Outcomes

5.2.1 Immune effects of single agent pembrolizumab and pembrolizumab combined with carboplatin and paclitaxel.

5.2.2 Objective response rate, duration of best response, disease control rate, and duration of disease control, as defined by section 8.1.

5.3 Secondary Outcomes

5.3.1 Toxicity and tolerability, as assessed by CTCAE version 4.0.

5.3.2 QOL, as assessed by EORTC QLQ-30 and EORTC QLQ-LC13 questionnaires.

5.3.3 Associations between change in immune markers and treatment response (irCR, irPR, irSD, irPD)

6.1 Treatment Plan

The proposed study is a randomized, two arm parallel assignment, open label, phase II, basic science study. The study consists of screening (≤ 14 days), subsequent treatment (until disease progression or treatment intolerance), and long-term follow-up. The enrollment period of the study is expected to be approximately 18 months. Enrollment in the study will end when 40 subjects have been randomized and have received at least one dose of therapy. The duration of participation will vary among individual subjects due to factors such as disease progression and time of enrollment. However, patients will receive active therapy up to two years if clinically indicated. Whenever possible, enrolled subjects should complete the study per protocol. However, individual subjects may withdraw from the study prematurely at any time, (e.g., subject decides to discontinue participation due to an adverse event). Subjects who are noncompliant with the study's requirements may also be removed from the study at any time by the investigator.

6.2 Study-Related Activities

After providing written informed consent, subjects will be screened for eligibility within 14 days of randomization (28 days for CT or PET/CT and 42 days for MRI) (Appendices A, B, and F). Qualified subjects will be staged by a CT chest/abdomen or CT portion of a PET/CT, and a brain MRI at baseline (Appendix E).

Qualified subjects will be randomized 1:1 ratio to receive single agent pembrolizumab every three weeks or the combination of pembrolizumab every three weeks and low dose carboplatin and paclitaxel given on a weekly schedule. Randomization of all subjects will be stratified by receipt of prior systemic chemotherapy for recurrent metastatic disease (yes or no) and histology (squamous vs. non squamous).

Target and non-target lesions will be followed by CT or MRI for PFS according to immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) at Week 8 (± 3 days), and every 12 weeks (± 7 days) thereafter (Appendix E). If there is suspicion of tumor progression at eight weeks, a second CT/MRI study four weeks after will need to be done as a confirmatory test (Appendix E). Treatment will be discontinued for subjects with confirmed radiographic disease progression. Upon discontinuation of treatment, subjects will complete the End of Treatment visit (Appendix G) and will be followed for survival (Appendix H).

	Pre-Study [a]	**Prior to Each Pembrolizumab Treatment** [b]	**Week 8(± 3 days), then every 12 weeks (± 7 days)**	**Every 12 weeks**	**Week 20 (± 3 days), then every 8 weeks (± 7 days)**	**End of Treatment visit** [c]	**Follow-up**
Informed consent	X						
Demographics	X						
Medical history[d]	X						
Concurrent meds	X	X				X	
Physical exam	X	X				X	
Vital signs[e]	X	X				X	
Height (Pre-Study and EOT only), Weight, M^2	X	X				X	
ECOG Performance Status	X	X				X	
Tumor measurements[f]	X		X			X[g]	
CBC w/diff, platelets	X	X				X	
Serum chemistry[h]	X	X				X	
B-HCG[i]	X						
TSH, T3, T4	X	X[j]					
Urinalysis	X	X				X	
Tumor biopsy[k]	X						
Tumor correlative studies[l]	X						
Blood correlative studies[m]		X[n]				X	
Quality of Life questionnaires[o]	X			X			
Adverse event evaluation	X	X	X	X	X	X	X

[a] Pre-study requirements listed in table must be completed **within 14 days** prior to randomization (**28 days for CT** or PET/CT and **42 days for MRI**). Tumor correlative studies report (Appendix M) can be obtained **within 28 days** of randomization.
[b] Appendix G.
[c] if not completed within the previous 14 days, and prior to initiation of other anti-cancer therapy. See Appendix G.

[d] Including history of prior anticancer interventions and histological or cytological confirmation of NSLC.
[e] temperature, T; blood pressure, BP; respiration rate, RR; heart rate, HR.
[f] Appendix E. Qualified subjects will be staged by a CT chest/abdomen or CT portion of a PET/CT (within 28 days of randomization, and a brain MRI (within 42 days prior to randomization).
[g] for subjects who have not had an imaging study within the previous 4 weeks.
[h] total bilirubin, BUN, creatinine, creatinine clearance, potassium, SGOT[AST], SGPT[ALT].
[i] Serum pregnancy test (women of childbearing potential).
[j] Prior to each infusion of pembrolizumab only.
[k] A fresh tumor tissue sample should be collected prior to enrollment for patients. See Inclusion Criteria 3.1.2 for additional information.
[l] Appendix M.
[m] Section 11.2 and Appendix N.
[n] prior to receiving the first dose of pembrolizumab treatment (C1D1), and on C2D1 and C3D1 prior to pembrolizumab treatment administration. Twenty (20) ml of blood is to be collected in two EDTA-containing vacutainers and sent to Dr. Triozzi's laboratory, Room 5029, Hanes Building.
[o] Appendices I – L.

6.3 Treatment Administration

Treatment can be administered on an inpatient or outpatient basis. Reported adverse events and potential risks are described in Section 9.0. Appropriate dose modifications for are described in Section 7.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Patients will receive active therapy up to two years if clinically indicated.

REGIMEN DESCRIPTION

Agent	Dose	Route	Schedule	Cycle Length
Cohort 1				
Pembrolizumab	200 mg	30 minute intravenous infusion	Day 1	3 weeks
Cohort 2				
Pembrolizumab	200 mg	30 minute intravenous infusion at least 1 hour prior to administration of paclitaxel and carboplatin	Day 1	3 weeks
Paclitaxel	25 mg/m^2	1 hour intravenous infusion beginning at least 1 hour after the completion of pembroluzumab	Days 1, 8 and 15	
Carboplatin	AUC = 1 mg/mL/min	1 hour intravenous infusion following completion of paclitaxel	Days 1, 8 and 15 for 4 cycles (12 weeks)	

6.3.1 Pembrolizumab treatment

Pembrolizumab will be given every three weeks with a dose of 200 mg on Cycle 1 Day 1 (C1D1) and every three weeks thereafter. Patients will

receive active therapy up to two years if clinically indicated. The drug will be administered as a 30 minutes intravenous (IV) infusion.

6.3.2 Paclitaxel treatment

Subjects assigned to the combination therapy will receive Paclitaxel 25 mg/m^2 as a 1 hour infusion on C1D1 and then weekly. Paclitaxel administration should begin ≥ 1 hour following completion of Pembrolizumab administration. Patients will receive active therapy up to two years if clinically indicated

6.3.3 Carboplatin treatment

Subjects assigned to the combination therapy will receive Carboplatin at an AUC of 1 mg/mL/min as a 1 hour infusion on C1D1 and then weekly. Carboplatin administration should begin following completion of Paclitaxel administration. The carboplatin dose will be based upon the subject's screening glomerular filtration rate (GFR) in mL/min. The Calvert formula will be used for carboplatin dosing:
Total Dose (mg) = (target AUC) x (GFR + 25). The carboplatin dose will be capped at 150 mg.
Patients will receive active therapy up to 12 weeks if clinically indicated

6.4 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable toxicity related to the administration of the study required medications,
- Patient lost to follow-up after repeated attempts to contact,
- Onset of an adverse event that would make ongoing treatment in the current clinical trial inadvisable, as deemed by the investigator, medical monitor, or

study sponsor (there will be no limit in the number of treatment cycles a patient can receive),
- Patient decides to withdraw from the study,
- Patient non-compliance with the study's requirements and/or procedures, as determined by the investigator, medical monitor, or study sponsor, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patient completed two years of therapy.

In the event a subject is withdrawn from treatment prematurely, the End of Treatment evaluations should be completed, and the subject should be followed for survival, if possible.

6.6 Duration of Follow Up

Patients will be followed for a minimum of 30 days after the last study drug is administered for adverse events monitoring.

Patients will be followed for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will be followed every 8 weeks until death for monitoring survival study endpoints, including vital status, disease state, and initiation of any new anticancer interventions (Appendix H).

7.1 Dosing Delays/Dose Modifications

In order to maintain dose-intensity and cumulative dose-delivery, reasonable efforts should be made to minimize dose reductions and treatment delays. Any subject whose treatment is delayed should be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met.

Toxicities may require the dose reduction of one or more of the study required medications. The investigator will carefully assess all treatment-associated toxicities and, whenever possible, determine if the toxicities can reasonably be attributed to a single agent or a causal relationship with one of the agents can reasonably be ruled out. If appropriate, dose reductions should not affect the dose of other products.

- Toxicity grades are defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0
- Any subject who requires a dose reduction due to drug-related toxicity will continue to receive the reduced dose for the remainder of study treatment
- Dose escalations are not allowed

7.2 Pembrolizumab dose modifications for immune-related adverse events

For the general management of immune-related adverse events due to pembrolizumab consider:

1) Patient evaluation to identify any alternative etiology.
2) In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
3) Symptomatic and topical therapy should be considered for low-grade events.
4) Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5) More potent immunosuppressives should be considered for events not responding to systemic steroids.

See table below for organ specific dose adjustments and management of pembrolizumab immune-related adverse effects.

Immune-related AE	Severity	Dose Modifications	Toxicity Management
Pneumonitis/ ILD	Any Grade		Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2 (Mild to Moderate New Symptoms) Monitor symptoms daily and consider hospitalization Discuss with study physician and consider systemic steroids (eg, prednisone 1-2mg/kg/day or IV equivalent Reimaging as clinically indicated If no improvement within 3 to 5 days, additional workup and treatment with IV methylprednisolone 2-4mg/kg/day should be considered If no improvement within 3 to 5 days, further immunosuppressive therapy (eg, infliximab) should be considered. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics Consider pulmonary and infectious disease consult

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening Discuss with study physician pulmonary and infectious disease consult Hospitalize the patient Supportive Care (oxygen, etc.) Initiate empiric IV corticosteroids (eg, methylprednisolone or equivalent) at 1 to 4 mg/kg/day If no improvement within 3 to 5 days, additional workup and treatment with additional immunosuppressive therapy (eg, infliximab) should be considered Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Diarrhea/ Enterocolitis	Any Grade		Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits) Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, etc.) Steroids should be considered if an alternative etiology is not determined, even for low grade events, in order to prevent potential progression to higher grade event Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1	No dose modification	For Grade 1: - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide If event is persistent (> 3 to 5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent If not responsive within 3 to 5 days, consider IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day If event is not responsive within 3 to 5 days or worsens, additional workup and treatment with IV methylprednisolone 2-4mg/kg/day should be considered If no improvement within 3 to 5 days, further immunosuppressives (eg, infliximab) should be considered Consult study physician if no resolution to Grade ≤1 in 3 to 4 days Once improving, gradually taper steroids over ≥4 weeks
	Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Discuss with study physician Monitor stool frequency and volume and maintain hydration Urgent GI consult and imaging as appropriate Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day If no improvement within 3 to 5 days, consider further immunosuppressives (eg, infliximab). Caution: Ensure GI consult to rule out bowel perforation and refer to label before using infliximab. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Hepatitis (Elevated LFTs)	Any Grade		Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications)
	Grade 1	No dose modification. If it worsens, treat as Grade 2 event	Continue LFT monitoring per protocol

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	Hold Study drug/study regimen dose until grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves to baseline then treat at next scheduled treatment date	Discuss with study physician if no resolution to Grade ≤1 in 1-2 days Recheck LFT's in 1 to 2 days. If event is persistent (> 3 to 5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent. If no improvement within 3 to 5 days, consider additional workup and treatment with IV methylprednisolone 2-4mg/kg/day If no improvement within 3 to 5 days, consider further immunosuppressives (eg, mycophenolate mofetil) Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 3	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN - Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline - Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue Study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria	For Grade 3 or 4: Discuss with the study physician Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day If no improvement within 3 to 5 days, consider further immunosuppressive therapy (eg, mycophenolate mofetil) If still no further improvement within 3 to 5 days consider other immunosuppressive therapy per local guidelines Hepatology consult, abdominal workup, and imaging as appropriate. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 4	Permanently discontinue study drug/study regimen	
Rash (excluding Bullous skin formations)	Any Grade		Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED**
	Grade 1		For Grade 1: Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume administration at next scheduled dose	For Grade 2 : - Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) - Consider moderate-strength topical steroid - If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening, discuss with study physician and consider systemic steroids prednisone 0.5 to 1 mg/kg/day or IV equivalent - Consider dermatology consult - Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: - Discuss with study physician - Consider hospitalization - Monitor extent of rash [Rule of Nines] - Consult dermatology - Consider skin biopsy (preferably more than 1) as clinically feasible. - Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day - Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade		Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections, etc.) Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 1	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) Monitor patient with appropriate endocrine function tests If TSH <0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 • If worsens then treat as Grade 3 or Grade 4 t • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: (including those with symptomatic endocrinopathy) Discuss with study physician Initiate hormone replacement as needed for management Evaluate endocrine function, and as clinically indicated, consider pituitary scan For subjects with abnormal endocrine work up, consider short-term, high-dose corticosteroids (eg, methylprednisolone or IV equivalent) with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones) For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3	Hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Resume study drug/study regimen administration if controlled at the next scheduled dose	For Grade 3 or 4: Discuss with study physician Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day Administer hormone replacement therapy as necessary
	Grade 4	Permanently discontinue study drug/study regimen	For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity Consult endocrinologist Once improving, gradually taper immunosuppressive steroids over ≥4 weeks
Immune mediated Neurotoxicity (except Myasthenia Gravis and Guillain-Barre)	Any Grade		- Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.) - Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) - Consider appropriate diagnostic testing (eg electromyogram and nerve conduction investigations) - Symptomatic treatment with neurological consult as appropriate

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 1	No modifications	
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1 For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens then treat as Grade 3 or Grade 4 If toxicity improves to baseline then treat at next scheduled treatment date	Discuss with the study physician Consider Neurology Consult Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) Consider systemic steroids prednisone 1-2mg/kg/day or IV equivalent at 0.5 to 1 mg/kg/day If no improvement within 3 to 5 days, consider additional workup and treatment with additional immunosuppressive therapy (eg IVIgG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to Grade ≤1 • Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days.	Discuss with study physician Consult Neurology Consult Consider hospitalization Consider empiric IV corticosteroids (eg, methylprednisolone or IV equivalent) at 1 to 2 mg/kg/day
	Grade 4	Permanently discontinue study drug/study regimen	If no improvement within 3 to 5 days, consider additional workup and treatment with additional immunosuppressants (eg IVIgG) Once stable, gradually taper steroids over ≥4 weeks

Immune-related AE	Severity	Dose Modifications	Toxicity Management
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis	Any Grade		The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapheresis (or IVIgG, as an alternative)
	Grade 1	No dose modification	Discuss with the study physician Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above Consider a neurology consult unless the symptoms are very minor and stable

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 : Moderate Discuss with the study physician Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above Obtain a Neurology Consult Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) MYASTHENIA GRAVIS Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIgG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
	Grade 3	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: Discuss with study physician Recommend hospitalization Monitor symptoms and obtain neurological consult MYASTHENIA GRAVIS

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 4	Permanently discontinue study drug/study regimen	Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. Subjects unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG. If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).

AChE acetylcholine esterase; AE Adverse event; ALP Alkaline phosphatase; ALT Alanine transaminase; AST Aspartate transaminase; CT Computed Tomography; GI Gastrointestinal; ILD Interstitial Lung Disease; IM Intramuscular; irAE immune-related adverse event; IV Intravenous; IVIgG Intravenous immunoglobulin G; LFT Liver function test; LLN Lower limit of normal; MRI Magnetic resonance imaging; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid stimulating hormone; ULN Upper limit of normal

7.3 Pembrolizumab dose modifications for non-immune-related adverse events

Dose modifications are not required for adverse events that are not deemed to be related to study treatment (ie events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.

Grade 1: No dose modification.

Grade 2: Hold Pembrolizumab dose until resolution to Grade ≤1 or baseline.

Grade 3: Hold Study Regimen until resolution to Grade ≤ 1 or baseline.

For adverse events that downgrade to Grade ≤ 2 within 7 days or resolve to Grade ≤1 or baseline within 14 days, resume Pembrolizumab administration at next scheduled dose. Otherwise, discontinue Pembrolizumab.

Grade 4: Discontinue Pembrolizumab

7.4 Management of infusion reactions related to Pembrolizumab

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. See table below for infusion reaction treatment guidelines.

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

7.5 Paclitaxel and carboplatin dose modifications

Grade ≥ 3 Toxicity	Chemotherapy Delay/Discontinuation	Outcome	Dose Modification
1st occurrence	Delay infusion by 1–2 weeks	Improvement	Reduce dose by 25%
		No improvement	Discontinue agent
2nd occurrence	Delay infusion by 1–2 weeks	Improvement	Reduce dose to 50%
		No improvement	Discontinue agent
3rd occurrence	Discontinue agent		

7.6 Chemotherapy-induced nausea and vomiting

Nausea and vomiting may be acute (onset 1–4 hours after infusion) or delayed (begins or persists ≥ 24 hours after infusion). To combat chemotherapy-induced nausea and vomiting, the following algorithm should be used:

a) Nonsteroidal anti-emetics, such as a 5-HT3 antagonist (e.g., ondansetron), should be utilized for first-line management of symptoms
b) If dexamethasone on Day 1 followed by nonsteroidal antiemetics on subsequent days does not sufficiently manage symptoms, dexamethasone 8 mg orally may be administered on Day 2 and/or Day 3.

8.1 Measurement of Effect

8.2 Antitumor Effect

Qualified subjects will be staged by a CT chest/abdomen or CT portion of a PET/CT, and a brain MRI at baseline (Appendix E). Target and non-target lesions will be followed by CT or MRI for PFS according to immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) at Week 8 (± 3 days), and every 12 weeks (± 7 days) thereafter (Appendix E). If there is suspicion of tumor progression at eight weeks, a second CT/MRI study four weeks after will need to be done as a confirmatory test.

8.2.1 Definitions

- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with pemetrexed
- 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.

8.2.2 Methods for Evaluation of Measurable Disease

Unscheduled evaluations may be done at the discretion of the investigator as needed to assess the subject's clinical status.

The imaging technique used for each subject (CT or MRI) is at the discretion of the investigator, but the same technique must be used for each individual subject throughout the study. Imaging should not be delayed in case of missed doses or dose delays.

8.2.3 Response Criteria - irRECIST

Total Measured Tumor Burden

The total measured tumor burden (TMTB) is established at baseline as the sum of the longest diameters (SOD)—the shortest axes should be used for lymph nodes—of all target lesions (≤ 2 lesions per organ, ≤ 5 lesions total). At each subsequent tumor assessment (TA), the SOD of new, measurable lesions (≥ 10 mm [lymph nodes ≥ 15 mm in shortest diameter]; ≤ 2 new lesions per organ, ≤ 5 new lesions total) is added to the SOD of the target lesions to provide the updated TMTB:

TMTB = SOD target lesions + SOD new, measurable lesions

Percentage changes in TMTB at each TA describe the size and growth kinetics of both old and new, measurable lesions as they appear. At each TA, the response in TMTB is defined as follows:

- Complete Response (irCR): Complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes which must decrease to < 10 mm in short axis
- Partial Response (irPR): Decrease in TMTB ≥ 30% relative to baseline

- Stable Disease (irSD): Not meeting criteria for irCR or irPR, in absence of irPD
- Progressive Disease (irPD): Increase in TMTB ≥ 20% relative to nadir

Response in Non-Target Lesions

The presence of non-target lesions is established at baseline; at each TA, the presence of any new, non-measurable lesions is assessed. The presence of new, non-measurable lesions will rule out an overall response of irCR. An increase in the size or number of new, non-measurable lesions does not necessarily imply an overall response of irPD; if these lesions become measurable (≥ 10 mm [lymph nodes ≥ 15 mm in shortest diameter]; up to 2 new lesions per organ, total 5 new lesions) at a subsequent TA, their measurement will, at that point, start to contribute to the TMTB.

The response in non-target lesions is defined as follows:

- Complete Response (irCR): Complete disappearance of all non-target lesions
- non-irCR/non-irPD: Non-target lesions do not meet the criteria for irCR or irPD
- Progressive Disease (irPD): Unequivocal increase in the number or size of non-target lesions. To achieve unequivocal progression of non-target lesions, there must be a substantial worsening of non-target disease of a magnitude that, according to the treating physician, warrants a change in anticancer therapy
  NOTE: Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD and treatment may continue until the next scheduled assessment.

Overall Response

The overall response according to irRECIST is derived from the responses in TMTB as well as the presence of any non-target lesions as follows:

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

8.2.4 Assessment for efficacy

The following efficacy parameters will be assessed by independent radiology review according to irRECIST, and are defined as follows:

Objective response rate: the proportion of subjects who achieve complete or partial response

Duration of best response: the duration of time from the date measurement criteria are first met for irCR, or irPR (if irCR is never met), until the first date that irPD is confirmed by independent radiology review or death, whichever comes first

Disease control rate: the percentage of subjects who achieved irCR, irPR, or irSD

Duration of disease control: the duration of time from the date measurement criteria are first met for irCR, irPR, or irSD, until the first date that irPD is confirmed by independent radiology review or death, whichever comes first

8.2.5 Survival Outcomes

Progression-free survival: the duration of time from randomization to the time of irPD or death, whichever comes first.

Overall survival is defined as the duration of time from randomization to the time of death due to any cause, or the date the subject was last confirmed to be alive.

9.1 Adverse Events List and Reporting Requirements

9.2 Adverse Event Lists

Pembrolizumab: Most common adverse reactions (reported in ≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. The most frequent serious adverse drug reactions reported in 2% or more of patients were renal failure, dyspnea, pneumonia, and cellulitis.

Paclitaxel: The most common adverse reactions (incidence ≥25%) include neutropenia, leukopenia, anemia, infections, hypersensitivity reactions, abnormal ECG, peripheral neuropathy, myalgia/arthralgia, nausea/vomiting, diarrhea, mucositis, and alopecia.

Carboplatin: Bone marrow suppression is the dose-limiting toxicity of Carboplatin. The most common adverse reactions (incidence ≥20%) during therapy with carboplatin as a single agent were thrombocytopenia, neutropenia, leukopenia,

anemia, nausea/vomiting, blood urea elevation, alkaline phosphatase elevation, electrolyte depletion, and pain.

9.3 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 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 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.

9.4 DSMC SAE Reporting Requirements

The Date and Safety Monitoring Committee is responsible for reviewing SAEs for WFBCCC Institutional studies are outlined in Appendix D. All Adverse Events that occur during protocol intervention 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 DSMC using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.5 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.

9.6 Sponsor Reporting Requirements

9.5.1 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

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. 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.

9.5.2 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 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.

1. Additional adverse events:

A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in Appendix O and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

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.

9.5.3 Sponsor Responsibility for Reporting Adverse Events

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

10.1 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.

10.2 Pharmaceutical Accountability

Pembrolizumab, paclitaxel and carboplatin are commercially available.

10.3 KEYTRUDA (pembrolizumab)

Product description: Include the available dosage forms, ingredients, and packaging, as appropriate. Also state the agent's supplier.

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.

Solution preparation:
Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).

- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage requirements:

Do not freeze. The product does not contain a preservative. Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Stability: Include the stability of the original dosage form, reconstituted solution, and final diluted product, as applicable.

Route of administration: Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line.

Disposal: To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel. If paclitaxel contacts the skin, immediately wash the skin thoroughly with soap and water. If paclitaxel contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

10.4 Taxol (paclitaxel)

Product description: Paclitaxel is a natural product with antitumor activity. Taxol (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. Taxol (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution.

Solution preparation: It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Taxol is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP. Taxol 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.
Storage requirements and Stability: Unopened vials of Taxol (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 Taxol 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. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours. Store the vials in original cartons between 20°–25° C (68°–77° F). Retain in the original package to protect from light.

Route of administration: Intravenous. Taxol should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

Drug interactions: The metabolism of Taxol is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when Taxol is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when Taxol is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Disposal: To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel. If paclitaxel contacts the skin,

immediately wash the skin thoroughly with soap and water. If paclitaxel contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

10.5 Carboplatin

Product description: The chemical name for Carboplatin is platinum, diammine [1,1-cyclobutanedicarboxylato(2-)-*O,O'*]-,(*SP*-4-2). It is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution.

Solution preparation: Carboplatin injection is a premixed aqueous solution of 10 mg/mL Carboplatin. Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. Needles or intravenous administration sets containing aluminum parts that may come in contact with Carboplatin injection should not be used for the preparation or administration of the drug. Aluminum can react with Carboplatin causing precipitate formation and loss of potency.

Storage requirements and Stability: When prepared as directed, Carboplatin aqueous solutions are stable for 8 hours at room temperature (25° C). Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin aqueous solutions be discarded 8 hours after dilution. Unopened vials of Carboplatin injection are stable to the date indicated on the package when stored at 20° - 25° C (68° to 77° F) [see USP Controlled Room Temperature]. Protect from light. Carboplatin injection multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Route of administration: Intravenous

Drug interactions: The renal effects of nephrotoxic compounds may be potentiated by Carboplatin.

Disposal: To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing Carboplatin injection. If Carboplatin injection contacts the skin, immediately wash the skin thoroughly with soap and water. If Carboplatin injection contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

11.1 Correlative Studies

11.2 Tumor Correlative Studies

Pre-therapy tumor that has been fixed with 10% buffered formalin solution and processed into paraffin embedded (FFPE) tissue blocks will be collected. The

following infiltrating cells will be quantified (0 to 3+) using standing immunofluorescence techniques:
CD4+, CD8+, CD68+ , PD 1+CD4+, PD 1+CD8+, PD-1+CD68+, PD-1L+, and CD4+Foxp3+. See Appendix M.

Methods: Immunohistochemical staining will be carried out on 4µm-thick sections utilizing an Autostainer Plus (Dako - Agilent Technologies) with appropriate positive and negative controls. Sections are baked for 60 minutes at 60 °C in a dehydration oven and heat-induced epitope retrieved in the PT link (Dako – Agilent technologies) using EnVision FLEX target retrieval solution for 20 minutes at 97 °C then cooled to room temperature in TBST Wash buffer for 5 minutes. Slides are incubated with the following antibodies at the following dilutions:

	Dilution	Source
PD-1	1:100	Cell Marque NAT105
PD-L1	1:1000	R&D Systems
CD4	1:100	Cell Marque SP35
CD8	1:200	Cell Marque SP16
FOXP3	1:200	Abcam AB22510
CD68	1:1000	Cell Marque KP-1

Antibody detection will utilize the Envision FLEX kit (K8023) with a DAB chromagen for visualization according to the manufacturer's instructions (Dako – Agilent technologies). Slides are then counterstained with hematoxylin. The percentage of tumor which have an infiltrate of lymphocytes or macrophages will be estimated and the average number of positive immune cells per high power field (HPF) in a minimum of 4 representative HPF areas will be determined utilizing a semi-quantitative four tiered scale used for scoring lymphocytes (0= no lymphocytes, 1= 1-10/HPF, 2= 11-50/HPF and 3= >50/HPF) and macrophages (0= no macrophages, 1= 1-50/HPF, 2= 50-100/HPF and 3=>100/HPF). Lymphocyte and macrophage infiltrate scores are obtained by multiplying these scores to attain a score from 0-300.

11.3 Blood Correlative Studies

Blood will be drawn prior to initiating treatment (C1D1), day 1 of cycle 2 (C2D1), day 1 of cycle 3 (C3D1), and End of Treatment (EOT). All blood samples are collected from the clinic and transported at room temperature within 3 hours after being drawn from each individual. Whole blood is collected in Vacutainer tubes containing EDTA (BD Vacutainer). Peripheral blood mononuclear cells (PBMC) are isolated from whole blood by density gradient centrifugation using Lymphocyte Separation Medium (Mediatech) and Leucosep tubes (Greiner Bio-one). Whole blood is centrifuged at 410 × g for 10 minutes and the plasma layer is collected, centrifuged for 10 minutes at 885 × g, and the supernatant frozen at −80°C for subsequent experiments. The whole blood is diluted 1:1 with RPMI (Mediatech) and the PMBCs isolated per manufacturer's guidelines. Cells at the

interface are harvested and washed once with RPMI, and red blood cells are lysed with ammonium chloride lysis buffer. Cells are washed, counted, and immediately used fresh for staining and flow cytometry analysis, or 10 million PBMCs are frozen per milliliter of freezing solution (10% DMSO 10% FBS-supplemented RPMI) per NUNC cryovial. PBMCs are frozen in a Nalgene Cryo 1°C freezing container per manufacturer's instructions and stored in liquid nitrogen thereafter.

See Appendix N. The following will be assessed:

- Frequency (flow cytometry) of Lin−CD14+HLA-DRlow/− MDSC; CD4+, CD8+, ICOS+CD4+, ICOS+CD8+ effector and CD4+FoxP3+ regulatory T cells

Method: Antibodies that will be used for flow cytometry analysis include CD4-BV421 (eBiosciences), CD8-PE (BD Pharmingen), CD14-APC (eBiosciences), HLA-DR-FITC (BD Pharmingen), lineage (CD3/CD16/CD19/CD20/CD56) cocktail FITC (BD Pharmingen), ICOS-efluro660 (eBiosciences), and FoxP3-Alexa480 (eBioscience). Isotype controls include the appropriate fluorochrome-conjugated mouse IgG1, IgG 1k, IgG2a, or IgG2b k (BD Pharmingen; Beckman Coulter; R&D Systems). Triplicate samples will be analyzed using the FACSCanto II (Becton Dickinson). Data will be analyzed using the BD FACSDiva software. Gates are set according to appropriate isotype controls. Absolute lymphocyte counts will also be determined. Frequency (%) of the following phenotypes will be determined.

Effector	CD4+
	CD8+
	ICOS+CD4+
	ICOS+CD8+
T regulatory	CD4+FoxP3+
Myeloid derived suppressor	Lin-CD14+HLA-DRlow/−

- Peripheral blood mononuclear cell Th1/Th2/Th17 cytokine production in vitro (BD Cytometric Bead Array) in response to WT-1, p53, Mage-A3, Her2/neu, telomerase, and survivin peptide mixtures (Proimmune Promix), tumor-associated determinants implicated in NSCLC, and to anti-CD3 plus anti-CD28 antibody (BD)

Methods: PBMC that have been separated by gradient centrifugation and cryopreserved are thawed at 37 ºC, diluted in 5 ml RPMI, and incubated at 37 ºC for 1 hour. Cells are then pelleted at 200g, resuspended in complete medium, counted with trypan blue, and suspended at 4x106/ml and plated in 100 µl in 96 well conical wells. PBMC are then cultured with 20 µg/ml of WT-1, p53, Her2/neu, Mage-A3, telomerase, and survivin peptide mixtures ProMix Peptide Pools (Proimmune Inc.). As a control PBMC are also stimulated with anti-CD3 plus anti-CD28 antibody (BD Pharmingen). After 3

days, culture supernatants are collected and assayed using BD Cytometric Bead Array Human Th1/Th2/Th17 Cytokine Kit according to the manufacturer's instructions. Positivity criteria include a ≥3.0-fold increase over unstimulated background control, expressed as a stimulation index (SI), as well as a minimum concentration (pg/ml) over background as follows: IL-2, 40; IL-4, 15; IL-6, 20; IL-10, 50; IFN-γ, 75; tumor necrosis factor-α, 30; and IL-17A, 20.

- Plasma levels (ELISA) of TGF-β, VEGF, IL-6, IL-8, PGE2 (metabolite), and sPD-1L.

  Methods: Commercially available ELISA kits will be used according to the recommendation of the manufacturer. Results are expressed as a concentration.

	Manufacturer
TGF-β	R&D Systems
VEGF	R&D Systems
IL-6	R&D Systems
IL-8	R&D Systems
PGE2 (metabolite)	Abcam
sPD-1L	MyBiosource

11.4 Quality of Life Correlative Studies

EORTC QLQ-30 and EORTC QLQ-LC13 will be completed by the patient at baseline and then every 12 weeks (Appendices I – L).[21]

The EORTC QLQ-C30 is reportedly the most frequently used QOL instrument in lung cancer clinical trials.[22] The QLQ-30 is a 30-item multi-dimensional questionnaire designed for use in cancer populations.[21] It contains nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale, requested by 4-point Likert or visual analogue scales. Several single-item symptom measures are also included. The QLQ-LC13 is a lung cancer-specific module to be used in conjunction with the QLQ-30 and is 13 additional items. These questionnaires have been shown to be reliable and valid in over 60 languages, can be self or interviewer-administered and take approximately 11 minutes to complete.[21,22] Both the QLQ-C30 and QLQ-LC13 will be available in Spanish for Spanish-speaking participants.

12.0 Data Management

Informed consent document	WISER
Protocol registration form	WISER
Tumor measurement form	REDCap
Screening form	REDCap
Study data collection form	REDCap
Follow-up form	REDCap
EORTC QLQ-C30 & QLQ-LC13	REDCap
Tumor correlative study form	REDCap
Blood correlative study form	REDCap

13.1 Statistical Considerations

13.2 Power, sample size, and accrual rate

This is a pilot study and will accumulate useful preliminary data to compare whether a combination of immunotherapy and chemotherapy shows more promising efficacy data than immunotherapy alone. To achieve this goal a total of 40 patients will be randomized, 20 patients will be randomized to single agent and 20 to the combination.

For the primary outcome of objective response rate, (ORR) patients will be dichotomized to being a success/failure based on whether they have a partial or complete response. Exact Clopper-Pearson 95% confidence intervals will be calculated for each group separately. With a sample size of 20 patients in a group, a two-sided 95% confidence interval (Exact Clopper-Pearson interval) will have a total width of 0.324 if the estimated proportion of successes is 50% (most conservative assumption for the confidence interval calculation). This level of precision will provide information (estimate and 95% confidence interval) as to whether this therapeutic approach is promising and worthy of future studies.

Furthermore, a comparison between groups will be made using a Fisher's Exact Test. If we observe a very large difference in ORR (greater than 43% in absolute percent if the ORR was 10%in the Control arm) we will have sufficient power to declare that difference statistically significant. However, since this is a pilot study it is not anticipated that a statistically significant difference will necessarily be observed.

Based on current projects, approximately 30 eligible patients will be enrolled in one year, so overall it is anticipated that the trial will take approximately 18 months to accrue 40 patients followed by a 12-month follow-up period for the patients.

13.3 Analysis of Primary Objective

13.3.1 The effects of the treatments on immune markers will be analyzed using paired t-tests (possibly after transformation) or the non-parametric

counterpart within each group separately. In addition, the two groups will be compared on these measures using two-sample t-tests for outcomes measured only post-randomization or analysis of covariance for measures that have an assessment made prior to randomization. If a measure is assessed a multiple post-randomization times then a longitudinal mixed model will be fit to examine the differences between groups over time accounting for the repeated measurements.

13.3.2 This study will enroll patients with recurrent or metastatic NSCLC and PS of 2. In this group of patients, the ORR's is approximately 10% with OS of about 2 to 4 months. With this pilot study, we would be able to conduct two hypothesis tests (one for each arm of the study) to determine whether there is evidence that the observed response rate, using RECIST criteria, is better than 10%. To do this, two one-sided binomial tests will be performed. For each test the null hypothesis is that the response rate is 10% and the alternative hypothesis is that the response rate is higher than 10%. With 20 patients in each analysis there is 80% power to detect a difference of 0.2133 with alpha=0.05 (one sided).

13.3.3 Duration of response will also be assessed in each group and compared using survival analysis methods. Furthermore, progression free and overall survival rates will be estimated in each group and compared using Kaplan-Meier curves. These comparisons will be for descriptive purposes since it is not anticipated that statistically significant differences will be observed with the small sample sizes.

13.4 Analysis of Secondary Objectives

13.4.1 Adverse events will be categorized by organ system and severity and summarized as frequency counts and percentages. A treatment will be considered too toxic if ≥6 of 20 patients in a cohort are removed from study because of toxicity.

13.4.2 Two instruments the EORTC QLQ-30 and EORTC QLQ0LC13 will be administered to patients at baseline and every 12 weeks during the study, thus it is anticipated that patients will have up to 5 assessments made during the trial. Summary scores from each instrument will be assessed at each time point and longitudinal comparisons will be made between groups using a repeated measure mixed model approach.

13.4.3 The association of immune response with clinical response will also be explored. Treatment response will be grouped into 4 categories as defined earlier in the protocol (irCR, irPR, irSD, irPD). The immune responses for patients within each of these 4 groups will be examined to determine whether there is evidence of an association. This comparison will be primarily descriptive, however we will be examining whether there is evidence that immune response improves as patients go from PD to CR (i.e. it is expected that patients with irPD will have worse immune

response than patients with irCR). For continuous measures of immune response the mean value within each response category will be compared. If we dichotomize the immune response assessment into responder yes/no then we will compare the proportion of responders in each category. As stated above, with a small sample size (n=20 per group) this examination will be exploratory since some categories may have less than 4 patients in them.

13.5 Interim Analysis Plan

There is no planned interim analysis for this study, however the DSMC will monitor this study and if there were to be an unexpected safety concern from unexpected Grade 4 or 5 events occurring on one or both arms of the study then the trial could be suspended or amended if necessary. However, this is not expected.

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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: _____

Prior Chemotherapy? ☐ Yes ☐ No

Prior Therapies/ Protocol # if applicable	Start / End Date of Prior Therapy	Best Response (CR, PR, Treatment Failure)	Date of Best Response	Date of Relapse	Duration of Best Response (in Months)
#1 _____	_____/_____		_____	_____	_____
#2 _____	_____/_____		_____	_____	_____
#3 _____	_____/_____		_____	_____	_____
#4 _____	_____/_____		_____	_____	_____

COMMENT:_____

_____

_____

Immune response in patients with recurrent or metastatic non-small cell lung cancer and performance status of 2 treated with a combination of pembrolizumab and low dose weekly carboplatin/paclitaxel
Comprehensive Cancer Center of Wake Forest University (CCCWFU)
CCCWFU # 62415

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. IRB00034830	**CCCWFU Protocol No. 62415**
Study Title: Immune response in patients with recurrent or metastatic non-small cell lung cancer and performance status of 2 treated with a combination of pembrolizumab and low dose weekly carboplatin/paclitaxel	
Principal Investigator: W. Jeff Petty, MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Patients must have histologically or cytologically confirmed NSCLC that is advanced/metastatic (stage IIIB/IV) or recurrent (progression after surgery or radiation or chemo-radiation treatment for loco-regional disease). Patients with epidermal growth factor (EGFR) mutation, anaplastic lymphoma kinase (ALK) gene rearrangement or ROS1 translocation must have received an approved EGFR, ALK, or ROS1-directed therapy and have signs of disease progression prior to receiving pembrolizumab.	☐	☐	
Patients 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 12 weeks (84 days) prior to date of signing consent. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen (up to 3 years) only upon agreement from the Sponsor. At least 4 mm of tumor tissue will be needed for PD-L1 staining.	☐	☐	
Patients who have received zero (0) to two (2) previous lines of systemic chemotherapy and are not currently receiving chemotherapy treatment (within 2 weeks of randomization).	☐	☐	
At least one measurable lesion as defined by RECIST v1.1 on screening CT or MRI	☐	☐	
Age ≥18 years.	☐	☐	
ECOG performance status of 2.	☐	☐	

Patients must have normal organ and marrow functions as described below: -white blood cell count > 2,500 cells/mcL -absolute neutrophil count ≥1,500/mcL -platelets ≥100,000/mcL -hemoglobin ≥ 9 g/dL -total bilirubin ≤ 2.0 x upper limit of normal (ULN) -AST(SGOT)/ALT(SGPT) ≤ 2.5 x ULN OR ≤ 5 x ULN in presence of liver metastases -creatinine within normal institutional limits OR creatinine clearance > 50 mL/min for patients with creatinine levels above institutional normal - potassium ≥ lower limit of normal	☐	☐	
Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for 4 weeks after the final administration of study drugs. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.	☐	☐	
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)**
Known active (untreated) central nervous system (CNS) metastases that require steroids. Subjects with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for at least 2 weeks before study entry, defined as: • No evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases. • Asymptomatic and receiving either no or stable doses of anticonvulsants and total doses of corticosteroids equivalent to 10 mg of prednisone or less.	☐	☐	
Current or previous other malignancy within 2 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy without sponsor approval.	☐	☐	
History of previous exposure to an anti PD1/PD-L1 agent	☐	☐	
Patients receiving any other investigational agents and or more than two different chemotherapy regimens for treatment of metastatic disease.	☐	☐	

Has had prior 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.	☐	☐	
History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab, paclitaxel or carboplatin.	☐	☐	
Current uncontrolled cardiac disease such as angina or myocardial infarction, congestive heart failure including New York Heart Association functional classification of 3, or arrhythmia requiring treatment.	☐	☐	
History of pneumonitis or active lung infection.	☐	☐	
Chronic or current active infectious disease requiring systemic antibiotics, antifungals, or antivirals.	☐	☐	
Patients receiving chronic steroids and or immunosuppression	☐	☐	
Known HIV infection, Hepatitis B virus (HBV) or hepatitis C virus (HCV) viremia or at risk for HBV reactivation. HBV DNA and testing for HCV RNA must be undetectable. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti-hepatitis B core antibody positive	☐	☐	
History of autoimmune disease(s).	☐	☐	
Psychiatric illness/social situations that would limit compliance with study requirements	☐	☐	
Any other condition or circumstance that could interfere with adherence to the study's procedures or requirements, or otherwise compromise the study's objectives such as history of, or any evidence of active, non-infectious pneumonitis	☐	☐	
Has an active infection requiring systemic therapy.	☐	☐	
Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants, breastfeeding should be discontinued prior to study entry.	☐	☐	

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:

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 DSMC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE)	Date: 2/11/2021

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** 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 DSMC.

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 DSMC 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 DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC 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 DSMC 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 DSMC.

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 DSMC.

DSMC 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 DSMC according to the schedule 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 DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time 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 DSMC 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 DSMC 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 DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. DSMC clinician name, date/time contacted 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 DSMC 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 DSMC -- ***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 DSMC" 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 DSMC 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 DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

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

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology [redacted]
Mercedes Porosnicu, MD-- Hematology Oncology [redacted]
Ryan Hughes, MD – Radiation Oncology [redacted]
Michael Goodman, MD -- Hematology Oncology [redacted]
Daniel Reed, MD -- Hematology Oncology [redacted]
Mary Beth Seegars, MD -- Hematology Oncology [redacted]

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 the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. 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 DSMC 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 DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC 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 DSMC. 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. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC 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 DSMC report then an immediate suspension of enrollment shouldbe 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 DSMC 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 information to be added.

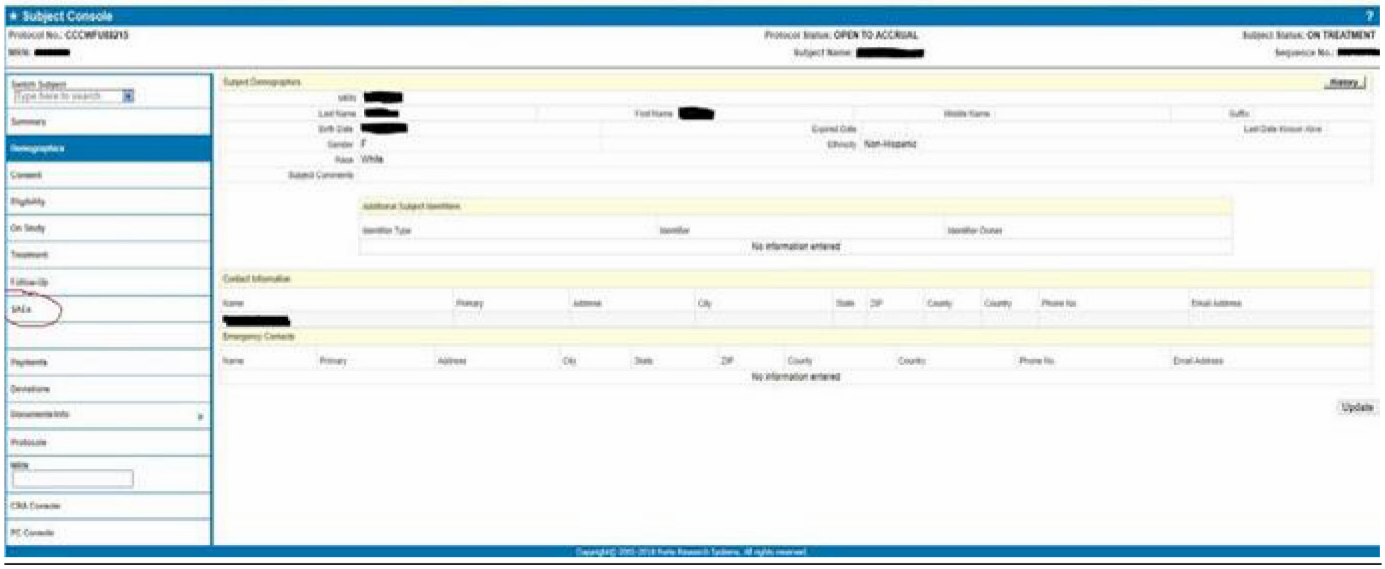
Acronyms

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

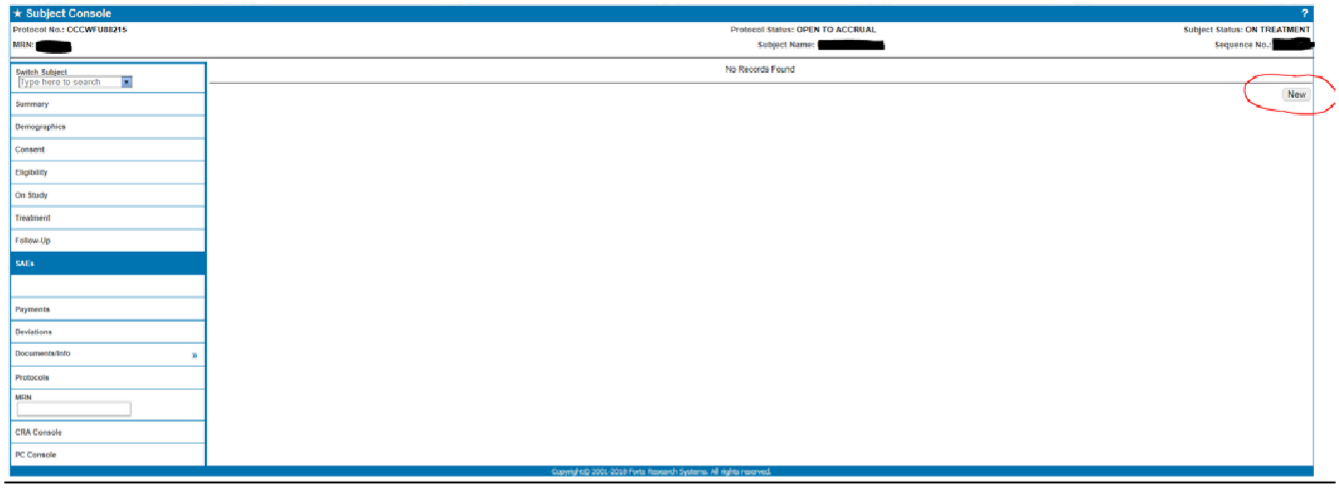
Screen Shots:

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

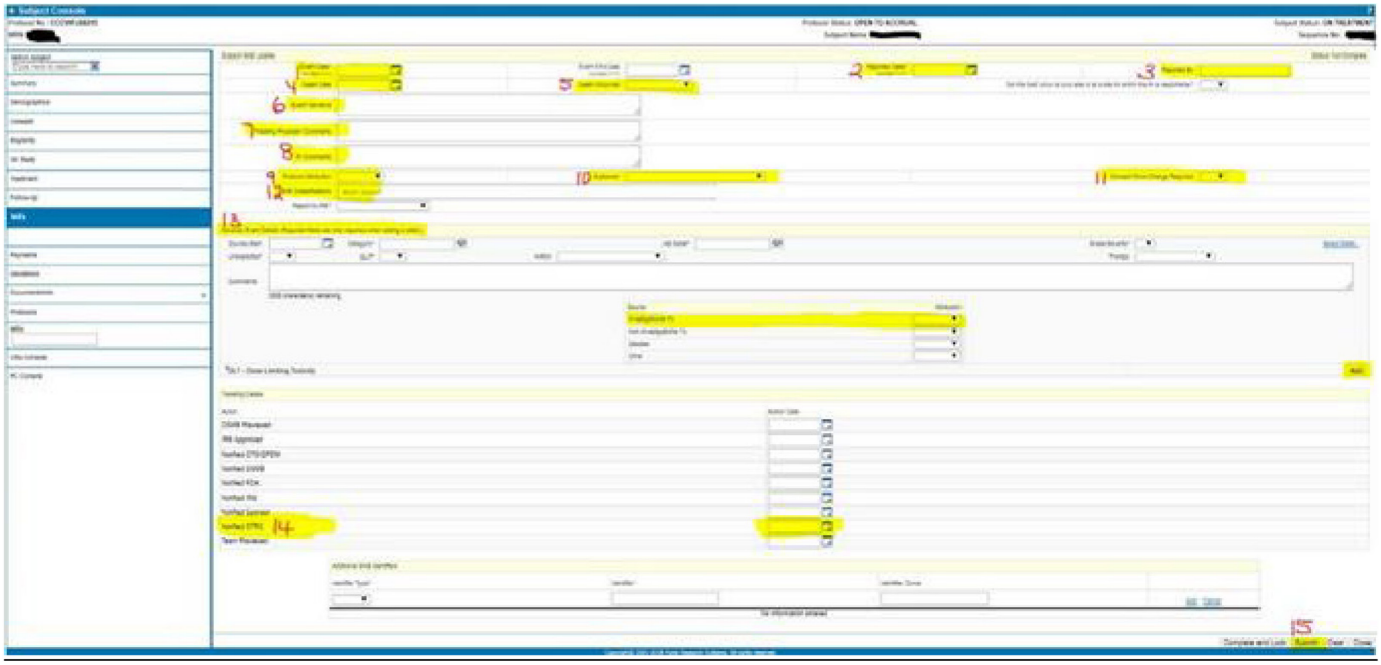
Screen Shot 1:



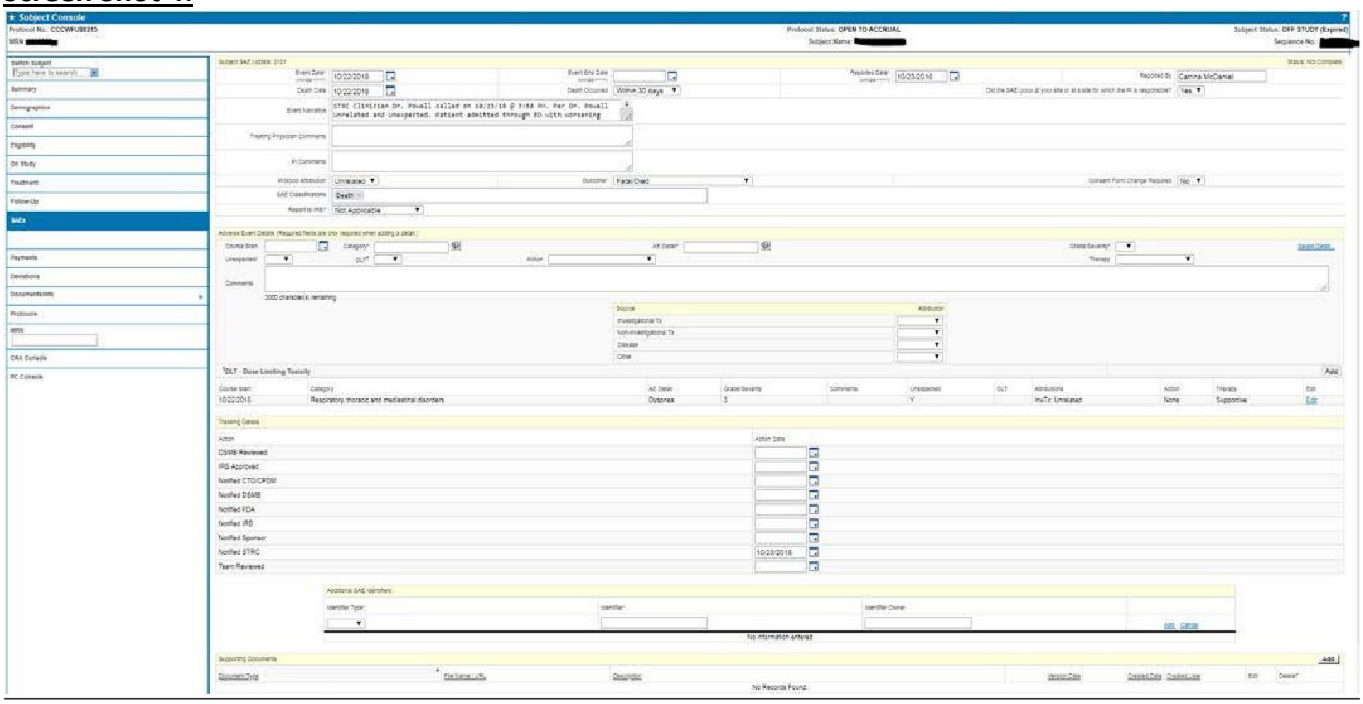
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix E - Tumor Response Worksheet

Immune-Related Response Criteria (irRC) Measurement Form

Patient Name: _____ MRN:_____Study: _____

Measurable Sites								
Lesion	**Site**	**Imaging (ie, CT, MRI)**	**Baseline Date:** *(Se,Im)*		**Evaluation Date:** *(Se,Im)*		**Evaluation Date:** *(Se,Im)*	
			Size of Lesion (mm x mm)	**Product of Measurements (mm^2)**	**Size of Lesion (mm x mm)**	**Product of Measurements (mm^2)**	**Size of Lesion (mm x mm)**	**Product of Measurements (mm^2)**
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
15.								

Sum of Product Measurements (mm^2)					
Non-Measurable Sites					
Lesion	**Site**	**Imaging (ie, CT, MRI)**	**Baseline Date:** *(Se,Im)*	**Evaluation Date:** *(Se,Im)*	**Evaluation Date:** *(Se,Im)*
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					

New Sites								
Lesion	**Site**	**Imaging (ie, CT, MRI)**	**Baseline Date:** *(Se,Im)*		**Evaluation Date:** *(Se,Im)*		**Evaluation Date:** *(Se,Im)*	
			Size of Lesion (mm x mm)	**Product of Measurements (mm^2)**	**Size of Lesion (mm x mm)**	**Product of Measurements (mm^2)**	**Size of Lesion (mm x mm)**	**Product of Measurements (mm^2)**
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
15.								
Sum of Product Measurements (mm^2)								
% Change (difference/nadir)								
Response (irCR, irPR, irSD, irPD)								
Radiologist Signature/Date								
Treating Physician Signature/Date								
PI Signature/Date								

Appendix F - Screening form

1. Medical history:

☐ Myocardial infarction

☐ Congestive heart failure

☐ Peripheral vascular disease

☐ Cerebrovascular disease

☐ Dementia

☐ Chronic pulmonary disease

☐ Connective tissue disease

☐ Peptic ulcer disease

☐ Liver disease – ☐ mild ☐ moderate ☐ severe

☐ Diabetes – end organ damage? Yes ☐ No ☐

☐ Hemiplegia

☐ Other cancer – specify _____

Prior anticancer interventions? Yes ☐ No ☐
If yes, specify_____Date:_____/_____/ _____

☐ AIDs

☐ Other medical condition – specify _____

2. Concurrent medications:_____
_____
_____
_____

3. Physical exam:

Derm – ☐ WNL ☐ Abnormal, specify _____

HEENT – ☐ WNL ☐ Abnormal, specify _____

CV – ☐ WNL ☐ Abnormal, specify _____

Pulm – ☐ WNL ☐ Abnormal, specify _____

GI – ☐ WNL ☐ Abnormal, specify _____

Other – Specify _____

4. Vital signs:
   a. HR_____
   b.BP _/____
   d. Temp _____
   e. Weight_____(kg)

   b. RR_____

   f. Height_____(cm)

5. Performance Status:

GRADE	ECOG
☐ **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 ☐ N/A ☐ If N/A, specify: _____

Appendix G - Study Data Collection Form

To be completed prior to each treatment and at the End of Treatment visit

Study Visit:
- ☐ Cycle 1
- ☐ Cycle 2
- ☐ Cycle 3
- ☐ Cycle 4
- ☐ Cycle 5
- ☐ Cycle 6
- ☐ Cycle 7
- ☐ Cycle 8
- ☐ Cycle 9
- ☐ Cycle 10
- ☐ Cycle 11
- ☐ Cycle 12
- ☐ Cycle 13
- ☐ End of Treatment
- ☐ Other (specify below):

_____

1. Concurrent medications:_____
   _____
   _____
   _____
2. Physical exam:
   - Derm – ☐ WNL ☐ Abnormal, specify _____
   - HEENT – ☐ WNL ☐ Abnormal, specify _____
   - CV – ☐ WNL ☐ Abnormal, specify _____
   - Pulm – ☐ WNL ☐ Abnormal, specify _____
   - GI – ☐ WNL ☐ Abnormal, specify _____
   - Other – ☐ Specify _____ ☐
3. Vital signs:
   a. HR_____
   b. BP _/_____
   c. RR_____
   d. Temp_____
   e. Weight _____
4. ECOG performance status

GRADE	ECOG
☐ **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

Appendix H - Follow-up Form

To be completed for long-term follow-up after treatment has finished

1. Vital status: Alive ☐ Dead ☐
   If deceased, date of death:_____/_____/ _____

2. Disease state (last known, if deceased): _____

3. Initiation of any new anticancer interventions since last contact?
   Yes ☐ No ☐
   If yes, specify_____
   Date:_____/_____/ _____

Appendix I - EORTC QLQ-C30 English

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

	During the past week:	Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4

		Not at All	A Little	Quite a Bit	Very Much
	During the past week:				
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with you family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix J - EORTC QLQ-LC13 English

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

	During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix K - EORTC QLQ-C30 Spanish

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

		En absoluto	**Un poco**	**Bastante**	**Mucho**
1.	¿Tiene alguna dificultad para hacer actividades que requieran un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo				

	largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4.	¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

	Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucl**
6.	¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4
8.	¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9.	¿Ha tenido dolor?	1	2	3	4
10.	¿Necesitó parar para descansar?	1	2	3	4
11.	¿Ha tenido dificultades para dormir?	1	2	3	4
12.	¿Se ha sentido débil?	1	2	3	4
13.	¿Le ha faltado el apetito?	1	2	3	4
14.	¿Ha tenido náuseas?	1	2	3	4

	Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
15.	¿Ha vomitado?	1	2	3	4
16.	¿Ha estado estreñido/a?	1	2	3	4
17.	¿Ha tenido diarrea?	1	2	3	4
18.	¿Estuvo cansado/a?	1	2	3	4
19.	¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20.	¿Ha tenido dificultad en concentrarse en cosas como leer el periódico o ver la televisión?	1	2	3	4

21.	¿Se sintió nervioso/a?	1	2	3	4
22.	¿Se sintió preocupado/a?	1	2	3	4
23.	¿Se sintió irritable?	1	2	3	4
24.	¿Se sintió deprimido/a?	1	2	3	4
25.	¿Ha tenido dificultades para recordar cosas?	1	2	3	4
26.	¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27.	¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28.	¿Le han causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor en las siguientes preguntas, ponga un círculo en el número del 1 al 7 que mejor se aplique a usted

29. ¿Cómo valoraría su salud general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

30. ¿Cómo valoraría su calidad de vida en general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

Appendix L - EORTC QLQ-LC13 Spanish

Los pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor Indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada. Por favor responda rodeando con un círculo el número que mejor se aplique a su caso.

	Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
31.	¿Cuánto tosió?	1	2	3	4
32.	¿Escupió sangre al toser?	1	2	3	4
33.	¿Le faltó la respiración cuando descansaba?	1	2	3	4
34.	¿Le faltó la respiración al caminar?	1	2	3	4
35.	¿Le faltó la respiración al subir las escaleras?	1	2	3	4
36.	¿Ha tenido algún dolor en la boca o en la lengua?	1	2	3	4
37.	¿Ha tenido problemas para tragar?	1	2	3	4
38.	¿Ha tenido hormigueos en las manos o en los pies?	1	2	3	4
39.	¿Ha perdido cabello?	1	2	3	4
40.	¿Ha tenido dolor en el pecho?	1	2	3	4
41.	¿Ha tenido dolor en el brazo o en el hombro?	1	2	3	4
42.	¿Ha tenido dolor en otras partes de su cuerpo?	1	2	3	4
	En caso afirmativo, ¿dónde? _____				
43.	¿Tomó alguna medicina para el dolor?				
	1 No 2 Si				
	En caso afirmativo, ¿cuánto le alivió?	1	2	3	4

Appendix M – Tumor Correlative Studies Form (Pre-Study)

1. Percentage of tumor with an infiltrate of lymphocytes: _____
2. Percentage of tumor with an infiltrate of macrophages: _____
3. Average number of positive immune cells per high power field (HPF) in a minimum of 4 representative HPF areas:
   a. Lymphocytes
      - ☐ 0 = no lymphocytes
      - ☐ 1 = 1-10/HPF
      - ☐ 2 = 11-50/HPF
      - ☐ 3 = >50/HPF
   b. Macrophages
      - ☐ 0 = no macrophages
      - ☐ 1 = 1-50/HPF
      - ☐ 2 = 50-100/HPF
      - ☐ 3 = >100/HPF
4. Lymphocyte infiltrate score: _____
5. Macrophage infiltrate score: _____

Appendix N – Blood Correlative Studies Form

Study Visit (circle one): C1D1 C2D1 (Pembro) C3D1(Pembro) EOT

Cellular regulators

1. Absolute lymphocyte count: _____
2. Frequency (%) of the following phenotypes:

		Frequency (%)
Effector	CD4+	
	CD8+	
	ICOS+CD4+	
	ICOS+CD8+	
T regulatory	CD4+FoxP3+	
Myeloid derived suppressor	Lin-CD14+HLA-DRlow/−	

Soluble regulators

	[Concentration]
TGF-β	
VEGF	
IL-6	
IL-8	
PGE2 (metabolite)	
sPD-1L	

Antigen specific response

PBMC response:

	Positivity criteria	
	Stimulation index	[concentration] (pg/mL)
IL-2, 40		
IL-4, 15		
IL-6, 20		
IL-10, 50		
IFN-γ, 75		
TNF-α, 30		
IL-17A, 20		

Appendix O – 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** (2-5) 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 DSMC= DSMC 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 DSMC = Data and Safety Monitoring CommitteeVersion 10/30/17

Appendix P – Pembrolizumab Guidance Document

Please refer to the package insert PDF for Pembrolizumab, available from www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
Last updated December 2018

Appendix Q – ECOG Performance Status

ECOG PERFORMANCE STATUS

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

Appendix R: Response Criteria

Study Visit:
- ☐ Pre-Study
- ☐ Week 8 (± 3 days)
- ☐ Week 20 (± 7 days)
- ☐ Week 32 (± 7 days)
- ☐ End of Treatment Visit
- ☐ Other visit: (please specify) _____

Evaluation of target lesions

☐ Complete Response (irCR): Complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes which must decrease to < 10 mm in short axis.

☐ Partial Response (irPR): Decrease in total measured tumor burden (TMTB*) ≥30% relative to baseline.

☐ Stable Disease (irSD): Not meeting criteria for irCR or irPR, in absence of irPD.

☐ Progressive Disease (irPD): Increase in TMTB ≥20% relative to nadir.

Evaluation of non-target lesions

☐ Complete Response (irCR): Complete disappearance of all non-target lesions.

☐ Non-irCR/Non-irPD: Non-target lesions do not meet the criteria for irCR or irPD.

☐ Progressive Disease (irPD): Unequivocal increase in the number or size of non-target lesions. To achieve unequivocal progression of non-target lesions, there must be a substantial worsening of non-target disease of a magnitude that, according to the treating physician, warrants a change in anticancer therapy.
NOTE: Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD and treatment may continue until the next scheduled assessment.

*TMTB=sum of the longest diameters (SOD) + SOD new, measureable lesions.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

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

PI Signature: _____ Date:_____/_____/ _____

BEST OVERALL Response Criteria

Study Visit:
- ☐ Pre-Study
- ☐ Week 8 (± 3 days)
- ☐ Week 20 (± 7 days)
- ☐ Week 32 (± 7 days)
- ☐ End of Treatment Visit
- ☐ Other visit: (please specify) _____

Evaluation of Best Overall Response

The overall response according to irRECIST is derived from the responses in TMTB as well as the presence of any non-target lesions as follows:

☐ Complete Response (irCR): Complete disappearance of all lesions (whether measureable or not); lymph nodes must decrease to < 10 mm in shortest dimension.

☐ Partial Response (irPR): Decrease in TMTB ≥30% relative to baseline.

☐ Disease (irSD): Not meeting criteria for irCR or irPR, in absence of irPD.

☐ Progressive Disease (irPD): Increase in TMTB ≥20% relative to nadir.

Confirmatory Measurement

Confirmation: If there is suspicion of tumor progression at eight weeks, a second CT/MRI study 4 weeks after will need to be done as a confirmatory test.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for irCR or irPR (if irCR is never met) until the first date that irPD is confirmed by independent radiology review or death, whichever comes first.

Duration of disease control: The duration of time from the date measurement criteria are first met for irCR, irPR, or irSD, until the first date that irPD is confirmed by independent radiology review or death, whichever comes first.

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

PI Signature: _____ Date:_____/_____/ _____