Phase II Pilot Study of Subsequent Line Gemcitabine and Nivolumab for Advanced SCLC
Wake Forest Baptist Comprehensive Cancer Center (WFBCCC)
WFBCCC # 62418

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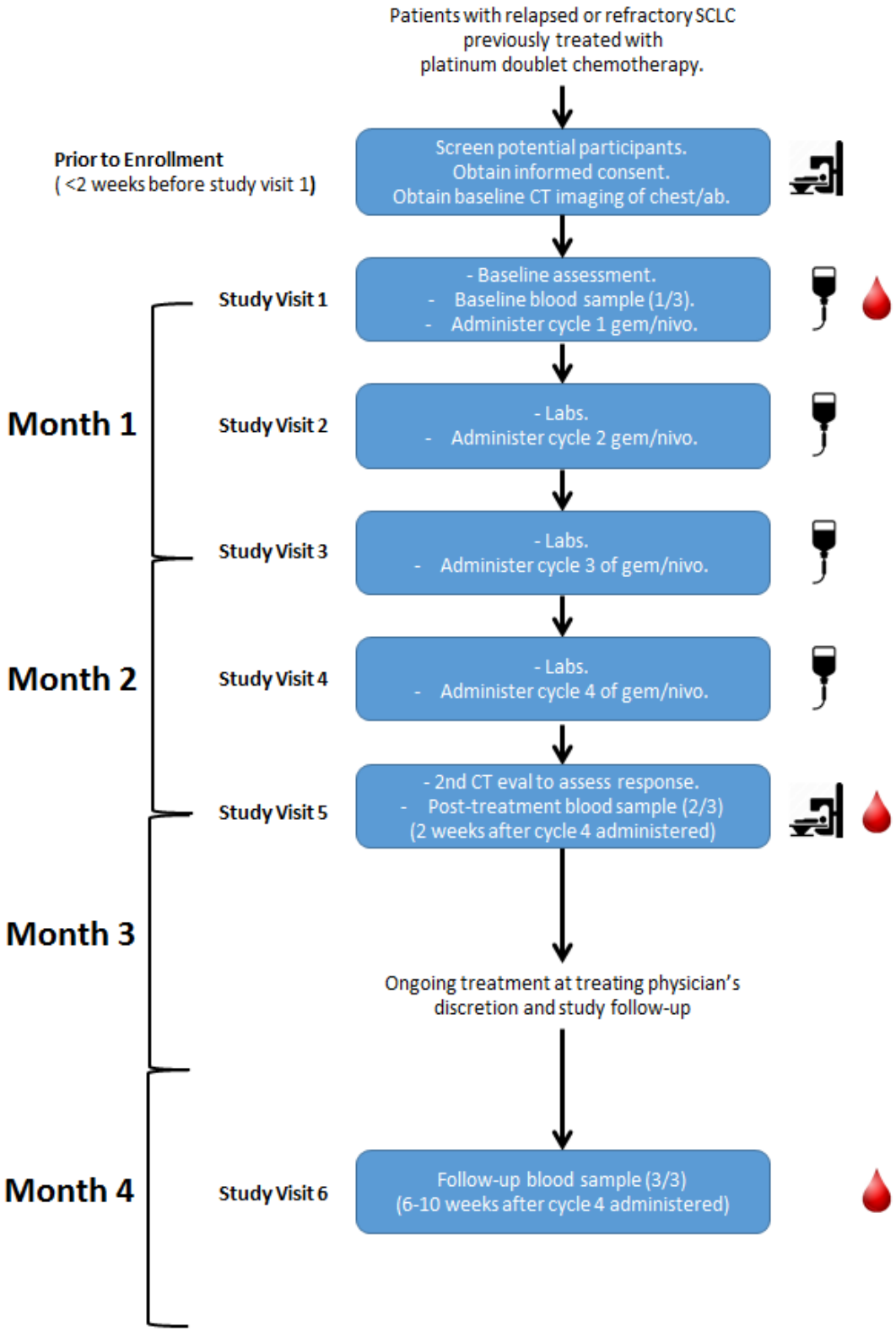
Schema


Patients with relapsed or refractory SCLC previously treated with platinum doublet chemotherapy.
Prior to Enrollment
(<2 weeks before study visit 1)
Screen potential participants.
Obtain informed consent.
Obtain baseline CT imaging of chest/ab.
Month 1
Study Visit 1
- Baseline assessment.
- Baseline blood sample (1/3).
- Administer cycle 1 gem/nivo.
Study Visit 2
- Labs.
- Administer cycle 2 gem/nivo.
Study Visit 3
- Labs.
- Administer cycle 3 of gem/nivo.
Month 2
Study Visit 4
- Labs.
- Administer cycle 4 of gem/nivo.
Month 3
Study Visit 5
- 2nd CT eval to assess response.
- Post-treatment blood sample (2/3)
(2 weeks after cycle 4 administered)
Ongoing treatment at treating physician's discretion and study follow-up
Month 4
Study Visit 6
Follow-up blood sample (3/3)
(6-10 weeks after cycle 4 administered)

1.0 Introduction and Background

Lung cancer (LC) is the third most common cancer in both men and women and the leading cause of cancer death, with only 15% of lung cancer cases diagnosed at the local stage.[1] Small cell lung cancer (SCLC) is a particularly aggressive neuroendocrine tumor of the lung that accounts for 13% of all lung cancer histologic types. Overall, there is a poor prognosis for advanced lung cancer and a need for novel treatment regimens.

Nivolumab is an IgG4 monoclonal antibody that blocks T-cell programmed cell death protein 1 (PD-1) and prevents it from interacting with PD-L1; thus, releasing the brakes on autoimmunity and allowing cytotoxic T-cell destruction of tumor cells. For their 2017 update, the National Comprehensive Cancer Network (NCCN) added nivolumab and the combination of nivolumab and ipilumumab as new category 2A options for subsequent systemic therapy of advanced SCLC.[2] This addition was based on the Checkmate 032 phase 1/2 trial of SCLC patients, which found a response rate ( ) of 10% for nivolumab 3 mg/kg; all responses were partial (PR) with no complete responses [CR]; there was also another 22% of participants who had stable disease (SD) as best response. Median PFS was **1.4 months** and median overall survival (OS) was **4.4 months**. Single agent nivolumab for SCLC had a 6% rate of therapy discontinuation due to treatment-related adverse events. The arms, which had combinations of nivolumab and ipilumumab, had higher RR (~20%) but with higher toxicity (10% treatment discontinuation) including three treatment-related deaths out of 115 participants.[3]

For comparison, oral topotecan is the only FDA-approved subsequent line therapy for relapsed or refractory SCLC with a RR of 51% and median overall survival of six months as compared to three months with best supportive care.[4] Nivolumab has a lower rate of serious grade 3-4 adverse events (5-10%) than oral topotecan and it is typically better tolerated. The most common mild symptoms associated with nivolumab are fatigue, anorexia, asthenia, nausea, and diarrhea. Immunotherapy is unique from traditional cytotoxic chemotherapy due to a risk of autoimmune complications such as pneumonitis, colitis, or hypophysitis.[5,6] These complications are treated with steroids and reversible if recognized in a timely manner but in rare cases can be fatal even after immunosuppression.[7]

Currently, the standard of practice for lung cancer patients treated with nivolumab is to assess initial response after four two-week cycles (total eight weeks) and, if there is a response, to continue nivolumab alone until there is either progression of disease, intolerance, or patient refusal. Assessing treatment response has traditionally been done with the Response Evaluation Criteria in Solid Tumors (RECIST) response criteria, with partial response defined by the target lesions decreasing in size to less than 70% of their original size and the absence of any new lesions.[8] SD is defined by traditional RECIST criteria as the stability of target lesions between 70% and 120% of their original size and with no new lesions noted.[8] PD is defined by traditional RECIST criteria as the enlargement of target lesions to >120% of their original size or the development of new lesions.[8]

Biomarkers may be predictive of response to immunotherapy for some patients. Tumor mutation burden (TMB) is determined by whole-exome sequencing on the tumor and is classified by the number of somatic mutations into low (0 to <143), medium (143 to 247),

or high (>248) tertiles. Immunohistochemistry (IHC) with increased PD-L1 expression on tumor cells may also be predictive of greater efficacy of nivolumab for non-small cell lung cancer (NSCLC).[9] However, SCLC has a lower prevalence of PD-L1 expression (~13% with ≥1% expression) and presence of PD-L1 did not correlate with response in the Checkmate 032 study.[3]

A relatively new strategy to augment the RR of immune checkpoint inhibitors in lung cancer is to combine them with traditional cytotoxic chemotherapy.[10] Safety data have been demonstrated for other tumor types. The phase I Checkmate 012 study of NSCLC patients reported a low rate of early dose-limiting toxicities when nivolumab (10 mg/kg) was combined with platinum-doublet chemotherapy, with 21% of participants receiving nivolumab/gemcitabine/cisplatin. [11] An abstract of preliminary results from a phase I study of squamous NSCLC patients combining nivolumab (10 mg/kg q3 weeks) with concurrent gemcitabine (1250 mg/m^2) and cisplatin (75 mg/m^2) for first-line treatment found that 45% of participants across all arms had grade 3/4 toxicities.[12] An abstract of preliminary results from another phase I study suggested that the addition of nivolumab to gemcitabine and *nab*-paclitaxel in advanced pancreatic cancer was also tolerated well.[13] These data suggest that the the combination of nivolumab and cytotoxic chemotherapy can be safely tested for the treatment of SCLC.

Gemcitabine, an analog of cytidine, which inhibits DNA replication, is a cytotoxic chemotherapy that causes cell cycle arrest in tumor cells. This cell stress increases cytokine release and up-regulates HLA expression; in turn leading to increased tumor cell killing by cytotoxic T-cells[14-16] Gemcitabine may have additional mechanisms of inducing an immune response against tumors. Gemcitabine has been shown to decrease the accumulation of myeloid-derived suppressor cells in cell culture[17] and in mouse models[18-20]; removing another potential inhibitor of immunotherapy. Immunophenotypic analysis of lymphocytes in the peripheral blood of pancreatic cancer patients also found that gemcitabine was associated with decreased memory T-cells (CD45RO+) and increased early activated T-cells (CD69+); suggestive that gemcitabine may promote naïve T-cell activation.[21] In current clinical practice, gemcitabine in combination with cisplatin is FDA-approved for the treatment of NSCLC; the recommended gemcitabine dosing is either 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or as 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle.[22] These dosing schedules can be difficult to tolerate and in typical clinical practice they are often dose-reduced; for example, to 1000 mg/m2 over 30 minutes on days 1 and 15 of each 28-day cycle. For relapsed or refractory SCLC, single agent gemcitabine is included as a category 2A recommendation by NCCN as it has an objective RR of 12% with a median survival of 7 months.[2,23] Serious adverse events with gemcitabine are uncommon for lung cancer patients and include cytopenias (3-6%), nausea/vomiting (6%), dyspnea (5%), infection (1%), and somnolence (1%).[24] Rarely, serious pulmonary toxicity can occur in <1% of patients; this can include pneumonitis or pulmonary edema/fibrosis.[25]

Nivolumab as a monotherapy has a low RR when used in subsequent line of therapy to treat SCLC. However, it may be possible to augment the effect of nivolumab with the addition of gemcitabine for both its cytotoxic and tumor immunogenic effects. The safety of this combination has already been reported in the phase I CheckMate 012 study of nivolumab/gemcitabine/cisplatin.[11] This proposed phase 2 study will test for efficacy of the addition of gemcitabine to nivolumab (G+N) to see if RR can be increased as

compared to a historical comparison group of SCLC patients who received nivolumab alone as part of the Checkmate 032 trial.[3]

Treatment tolerability, the extent to which adverse effects and other aspects of treatment can be tolerated by a patient, is a critical complement to efficacy data. Patients who are unable to tolerate treatment experience dose delays or discontinue treatment. Patient reported outcomes (PROs) assess subjective tolerability. This may include the extent to which patients are bothered by side effects, side effect and symptom severity, and functional impact of treatment.[26] The National Cancer Institute has developed a library of PROs to complement clinician-rated toxicities. These items are intended to be reviewed alongside CTCAE grading for a more accurate and comprehensive understanding of treatment-related adverse events. These items have demonstrated validity, reliability, and sensitivity to change, but do not capture overall health-related quality of life, an important subjective component of tolerability.[27,28] The Functional Assessment of Chronic Illness Therapy (FACIT) system is a PRO measurement system and gold standard in evaluating health-related quality of life. Some evidence suggests that a single item from this system, "I am bothered by the side effects of treatment," may predict treatment adherence and correlate with clinician-rated AEs.[29] This item may be an important measure of treatment tolerability in and of itself. Therefore, in an exploratory aim, this phase 2 study will assess patient-reported outcome measures of adverse events, treatment tolerability, and health-related quality of life.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 To compare RR of G+N after 4 cycles (8 weeks) to historical controls treated with nivolumab alone.

2.2 Secondary Objective(s)

2.2.1 To compare median overall survival (OS) of G+N to historical controls treated with nivolumab alone.

2.2.2 To compare median progression-free survival (PFS) of G+N to historical controls treated with nivolumab alone.

2.2.3 To evaluate for tolerability of G+N at each treatment cycle and then until 2-6 weeks after treatment is completed.

2.3 Exploratory Objectives

2.3.1 To correlate immunophenotypic changes among lymphocytes (quantitative measurements of CD4 and CD8 T-cells) with radiographic response and overall survival before treatment, after treatment and between 8-12 weeks after treatment.

2.3.2 Among those patients with TMB status available, to describe the association between TMB (low, medium, or high) and RR, OS, and PFS.

2.3.3 Assess the patient perspective of symptomatic adverse events, treatment tolerability, and health-related quality of life using self-reported items from

the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) and Functional Assessment of Chronic Illness Therapy (FACIT).

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed incurable SCLC and have had prior treatment with platinum-based chemotherapy. High-grade neuroendocrine tumors that are suspected to be of bronchopulmonary origin can be enrolled if they have had prior treatment with a SCLC chemotherapy regimen (e.g. platinum plus etoposide).

3.1.2 Patients should not be demonstrating end-organ damage due to rapid progression of disease based on the most recent assessment of the treating physician.

3.1.3 Patients must have radiographically measurable metastatic disease by RECIST criteria.

3.1.4 ECOG performance status of 0-2.

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

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL

3.1.6 Chemotherapy agents are known to be teratogenic, therefore women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

3.2 Exclusion Criteria

3.2.1 Emergent need for palliative radiation.

3.2.2 Patients may not be receiving any other investigational agents for the treatment of SCLC.

3.2.3 History of allergic reaction to gemcitabine.

3.2.4 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina

pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects with chemotherapy. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with chemotherapy, breastfeeding should be discontinued.

3.3 Inclusion of Women and Minorities

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

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on CCCWFU population estimates, we expect approximately 40% of participants to be women. Translating this to our expected enrolled sample size of 60 we plan to enroll at least 20 women. Similarly, we expect approximately 5% of study participants to be Hispanic/Latino (N=3). We plan to enroll at least 15% Black or African American (N=9), no American Indian/Alaska Natives, and 5% Asian (N=3). Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be linked to a study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

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

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

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

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.
4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

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

To complete the registration process, the Registrar will:

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

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 Radiographic RR after 4 cycles (8 weeks) of G+N as compared to baseline CT scan obtained within 2 weeks prior to cycle 1.

5.2 Secondary Outcomes

5.2.1 OS of G+N assessed every 8 weeks from the start of therapy until death among all enrolled participants.

5.2.2 PFS of G+N as determined by investigator assessment. Assessed every 8 weeks from the start of therapy until progression or death among all enrolled participants.

5.2.3 Toxicities will be measured using CTC AE version 5.0 at every treatment cycle and until 2-6 weeks after treatment is completed. Assessed among all enrolled participants.

5.3 Exploratory Outcomes

5.3.1 Clinical outcomes (RR, OS, PFS) and association with immunophenotypic changes among lymphocytes (CD4 vs. CD8).

5.3.2 Clinical outcomes (RR, OS, PFS) and association with TMB (low, 0 to <143; medium, 143 to 247; or high, >248).

5.3.3 Descriptive analysis of patient responses to PRO-CTCAE and FACIT items.

6.0 Treatment Plan

6.1 Study-Related Interventions

	Pre-Study[a]	At Each Treatment	While on treatment[b]	Post-Treatment Visit	Follow-up
Informed consent	X				
Demographics	X				
Medical history	X				
Baseline tobacco (Appendix E)	X				
Concurrent meds	X				
Physical exam	X	X[b]	X	X	
Vital signs	X	x	X	X	
Height, Weight, M^2	X				
Performance Status	X			X	
Tumor measurements	X			X	
CBC w/diff, platelets	X	X		X	
Serum chemistry[c]	X	X		X	
B-HCG[d]	X				
Adverse event evaluation[f]		X	X	X	X
PRO-CTCAE and selected FACIT items[e]	X	X	X	X	X
Research Blood Draw[g]	X			X	X

a:Pre-study requirements listed in table must be completed within 14 days prior to registration. Scans must be done within 28 days prior to registration..
b: Physical exam not necessary at every treatment visit.
c:Alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, SGOT[AST], SGPT[ALT]
d:Serum pregnancy test (women of childbearing potential).
e: to be performed at patient preference
f: There are 3 research blood draws in total. The first “baseline” blood draw will be within 2 weeks prior to administration of cycle 1; it can be drawn on the date of first treatment as long as it is collected before infusion is started. The second “post-treatment” blood draw should be drawn within 2-4 weeks after administration of cycle 4. The third “follow-up” blood draw should be within 6-10 weeks after administration of cycle 4.

6.2 Treatment Administration

Patients who have relapsed or refractory SCLC, have previously had platinum-based chemotherapy, and have radiographically measurable metastatic disease will be registered and consented.

Regimen
The treatment regimen will consist of four - two-week cycles for both gemcitabine and nivolumab that will be administered initially as directed below, unless otherwise indicated by the treating physician.

G+N Treatment Regimen:

- Day 1of each cycle:
  - Gemcitabine: 1000mg/m^2 IV.
  - Nivolumab: 240 mg IV.
- Treatment will be repeated every 2 weeks +/- 3 days
- Days 2-14: No Treatment

Treatment among all groups will be administered on either an inpatient or outpatient basis as per the treating physician. Reported adverse events and potential risks are described in Section 8.0. Appropriate dose modifications are described in Section 6.2.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.2.1 Premedication regimen and concurrent medications

Anti-emetics:

Anti-emetics should consist of standard 5HT3 antagonist medications at the investigators discretion. Use of corticosteroids as prophylactic anti-emetics should generally be avoided and reasons for the use of these drugs as pre-medications should be documented.

6.2.2 Dose Modifications

For nivolumab and gemcitabine, dose adjustments during treatment will be made at the investigator's discretion in accordance with standard medical practice. Reasons for dose interruption and dose reduction must be documented.

For non-hematologic toxicities, general guidelines include intervention for intolerable grade 2, any grade 3, or any grade 4 toxicities related to treatment. Intervention may include: addition of a medication to ameliorate symptoms; temporary suspension of dosing; or dose reduction.

For hematologic toxicities, general guidelines include delay in treatment for absolute neutrophil count less than 1500 cells/uL or platelet count less than 100,000 cells/uL. Addition of colony stimulating factors (including neupogen or neulasta) is allowed at the investigator's discretion for treatment of neutropenia.

6.3 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 in the medical record.

6.4 Duration of Therapy

The duration of the research treatment is through the first follow-up CT scan. Treatment may continue beyond this point at the investigator's discretion. 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 adverse event(s), specifically if Grade 3 or 4 neurotoxicity is observed
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.5 Duration of Follow Up

Patients have one follow-up assessment (either in clinic or over phone) between 2-6 weeks (14-42 days) after administration of cycle 4for adverse events monitoring. If no clinic visit occurs during this window, a phone call confirmation should be made to the patient to determine vital status and whether any adverse events and in particular, Grade 4 unexpected adverse events occurred during that window of time and recorded on Appendix G.

7.0 Measurement of Effect

7.1.1 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.

7.1.2 Response Criteria - RECIST

Target Lesions
At time of each tumor assessment, the response in target lesions is defined as follows:

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): Decrease by ≥ 30% in sum of longest diameter of target lesions.
- Stable Disease (SD): Not meeting criteria for CR, PR, or PD.
- Progressive Disease (PD): Increase by ≥ 20% in sum of longest diameter of target lesions *or* the appearance of one or more new lesions.

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 CR.

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

- Complete Response (CR): Complete disappearance of all non-target lesions.
- Stable Disease (SD): Persistence of one or more non-target lesion(s).
- Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

7.1.3 Assessment for efficacy

RR will be assessed after 4 cycles (8 weeks) of treatment with gemcitabine and nivolumab.

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

Objective RR: 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 CR, or PR (if CR is never met), until the first date that PD is confirmed by independent radiology review or death, whichever comes first

Disease control rate: the percentage of subjects who achieved CR, PR, or SD

Duration of disease control: the duration of time from the date measurement criteria are first met for CR, PR, or SD, until the first date that PD is confirmed by independent radiology review or death, whichever comes first

Tumor measurement imaging after 4 cycles at 8 weeks +/- 1 week of treatment with gemcitabine and nivolumab.

7.1.4 Survival Outcomes

Progression-Free Survival (PFS) is defined as the duration of time from the start of treatment to the time of investigator assessed progression or death. PFS will be assessed every 4 cycles (8 weeks) among all registered participants. Following the completion of the intervention, PFS will be assessed approximately every 8 weeks by chart review. Any participants who are lost to follow up will be censored.

Overall Survival (OS) is defined as the duration of time from the start of treatment to date of death. OS will be assessed every 4 cycles (8 weeks) among all registered participants. Following the completion of the intervention, OS will be assessed approximately every 8 weeks by chart review. Any participants who are lost to follow up will be censored.

8.0 Adverse Events List and Reporting Requirements

8.1 Adverse Event List for Gemcitabine

Bone marrow suppression is the most common dose-limiting toxicity of gemcitabine. Other common side effects include edema, alopecia, rash, hyperglycemia, hypomagnesemia, constipation, diarrhea, nausea, vomiting, stomatitis, anemia, neutropenia, thrombocytopenia, elevated liver function tests, infections, lymphocytopenia, paresthesia, neuropathy, hematuria, proteinuria, elevated creatinine, dyspnea, fatigue, and fever.

8.2 Adverse Event List for Nivolumab

Most common adverse reactions have included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, thyroid function abnormalities, and diarrhea. The most frequent serious adverse drug reactions were renal failure, dyspnea, and pneumonitis.

8.3 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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A

copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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

- **Attribution** of the AE:

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

8.4 STRC SAE Reporting Requirements

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

8.5 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.

9.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

9.1 Pharmaceutical Accountability

All drugs used in this protocol are commercially available.

9.2 Gemcitabine (Gemzar)

Product Description: Gemcitabine is supplied in 200 mg and 1000 mg vials. Two hundred mg vials are reconstituted in 5 cc sodium chloride then diluted to a concentration of as low as 0.1 mg/ml if necessary for infusion. The dose is usually 1000 or 1250 mg/m^2 given over 30 minutes. One thousand mg vials are reconstituted with 25 cc sodium chloride. It is stored at room temperature until given.

Preparation:
Caution should be exercised in handling and preparing Gemzar solutions. The use of gloves is recommended. If Gemzar solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The

appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

Route of Administration: Intravenous

Storage: Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F). Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined controlled room temperature as “A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Stability: When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

Disposal: Dispose through the Institutional waste stream and guidelines.

Nivolumab (OPDIVO)

Product description:

OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. OPDIVO for injection is supplied at 40 mg/4 mL and 100 mg/10 mL in a single use vial.

Solution preparation:

Caution should be exercised in handling and preparing OPDIVO for Injection, USP. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing OPDIVO for Injection, USP.

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.

- Mix diluted solution by gentle inversion.
- Do not shake.
- Discard partially used vials or empty vials of OPDIVO

Storage requirements:
The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

Stability:
OPDIVO is stable for no more than 4 hours at room temperature from the time of preparation and for no more than 24 hours under refrigeration 2°C-8°C (36°F to 46°F)

Route of administration:
Intravenous

Administration

- Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Do not co-administer other drugs through the same intravenous line.
- Use separate infusion bags and filters for each infusion.

Disposal: Dispose through the Institutional waste stream and guidelines.

10.0 Exploratory Studies Collections and Processing

To address the exploratory objective, 2.3.1, at 3 separate timepoints, blood samples for research draw will be obtained for plasma and other biomarker analyses. The first "baseline" blood draw will be within 2 weeks prior to administration of cycle 1. The second "post-treatment" blood draw will be within 2-4 weeks after administration of cycle 4. The third "follow-up" blood draw will be within 6-10 weeks after administration of cycle 4. In most cases, blood testing will be added on to regularly scheduled phlebotomy for clinical labs which are drawn as part of routine oncology care. Some participants may require an additional blood draw if insufficient blood samples were collected. For the purposes of our study, 6 mL of venous blood will be collected in a sodium heparin (green-top) collection tube and then transferred directly to Dr. Triozzi's lab in the Department of Cancer Biology for processing per laboratory protocols for downstream

analysis. Venous blood will be stored in lab refrigerator prior to transfer (in oncology lab) and after transfer (in Dr. Triozzi's lab) prior to processing and then freezing. Plasma will be stored and analyzed by the Genetics Core and Biomedical Engineering laboratories at Wake Forest School of Medicine or Dr. Triozzi's laboratory for future studies that may include changes in ctDNA markers (Dr. Greg Hawkins and Dr. Adam Hall). Assessed among all enrolled participants as permitted by research funding. .

A patient-reported outcome measures of treatment-related adverse events, treatment tolerability, and health-related quality of life will be filled out by patients at patient preference.

11.0 Data Management

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Baseline Tobacco Use (Appendix E)	WISER/OnCore
Tumor Measurement Form (Appendix F)	WISER/OnCore
30 Day Treatment Follow-up Form (Appendix G)	WISER/OnCore
Adverse Events Form (Appendix H)	WISER/OnCore
Survival Data (Appendix I)	WISER/OnCore
Treatment Response Form (Appendix J)	WISER/OnCore
Evaluation of Best Response (Appendix K)	WISER/OnCore
Off-Study Form (Appendix L)	WISER/OnCore
Exploratory Studies Form (Appendix M)	WISER/OnCore
PRO-CTCAE and FACIT items (Appendix N)	WISER/OnCore/REDCap

12.0 Statistical Considerations

12.1 Power and Sample Size

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis of the historical RR 10% will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued. Accrual will continue until the first 10 patients have either been evaluated for response or withdrawn from the study. If there is 1 or fewer responses in the first10 patients, the study will be stopped and no further patients will be accrued' patients who have already been enrolled on the study will complete their treatment per protocol. If there are 2 or more responses in the first 10 patients, 19 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 6 or more responses are observed in 29 patients. This design yields a type I error rate of 0.047 and power of 0.8 when the true response rate is 30%.

12.3 Analysis of Primary Objective

Response by RECIST comparing CT scan at the time of registration to CT scan following 4 cycles of treatment. Objective RR (CR+PR) will be compared between this study sample and a historical benchmark value of 10%.[3] For this comparison we will use a one-sample test of proportion.

12.4 Analysis of Secondary Objectives

Overall survival and progression free survival rates will be estimated in our sample using standard Kaplan Meier survival analysis methods. Median PFS from all participants treated with G+N will be compared to historical control of median 1.4 months among 98 participants treated with nivolumab for SCLC. Median OS from all participants treated with G+N will be compared to historical control of median 4.4 months among 98 participants treated with nivolumab for SCLC.[3] Toxicity rates will be estimated by responder status and presented overall and by body site.

12.5 Analysis of Exploratory Objective

Changes in T regulatory cell concentrations will be assessed in each arm (Dr. Triozzi). These measures will be compared longitudinally to examine whether changes in certain biomarkers are associated with patients who experience an objective response. Peripheral blood samples at 3 time points (baseline before study treatment, post-treatment, and at follow-up [between 6 and 10 weeks post-treatment]) will be analyzed by flow cytometry (flow cytometry core, Dr. Triozzi).

TMB status (low, medium, or high) will be assessed as to how they relate to RR, OS, and PFS. This subgroup analysis will be in a descriptive manner only due to the small size of the study.

Participants self-reported adverse events (PRO-CTCAE assessment), treatment tolerability (FACIT item), and health-related quality of life (FACIT items) will be assessed at patient preference; these scores will be reported in a descriptive manner only due to the small size of the study. We will also report the numbers of participants who were offered and completed this optional measure; this is to assess acceptability of obtaining this measure routinely among lung cancer participants at this institution.

12.6 Estimated Accrual Rate

We estimate that we will enroll approximately 15 patients per year. Given our target completed enrollment of 29 patients, and allowing for 5% drop out, we estimate it will take approximately 25 months to enroll 31 patients.

12.7 Estimated Study Length

Approximately 31 months, allowing for 6 months' follow-up on last patient.

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Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

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

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

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

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

Date Consent Signed (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

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

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 336-713-6772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

IRB Protocol No. 00051024	**CCCWFU Protocol No.62418**
Study Title: Phase II Pilot Study of Subsequent Line Gemcitabine and Nivolumab for Advanced SCLC	
Principal Investigator: Thomas Lycan, DO	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm ***
Patients must have histologically or cytologically confirmed incurable small cell lung cancer and have had prior treatment with platinum-based chemotherapy. High-grade neuroendocrine tumors that are suspected to be of bronchopulmonary origin can be enrolled if they have had prior treatment with a SCLC chemotherapy regimen (e.g. platinum plus etoposide).	☐	☐	
Patients should not be demonstrating end-organ damage due to rapid progression of disease based on the most recent assessment of the treating physician	☐	☐	
Patients must have radiographically measurable metastatic disease by RECIST criteria	☐	☐	
ECOG performance status of 0-2	☐	☐	
Absolute neutrophil count ≥1,500/mcL	☐	☐	
Platelets ≥100,000/mcL	☐	☐	
Chemotherapy agents are known to be teratogenic, therefore women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. 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 ***
Emergent need for palliative radiation	☐	☐	
Patients may not be receiving any other investigational agents for treatment of small cell lung cancer	☐	☐	

History of allergic reaction to gemcitabine	☐	☐	
Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	☐	☐	
Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects with chemotherapy. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with chemotherapy, breastfeeding should be discontinued	☐	☐	

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

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____
Date (mm/dd/yy): ___ ___/___ ___/___ ___

Signature of Treating Physician: _____
Date (mm/dd/yy): ___ ___/___ ___/___ ___

Signature of Principal Investigator**: _____
Date (mm/dd/yy): ___ ___/___ ___/___ ___

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

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

Appendix C - Race & Ethnicity Verification Form

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

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

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

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____

_____

_____

Appendix D – Mandatory STRC SAE Reporting Guidelines

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

Mandatory STRC SAE Reporting Requirements in WISER

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

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

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

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the STRC.

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

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

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

What is considered during protocol intervention?

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

What is considered as an Unexpected Grade 4 event?

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

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

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the STRC members will not be notified until a date is entered into the STRC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the STRC has been contacted. Indicate the name of

the STRC clinician that was contacted in the Event Narrative field in the SAEconsole of the particular subject.

4. Document whether or not the protocol should be suspended based on the discussion with the STRC clinician. This is the major function of the email notification. Enterwhether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of STRC regarding any new developments orinformation obtained during the course of the SAE investigation and reporting process.

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

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the STRC clinician who was notified and Date/Time notified. In addition, state attribution by STRC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. STRC clinician name and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with STRC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification *This is required in order for the email notification to be sent*
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified STRC -- *This is required for the email notification to be sent*
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do

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

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

Bayard Powell, MD – Director-at-Large, WFBCCC; Section Head, Hematology/Oncology 6-7970 / 6-2701 / Pager 336-806-9308
Glenn Lesser, MD – Hematology Oncology 6-9527 / 6-7972 / Pager 336-806-8397
Stefan Grant, MD, JD-Hematology Oncology 3-5172/ 6-5772 Pager 336-806-6453
Jimmy Ruiz, MD-Hematology Oncology 6-0230/ Pager 336-806-9710
Mercedes Porosnicu, MD- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150
Michael Farris, MD – Radiation Oncology 3-6540 / 3-6505 Pager 336-806-8541

Definition of Unavailable:

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

STRC CLINICAN RESPONSIBILITY:

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

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the STRC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This

information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click update. This will allow additionalinformation to be added

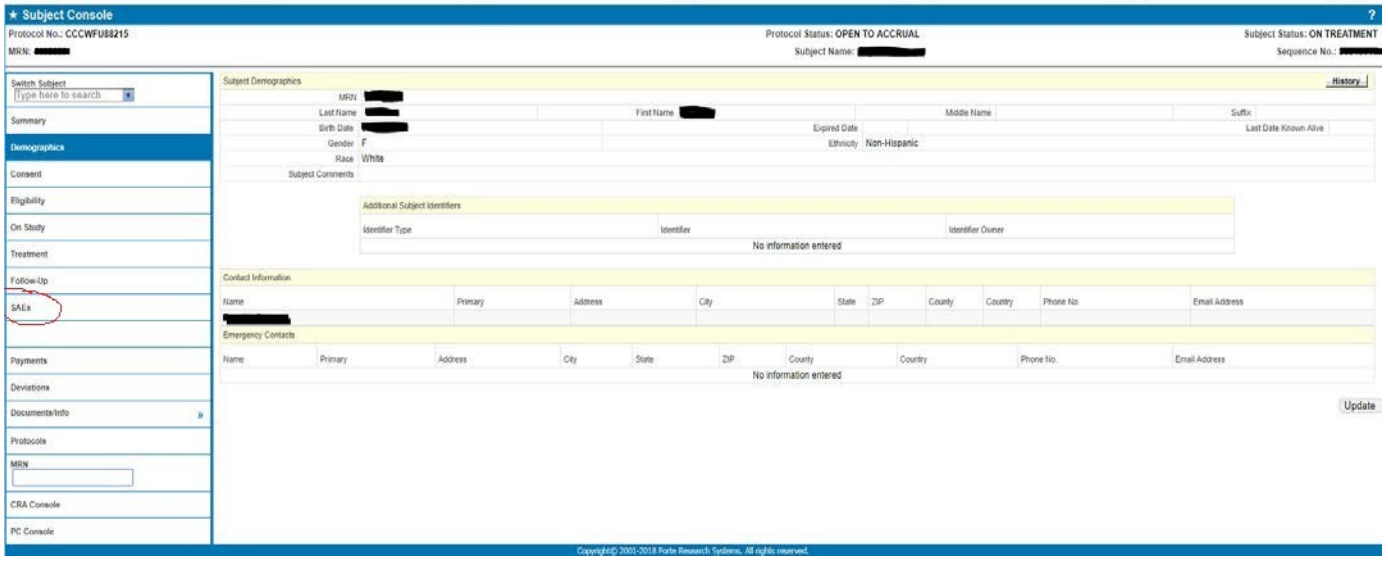
Acronyms

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

Screen Shots:

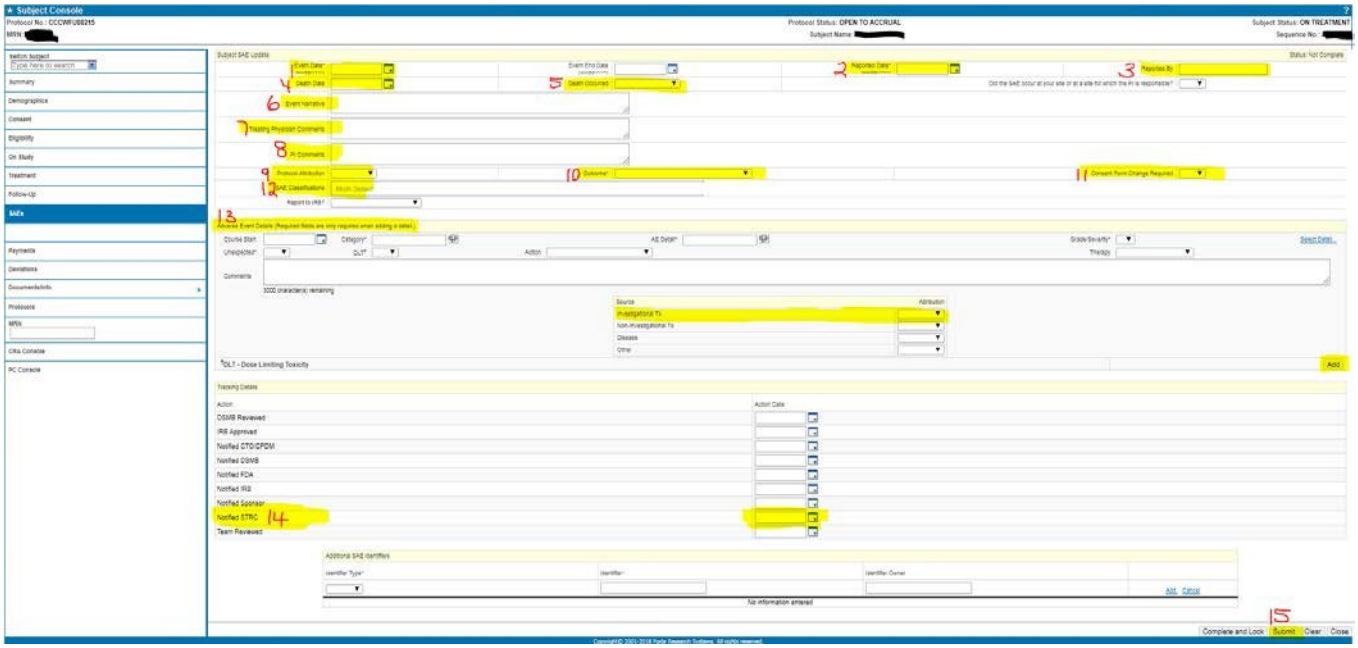
The following screen shots come from the SAE Console within the Subject Console in WISER.

Screen Shot 1:

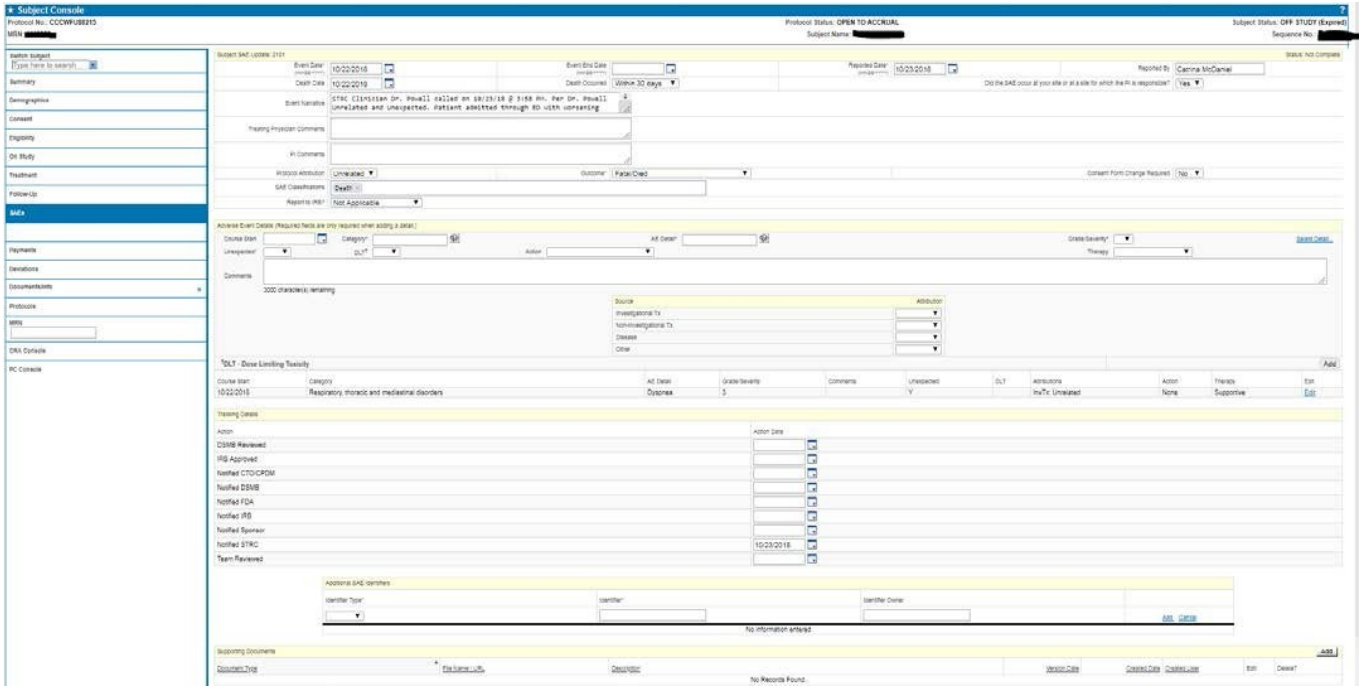


Screen Shot 2:

Screen Shot 3:



Screen Shot 4:



Appendix E – Baseline Tobacco Use

Instructions: Case Report Study Form for patient tobacco use to be used at baseline

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Thomas Lycan, DO Date(mm/dd/yy): ___ ___/___ ___/___ ___

CANCER PATIENT TOBACCO USE QUESTIONNAIRE (C-TUQ)

Please answer the following questions. This information is confidential and will not be shared with your medical providers.

Section 1. Basic Tobacco Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?

☐ Yes
☐ No **Go to Section 2 (page 2).**
☐ Don't know/Not sure **Go to Section 2 (page 2).**

2. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.

_____ Years *If you smoked less than one year, write "1."*

3. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day?

A pack usually has 20 cigarettes in it.

_____ Number of cigarettes per day

4. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff).
☐ 1-7 days. Number of days since last cigarette: _____

☐ Less than 1 month. Number of weeks since last cigarette: _____
☐ Less than 1 year. Number of months since last cigarette: _____
☐ More than 1 year. Number of years since last cigarette: _____
☐ Don't know/Don't remember

5. In the past 30 days, have you smoked any cigarettes, even one or two puffs?

☐ Yes
☐ No → Go to Question 7.

6. In the past 30 days, have you been trying to quit (or trying to stay off) smoking cigarettes?

☐ Yes
☐ No

Section 2. Use of Other Products

7. Which of the following products have you ever used regularly?

Check all that apply.

☐ Cigarettes
☐ E-cigarettes or other electronic nicotine delivery system
☐ Traditional cigars, cigarillos or filtered cigars
☐ Pipes
☐ Hookah
☐ Clove cigarettes or kreteks
☐ Bidis
☐ Smokeless tobacco, like dip, chew, or snuff
☐ Snus
☐ Paan with tobacco, gutka, zarda, khaini
☐ None
☐ Other, *Please specify*: _____

8. In the past 30 days, which of the following products have you used?

Check all that apply.

☐ Cigarettes
☐ E-cigarettes or other electronic nicotine delivery system
☐ Traditional cigars, cigarillos or filtered cigars

☐ Pipes
☐ Hookah
☐ Clove cigarettes or kreteks
☐ Bidis
☐ Smokeless tobacco, like dip, chew, or snuff
☐ Snus
☐ Paan with tobacco, gutka, zarda, khaini
☐ None
☐ Other, Please specify: _____

Section 3. Second-Hand Smoke Exposure

9. Are you currently living with a smoker?

☐ Yes
☐ No

10. In the past 30 days, have you…

	Yes	No
a. Lived in a place where other people smoked cigarettes indoors?	☐	☐
b. Worked in a place where other people smoked cigarettes indoors?	☐	☐

11. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?

☐ Yes →In total, for about how many years? ____ *If less than 1, write "1."*
☐ No

12. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?

☐ Yes →In total, for about how many years? ____ *If less than 1, write "1."*
☐ No

Thank you for completing this questionnaire.

Appendix F - Tumor Measurement Worksheet

Target Lesions

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

Non-Target Lesions

NON-TARGET Lesions	Lesion	Site	Imaging	Baseline	Cycle_____	Cycle_____	Cycle_____	Cycle_____	Cycle_____
	01								
	02								
	03								
	04								
	05								
	Non-Target Lesion Response			**N/A**					

New Lesions

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

Overall Tumor Response	**Cycle___**	**Cycle___**	**Cycle___**	**Cycle___**	**Cycle___**
Radiologist Signature:					

Treating Physician Signature:						
PI Signature:						

***Terms & Calculations**

Baseline: *The set of data collected prior to randomization*
Nadir: *The lowest point*

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

LIST ALL TARGET AND NON-TARGET SITES TO BE USED FOR RESPONSE:

Appendix G – 30 - day Treatment Follow-up Form

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Thomas Lycan, DO Date(mm/dd/yy): ___ ___/___ ___/___ ___

Instructions: Complete this form to follow-up with patients for adverse events.

Name of Person Competing form_____

Did the subject have any adverse events in the last 30 days? ☐Yes ☐No

If yes, please describe nature and grade of AE (Note*: If an SAE occurs in this period, report the event as required in Appendix D of this protocol):

_____
_____
_____
_____
_____
_____

Was the subject removed from the study by the PI? ☐Yes ☐No

Did the subject withdraw from the study? ☐Yes ☐No

Did the subject complete the study? ☐Yes ☐No

Appendix H - Adverse Events Log

PID #: _____	MRN #: _____				CYCLE #: _____	
Adverse Event CTC Term (Version 5.0)	Lab Value	Grade (1-5) per CTC	Start/ End Date	Attribution DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated	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

Appendix I - Survival Data

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Thomas Lycan, DO Date(mm/dd/yy): ___ ___/___ ___/___ ___

Study Visit:
- ☐ End of Cycle 4 (8 weeks)
- ☐ 2 months post-treatment
- ☐ 4 months post-treatment
- ☐ 6 months post-treatment
- ☐ 8 months post-treatment
- ☐ 10 months post-treatment
- ☐ 12 months post-treatment
- ☐ 14 months post-treatment
- ☐ 16 months post-treatment
- ☐ 18 months post-treatment
- ☐ 20 months post-treatment
- ☐ 22 months post-treatment
- ☐ 24 months post-treatment
- ☐ 26 months post-treatment
- ☐ 28 months post-treatment
- ☐ 30 months post-treatment
- ☐ 32 months post-treatment
- ☐ 34 months post-treatment
- ☐ 36 months post-treatment
- ☐ 38 months post-treatment
- ☐ 40 months post-treatment
- ☐ 42 months post-treatment
- ☐ 44 months post-treatment
- ☐ 46 months post-treatment
- ☐ 48 months post-treatment
- ☐ Other visit: (please specify) _____

DATE OF LAST CONTACT (mm/dd/yy): ___ ___ / ___ ___ / ____ ___

DECEASED: Y____ N____ Unknown ____

DATE OF DEATH (mm/dd/yy): ___ ___ / ___ ___ / ____ ___

Appendix J – Treatment Response Evaluation Form

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator Thomas Lycan, DO. Date (mm/dd/yy): __ __/__ __/__ __

Study Visit:

☐ After Treatment (Visit 5)
☐ Other visit: (please specify) _____

Date of Scan (mm/dd/yyyy): ___ ___ /___ ___ /___ ___ ___ ___

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

Evaluation of Target Lesions

☐ Complete Response (CR)

☐ Partial Response (PR)

☐ Progressive Disease (PD)

☐ Stable Disease (SD)

☐ NE

Evaluation of Non-Target Lesions

☐ Complete Response (CR)

☐ Non-CR/Non-PD

☐ Progressive Disease (PD)

☐ NE

Overall Response this Visit

☐ Complete Response (CR)

☐ Partial Response (PR)

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

☐ Stable Disease

☐ NE

Treating Physician Signature: _____
Date (mm/dd/yyyy): ___ ___ /___ ___ /___ ___ ___ ___

PI Signature: _____
Date (mm/dd/yyyy): ___ ___ /___ ___ /___ ___ ___ ___

Appendix K-Evaluation of Best Overall Response

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator Thomas Lycan, DO Date (mm/dd/yy): __ __/__ __/__ __

Study visit of best response:

☐ After Treatment (Visit 5)
☐ Other visit: (please specify) _____

Date of scan for best response (mm/dd/yy)**:** ___ ___ /___ ___ /___ ___

Best Response:

Target Lesion	Non-Target Lesion	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Please check one based on clinical review of imaging:

☐ Complete Response (CR)
☐ Partial Response (PR)
☐ Progressive Disease (PD) Date of progression (mm/dd/yy): ___ ___ /___ ___ /___ ___
☐ Stable Disease (SD)
☐ NE

Please check if patient removed from study due to clinical deterioration for any reason:

☐ Symptomatic deterioration

Please explain: _____

Treating Physician Signature: _____

Date(mm/dd/yy): ___ ___ /___ ___ /___ ___

PI Signature: _____

Date(mm/dd/yy): ___ ___ /___ ___ /___ ___

Appendix L – Off-Study Form

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Thomas Lycan, DO Date (mm/dd/yy): __ __/__ __/__ __

Instructions: Complete this form if the patient either withdraws consent or is removed from the study.

Name of Person Competing form_____

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Was the subject removed from the study per physician decision? Yes ☐ No ☐
(if yes, move to #6)

Did the patient withdraw consent to participate in the study? Yes ☐ No ☐
(if yes move to #1)

Reason for patient withdrawal:

1. ☐ Unacceptable toxicity from Gemcitabine
2. ☐ Unacceptable toxicity from Nivolumab
3. ☐ Did not want to participate anymore. Reason:
   _____
4. ☐Other: _____
5. Please specify what portion of the study the subject wishes to withdraw from:

   ☐ For just the (circle) *Gemcitabine* and/or *Nivolumab* administration only
   ☐ For all components of the research study (including follow up in the medical record)

Reason(s) for Removal:

6. ☐ Patient exhibited progression of disease

7. ☐ Unacceptable toxicity from:
   a. ☐ Gemcitabine
   b. ☐ Nivolumab

8. ☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest (*Describe below)

9. ☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible (*Describe below)

10. ☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment (*Describe below)

11. ☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits (*Describe below)

12. ☐ Termination of the clinical trial by the clinical sponsor

Comment:

If reason for withdrawal includes options 8-11 then please add comments clarifying this information)_____

_____

_____

_____

Appendix M – Exploratory Studies Form

Instructions: Use this form to record data related to the exploratory objectives

Study Number: CCCWFU 62418 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Thomas Lycan, DO Date (mm/dd/yy): __ __/__ __/__ __

1. Blood Studies
Visit ☐ Baseline ☐ Post-Treatment ☐ Follow-up (8-12 weeks after treatment)

CD4+ T cells: _____

CD8+ T cells: _____

2. Tumor mutation burden classification (record when results are available)

☐ Low (0 to <143 mutations)

☐ Medium (143 to 247 mutations)

☐ High (>248 mutations)

Appendix N – PRO CTCAE & Selected FACIT Items

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

English

Form created on 12 December 2018

This survey is OPTIONAL for study participants. It is designed to assess the patient perspective of symptomatic adverse events, treatment tolerability, and health-related quality of life using self-reported items.

[ ] Please check here if the questionnaire was offered and the patient DECLINED.

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an in the one box that best describes your experiences over the past 7 days…

1. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

2. In the last 7 days, how OFTEN did you have NAUSEA?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

3. In the last 7 days, how OFTEN did you have VOMITING?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

4. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

5. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

6. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

7. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

8. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

9. In the last 7 days, what was the SEVERITY of your WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

10. In the last 7 days, did you have any RASH?
○ Yes ○ No

11. In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

12. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

13. In the last 7 days, how OFTEN did you have PAIN?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your PAIN at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

14. In the last 7 days, how OFTEN did you have a HEADACHE?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

15. In the last 7 days, how OFTEN did you have ACHING MUSCLES?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or dailyactivities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

16. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

17. In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

18. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

19. In the last 7 days, how OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES/FLUSHES)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES/FLUSHES) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

FACIT Items

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to <u>the past 7 days.</u>**

8. I am bothered by the side effects of treatment.

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

9. I am able to do my usual activities.

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

10. I am able to enjoy life.

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much