Phase II Pilot Study Evaluating Strategies to Overcome Resistance at the Time of Progression for Patients with Non-Small Cell Lung Cancers Harboring Major Oncogenic Drivers
Wake Forest Baptist Comprehensive Cancer Center (CCCWFU)
CCCWFU 62716
ClinicalTrials.gov: NCT02949843

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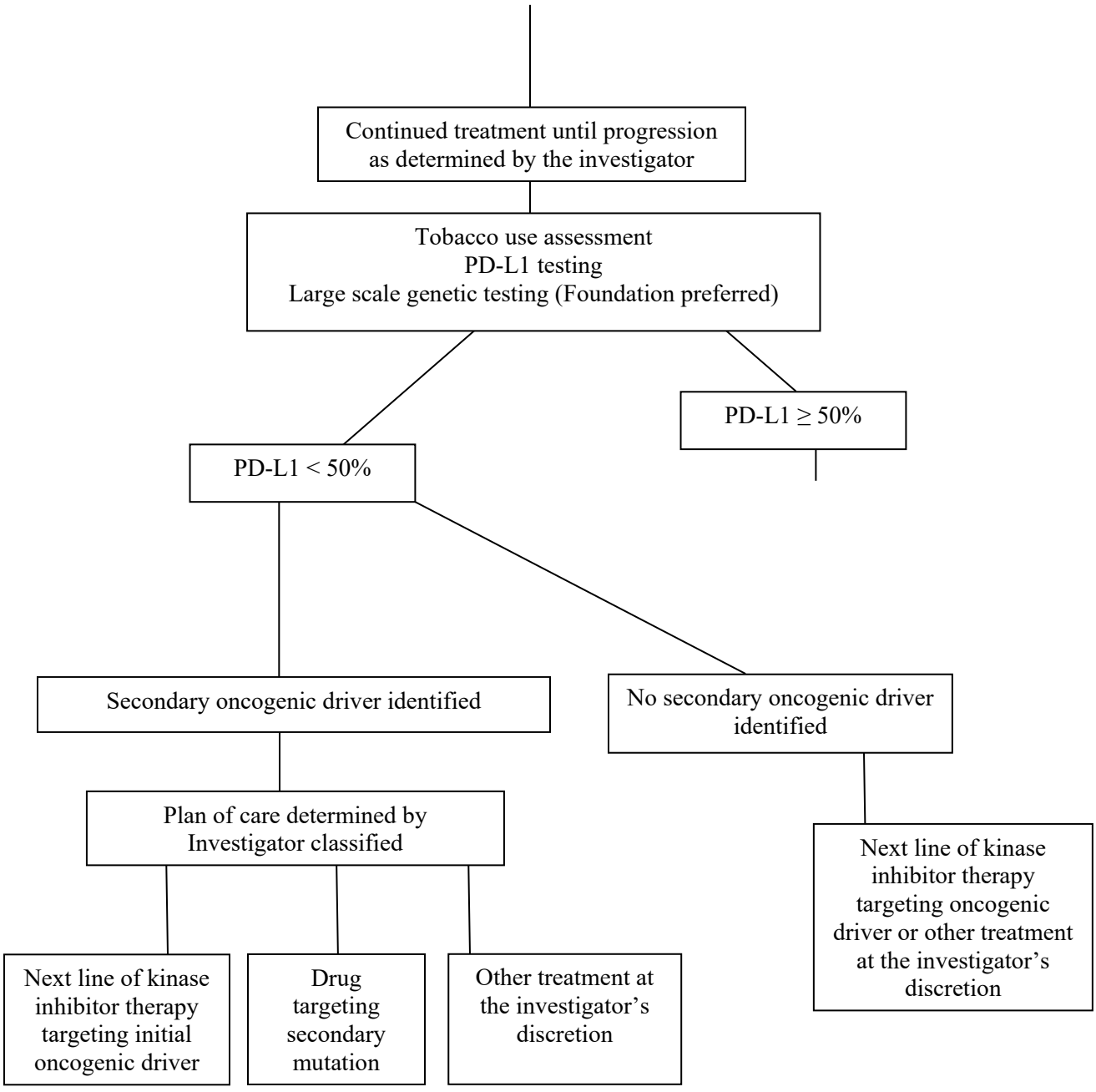

1.0 Introduction and Background

Lung cancer (LC) is the third most common cancer in both men and women and the leading cause of cancer death.[1] Non-small cell (NSC) lung cancer includes three main subtypes, squamous cell carcinoma (25%), adenocarcinoma (40%), and large cell carcinoma (10%).[2] Only approximately 15% of lung cancer cases are diagnosed at the local stage.[1]

Major oncogenic drivers in non-small cell lung cancer include mutations in EGFR, translocations in Alk, and translocations in ROS-1. National Comprehensive Cancer Network (NCCN) guidelines also have supported the use of medications targeting BRAF, Met, HER-2, and RET. Investigators have reported emergence of mutations in a secondary oncogenic drivers at the time of progression on tyrosine kinase inhibitor therapy for patients whose tumors harbor primary activating mutations in one of the major three (EGFR, Alk, or ROS-1) drivers.

The plan of care for patients whose cancer progresses on treatment with one of the major 3 driver mutations may include sequencing of the primary driver gene for emergence of an additional mutation in that gene. Immunotherapy may also benefit some patients with acquired resistance, but the role of these medications is not well defined. High PD-L1 expression and response to immunotherapy has been reported in patients with oncogenic drivers who smoke cigarettes.

The use of expanded genetic testing in this situation to identify mutations in genes other than the primary driver gene (secondary mutations) is attractive for exploring all available treatment options. The outcomes of patients who undergo testing and have mutations in a secondary gene have not been prospectively studied. Available options include alternative agent targeting the original driver mutation, changing treatment to target the mutation in the secondary gene, combination therapy targeting both, or other treatments such as chemotherapy, immunotherapy, or clinical trials.

The goal of this protocol is to evaluate the efficacy of treatment tailored to the immunogenic and mutation profiles of patients on EGFR, MET, BRAF, V600E, RET, HER2, Alk, or ROS-1inhibitors at the time of progression. This pilot study will compare the clinical outcomes for treatment of resistance targeting the primary mutations, secondary mutations, or immunotherapy.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 To estimate the objective response rate among patients with high PD-L1 expressing cancers after failure of targeted therapy.

2.2 Secondary Objective(s)

2.2.1 To compare the overall survival for patients receiving treatment targeting primary mutations, secondary mutations, or immunotherapy at the time of progression on tyrosine kinase inhibitor therapy

2.2.2 To assess the incidence of secondary mutations in this population according to smoking status.

2.2.3 To evaluate the response rates of patients treated using these different approaches.

2.2.4 To correlate outcomes with specific secondary genetic changes.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed incurable non-small cell lung cancer that harbors an activating mutation in EGFR, MET, BRAF, V600E, RET, HER2, translocation in Alk, or translocation in ROS-1.

3.1.2 Patients must be receiving treatment or planning to start treatment with a tyrosine kinase inhibitor targeting the activated gene.

3.1.3 Patients may not be receiving the treatment targeting the activated gene as part of a clinical treatment trial other than the Precision Oncology Trial.

3.1.4 ECOG performance status of 0-3.

3.1.5 Patients must have normal organ function as defined below:

- AST(SGOT)/ALT(SGPT) $\leq$2.5 X institutional upper limit of normal

3.1.6 These agents may 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 non-small cell lung cancer.

3.2.3 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.

3.2.4 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 WFBCCC population estimates, we expect approximately 44% of participants to be women. Translating this to our sample size estimate of up to 75, we plan to enroll at least 33 women. We plan to enroll at least 11% Black or African Americans (N=8). Because of the low incidence of lung cancer in our catchment area in the Hispanic/Latino (.8% or possibly an N=1), Asian, and American Indian/Alaska native populations we would not expect to obtain individuals from these populations in this particular study. 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 WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be registered with the WFBCCC 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 A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

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

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

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

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

To complete the registration process, the Registrar will:

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

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The primary outcome measure is the objective response rate among patients with high PD-L1 expressing cancers after failure of targeted therapy

5.2 Secondary Outcomes

5.2.1 Overall survival (OS) of three patient cohorts (immunotherapy sensitive, primary targetable mutation, and secondary targetable mutation is the first secondary outcome.

5.2.2 Objective response rates for the other patient cohorts (patients without high PD-L1 expressing cancers) and the combined population to historical controls receiving second or third line targeted agents.

5.2.2 Toxicities which will be measured using CTCAE version 4.0

5.2.3 Incidence of mutations in secondary genes

5.2.4 Rate of tobacco use and mutation burden by patient group based on PD-L1 expression (yes/no) at the time of progression.

6.0 Treatment Plan

6.1 Study-Related Interventions

	Pre-Study[a]	At Each Treatment	After First-Progression	Follow-up
Informed consent	X			
Demographics	X			
Medical history	X			
Concurrent meds	X			
Physical exam	X		X	X
Vital signs	X		X	X
Height, Weight, M^2	X			
Performance Status	X		X	X
Tumor measurements			X	X[d]
CBC w/diff, platelets	X	X	X	X
Serum chemistry[b]	X	X	X	X
B-HCG[c]	X			
Adverse event evaluation		X	X	X
Tobacco Use Assessment	X		X	
Research blood (plasma)	X		X	
Tumor Biopsy			X	

a: Pre-study requirements listed in table must be completed **within** 14 days prior to registration.
b: Alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, SGOT[AST], SGPT[ALT]
c: Serum pregnancy test (women of childbearing potential).
d: After the patient receives first dose of study drug they should be followed for progression on the following time line: for patients receiving nivolumab, imaging should be performed every 8 weeks +/- 3 days for the first two imaging studies. For patients receiving pembrolizumab, imaging should be performed every 9 weeks +/- 3 days for the first two imaging studies. After the first two imaging studies, additional follow-up imaging interval will be at the investigator's discretion. For patients receiving other treatments, all follow-up imaging intervals will be at the investigator's discretion.

6.2 Treatment Administration

Patients currently receiving or about to start treatment with an oral tyrosine kinase inhibitor for one of the major oncogenic drivers (EGFR, MET, BRAF, V600E, RET, HER2, Alk, or ROS-1) will be eligible. At the time of registration, blood samples will be obtained for plasma and other biomarker analyses (Appendix J), tobacco use (Appendix D) and performance status (Appendix K) will be determined. Treatment with an agent targeting the primary oncogenic driver will be continued until progression. If a new agent is approved for treatment of the primary driver, patients may be changed prior to progression at the investigator's discretion.

At the time of progression, patients will undergo repeat biopsy to determine PD-L1 staining and large scale genetic testing. Foundation Medicine testing is preferred but patients may have testing performed by other platforms including Guardant 360. Other platforms may be used after discussion with the principal investigator. Research plasma and tissue will be collected (Appendix J). Patients will also complete a detailed tobacco use questionnaire at the time of progression (Appendix E). Further, Performance Status will be determined (Appendix K). While awaiting results of testing, patients may continue the current treatment targeting the primary oncogenic driver.

If the PD-L1 testing result is ≥ 50%, patients will receive immunotherapy with either nivolumab or pembrolizumab as subsequent treatment. If patients have PD-L1 testing result that is < 50%, the large scale testing will be used to determine the presence of absence of a secondary driver. For the purposes of the study, a secondary oncogenic driver will be considered an activating genetic change in a gene other than the primary oncogenic driver gene that has an effective treatment. These would include EGFR, Alk, ROS-1, MET, BRAF V600E, RET, and HER2. Classification of a genetic alteration as a secondary driver will be determined by the investigator.

For patients without secondary oncogenic drivers, treatment will be categorized as subsequent line of treatment, targeting the primary oncogenic driver, or other treatment. For patients with secondary oncogenic drivers, treatment will be categorized as treatment targeting secondary oncogenic driver, subsequent line of treatment targeting the primary oncogenic driver or other treatment. Targeted treatments may include those treatments listed on NCCN Guidelines. Initial medication dose and dose modifications should be implemented according to standard of care guidelines.

Treatment will be administered on an inpatient or outpatient basis. Reported adverse events and potential risks are described in Section 9.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.2.1 Other Studies/Procedures

In relation to additional or optional tissue contribution for study subjects, all subjects will have blood taken at study entry and tumor biopsies and/or blood draws for plasma isolation at the time of first progression after initial driver mutation targeted therapy. If they choose to allow a portion of that tissue to be used for future research it will be stored in the below location:

All samples and specimens should be shipped to:
Wake Forest Cancer Center
Tumor Tissue Core Facility
Care of Dr. Greg Kucera
Hanes Building Rm 4049
Medical Center Blvd
Winston-Salem NC 27157

6.2.2 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.

6.3 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 on the flow sheets.

6.4 Duration of Therapy

The duration of the research treatment is through the first follow-up CT scan after the addition of second-line treatment with nivolumab or pembrolizumab. 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 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 until death for monitoring survival study endpoints.

6.6 Criterial for Removal from Study

Patients will be removed from the study when any of the criteria listed in section 6.4 are met.

Dose Delays/Modifications

6.7 Recommended Dose Modifications for Nivolumab (OPDIVO™)

Table 1: Adverse Reaction	**Severity**	**Dose Modification**
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	
	Single-agent OPDIVO	Withhold dose[a]
	OPDIVO, in combination with ipilimumab	Permanently discontinue
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose[a]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose[a]
	Grade 4 rash	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose[a]
	Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

[a] Resume Treatment when adverse reaction returns to Grade 0 or 1

6.8 Recommended Dose Modification for Pembrolizumab (Keytruda)

Withhold KEYTRUDA for any of the following:

Grade 2 pneumonitis *[see Warnings and Precautions (5.1) of FDA insert]*

Grade 2 or 3 colitis *[see Warnings and Precautions (5.2) of FDA insert]*

Grade 3 or 4 endocrinopathies *[see Warnings and Precautions (5.4) of FDA insert]*

Grade 2 nephritis *[see Warnings and Precautions (5.5) of FDA insert]*

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN

Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.6) of FDA insert]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)

Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity *[see Warnings and Precautions (5.1) of FDA insert]* □

Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5) of FDA insert]*

AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN

For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week □

Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7) of FDA insert]*

Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within
12 weeks

Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA

Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.6) of FDA insert]*

7.0 Measurement of Effect

7.1 Assessment for efficacy

The following efficacy parameters will be assessed by the investigator and are defined as follows:

Objective response rate: the proportion of subjects who achieve complete or partial response according to the investigator's assessment. RECIST measurements should be performed by the investigator as the gold-standard for classifying response.

Duration of best response: the duration of time from the date of response until the first date of progression as determined by the investigator or death, whichever comes first

Disease control rate: the percentage of subjects who achieved CR, PR, or SD which is sustained for at least 3 months.

Duration of disease control: the duration of time from the date of first response until the first date or progression or death, whichever comes first

7.2 Survival Outcomes

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

Overall Survival is defined as the duration of time from the date of progression on current treatment targeting the primary oncogenic driver to date of death or date of last contact.

8.0 Adverse Events List and Reporting Requirements

8.1 Adverse Event list for Pembrolizumab

Most common adverse reactions (reported in ≥20% of patients) with:

- NSCLC included fatigue, decreased appetite, dyspnea and cough.

Adverse Reactions in ≥10% of Patients with NSCLC Pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks N=550		
Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue†	44	4
Pyrexia	12	1
Peripheral Edema	10	0
Metabolism and Nutrition Disorders		

Decreased appetite	25	1
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	23	4
Cough‡	29	<1
Gastrointestinal Disorders		
Nausea	18	1
Diarrhea	15	1
Constipation	15	<1
Vomiting	12	1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	15	1
Back pain	10	2
Blood and Lymphatic System Disorders		
Anemia	12	2
Skin and Subcutaneous Tissue Disorders		
Pruritus	12	0
Rash§	18	<1

* Of the ≥10% adverse reactions, none was reported as Grade 4 or 5.
† Includes the terms fatigue and asthenia
‡ Includes the terms cough, productive cough and hemoptysis
§ Includes the terms dermatitis, dermatitis acneiform, erythema multiforme, drug eruption, rash, rash generalized, rash pruritic, rash macular/maculopapular, papular

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. Additional AEs are listed below:

Adverse Effects

>10% (All grades)

NSCLC

- Fatigue (50%)
- Lymphopenia (47%)
- Dyspnea, hyponatremia (38%)
- Musculoskeletal pain (36%)
- Cough (32%)
- Nausea (29%), anemia (28%), constipation (24%)
- Increases creatinine (22%)
- Hypercalcemia, hypokalemia, hypomagnesemia (20%)
- Vomiting, asthenia (19%)
- Hypocalcemia, hyperkalemia, diarrhea (18%)

- Edema, pyrexia (17%)
- Abdominal pain, rash, increased AST (16%)
- Increased alkaline phosphatase, thrombocytopenia (14%)
- Chest pain, arthralgia, decreased appetite and weight (13%)
- Increased ALT (12%), pruritus (11%)

1-10% (all grades)

NSCLC

- Pneumonia (10%)
- Pain (10%)

1-10% (grades 3-4)

NSCLC

- Dyspnea (9%)
- Fatigue (7%)
- Musculoskeletal pain (6%)
- Pneumonia (5%)
- Decreased appetite (2.6%)
- Pain (2.6%)
- Nausea (1.7%)
- Abdominal pain (1.7%)
- Asthenia (1.7%)
- Edema (1.7%)
- Cough (1.7%)

1-10% (other clinically important adverse effects)

NSCLC

- General disorders and administration site conditions: Stomatitis
- Nervous system disorders: Peripheral neuropathy
- Infections and infestations: Bronchitis, upper respiratory tract infection

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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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

- **Attribution** of the AE:

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

8.4 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC 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 9.2 for the drugs listed here.

For experimental or targeted drugs directed at secondary mutations, please refer to the FDA or Company package insert for Pharmaceutical information related to adverse events, preparation, administration, storage, stability and disposal.

9.1 Pharmaceutical Accountability

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

9.2 Pembrolizumab(Keytruda)

Product description:

Pembrolizumab for injection: 50 mg lyophilized powder in single-use vial for reconstitution (3). Pembrolizumab for injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial. The solution should be clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed

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: 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.

- Do not freeze

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.

- Do not freeze.

Stability: Keytruda is stable for no longer that 6 hours at room temperature from the time of reconstitution and no longer than 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F)

9.3 Nivoloumab (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:

- 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 coadminister other drugs through the same intravenous line.
- Flush the intravenous line at end of infusion. When administered in combination with ipilimumab, infuse OPDIVO first followed by ipilimumab on the same day.
- Use separate infusion bags and filters for each infusion.

Disposal: 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. Dispose through the Institutional waste stream and guidelines.

10.0 Correlative Studies

NA

11.0 Data Management

Informed consent document	ORIS
Patient eligibility form (Appendix A)	ORIS
Protocol registration form (Appendix B)	ORIS
Tobacco Use Case Report form: Baseline (Appendix D)	REDCap
Tobacco Use Case Report form: Progression (Appendix E)	REDCap
Adverse Event Log (Appendix F)	ORIS
RECIST Data collection form (Appendix H)	REDCap
Enrollment Mutation Case Report form (Appendix I)	REDCap
Progression Mutation Case Report form (Appendix J)	REDCap
Data Collection Form: Performance Status (Appendix L)	REDCap

12.0 Statistical Considerations

12.1 Introduction

By design patients will be enrolled in this study prior to the determination of their PD-L1 status. In addition, among patients with low PD-L1 expression (<50%) it cannot be determined prospectively how many patients after disease progression will have a secondary oncogenic driver identified. Thus, patients upon enrollment may enter one of three arms to be determined at a later time – 1) PD-L1 expression ≥ 50%, 2) PD-L1 expression <50% with secondary oncogenic driver identified and 3) PD-L1 expression <50% without secondary oncogenic driver identified. It is anticipated that less than 50% of patients will have PD-L1 expression ≥ 50%, thus this arm – which is the focus of the primary objective – will take longer to fill. In order to manage the overall sample size expectations of this study, the design will allow enrollment to continue until 15 patients are enrolled in the PD-L1 expression ≥ 50% arm (sample size needed based on Simon's two stage design described below). Each of the other two arms will allow enrollment until a minimum of 15 and maximum of 30 patients are enrolled into each arm. If the maximum (n=30) is reached in either of the PD-L1 expression < 50% arms, then new patients eligible for those arms will not be included in the follow-up assessments.

12.2 Analysis of Primary Objective

Objective response rate in the patients with high PD-L1 expressing cancers after failure of targeted therapy is the primary outcome of interest. To examine this, a Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true objective response rate is 10% will be tested against a one-sided alternative. In the first stage, 8 patients will be accrued. If there are zero responses in these eight patients, the study will be stopped. Otherwise, seven additional patients will be accrued for a total of 15. The null hypothesis will be rejected if 4 or more responses are observed in 15 patients. This design yields a type I error rate of 0.054 and power of 90.5% when the true objective response rate is 40%.

12.3 Analysis of Secondary Objectives

Overall survival (OS) will be determined from the date of progression on primary targeted treatment to death. The three cohorts of interest, described above, will have OS estimated using Kaplan-Meier methods and survival rates will be compared using log-rank tests. Next, objective response rates will be estimates in the two PD-L1 expression < 50% arms. Confidence intervals for each of these rates will be estimated. An exploratory comparison will be made among the three groups comparing CR/PR vs SD/PD among the groups using a Fisher's exact test (for the 2x3 table).

Toxicities for each group will be estimated and described using counts and frequencies by grade, location and relatedness.

The incidence of mutations in secondary genes will be determined for patients in the two PD-L1 expression < 50% arms as well. Next, we will examine whether smoking status (defined as Current, Former, Never) is related to the prevalence of any mutations identified (present/absent) using Cochran-Maentel Haenzel tests. These tests will be performed overall and then separately in the three arms defined above

12.4 Power and Sample Size

As described above the primary power calculation for this study is based on the Simon two-stage design to test the null hypothesis that the objective response rate is 10% versus the alternative that it is 40% in the high PD-L1 expressing group. With the design described above there is 90% power with a sample size of 15. Furthermore, in the two other arms (with sample sizes between 15 to 30 total patients each), we can estimate the rate of CR/PR (for objective response rate) with precision of ±18.7% (for n=30) or ± 26.1% (for n=15) using 2-sided Exact Clopper-Pearson confidence intervals.

12.5 Estimated Accrual Rate

It is estimated that 20 patients per year will be accrued.

12.6 Estimated Study Length

With a total sample size needed of between 45 (allowing for 15 per arm) and 75 (allowing for up to 30 in the two PD-L1 expression < 50% arms) the study is expected to take at least 3 years to complete. It is anticipated that additional sites may be invited to participate after the trial is open and if this occurs the total study length will decrease

References

1. SEER Cancer Statistics Review, 1975-2011. Bethesda, MD: National Cancer Institute; 2014.
2. PDQ® Non-Small Cell Lung Cancer Treatment. 08/06/14 ed. Bethesda, MD: National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional. .
3. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.
4. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *The New England journal of medicine.* Jun 28 2012;366(26):2443-2454.
5. Johnson DB, Rioth MJ, Horn L. Immune checkpoint inhibitors in NSCLC. *Current treatment options in oncology.* Dec 2014;15(4):658-669.

Appendix A: Subject Eligibility Checklist

IRB Protocol No. 00041150	**WFBCCC Protocol No. 62716**
Study Title: Phase II Pilot Study Evaluating Strategies to Overcome Resistance at the Time of Progression for Patients with Non-Small Cell Lung Cancers Harboring Major Oncogenic Drivers	
Principal Investigator: W. Jeff Petty, MD	

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 non-small cell lung cancer that harbors an activating mutation in EGFR, MET, BRAF, V600E, RET, HER2, translocation in Alk, or translocation in ROS-1	☐	☐	
Patients must be receiving treatment or planning to start treatment with a tyrosine kinase inhibitor targeting the activated gene.	☐	☐	
Patients may not be receiving the treatment targeting the activated gene as part of a clinical treatment trial other than the Precision Oncology Trial.	☐	☐	
ECOG performance status of 0-3	☐	☐	
These agents may 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	☐	☐	
AST(SGOT)/ALT(SGPT) $\leq$2.5 X institutional upper limit of normal	☐	☐	
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 non-small cell lung cancer	☐	☐	
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.	☐	☐	
Pregnancy	☐	☐	

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: _____

Signature of Principal Investigator**: _____
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 B: 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: ___ ___ /___ ___/___ ___

Performance Status: ___ ___ ___ ☐ ECOG ☐ Karnofsky

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 C: Mandatory STRC SAE Reporting Guidelines

Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP	**Date: 6/20/2016**

Mandatory STRC SAE Reporting Requirements

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on CCCWFU Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI Data Table 4 reporting guidelines, **CCCWFU Institutional Interventional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional Interventional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to the STRC for review. All Clinical Protocol and Data Management (CPDM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone (or in-person), followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO any faculty or staff member on the study team for a CCCWFU Institutional Interventional trial. Once an event is observed, it is the responsibility of the person who observed the event to be sure that it is reported.

What is considered an SAE under this mandatory procedure?

Any **unexpected grade 4** event and **all grade 5 events** (death during protocol intervention) should be reported. These events should be reported if they occur while a patient is on study treatment or if they occur within 30 days of last study treatment (even if patient begins a new 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. In addition, if it is not clear whether the Grade 4 is unexpected it should be reported.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		Grade 4		Grade 5	
	Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx.
   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 your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate person(s) on the STRC has been contacted. This documentation is placed on the STRC Notification form described above.
4. Follow up with/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements to complete the electronic STRC form:
Please use 'reply to All' when responding with one of these terms: Definite, Probable, Possible, Unlikely, or Unrelated

1. Patient ID (ORIS PID)
2. Patient Name
3. Patient MR#
4. CCCWFU(ORIS) Study Number
5. Title
6. PI Name
7. PI Contact Number
8. PI Comments
9. STRC Clinician notified by Phone
10. Notified Date
11. Notified Time
12. STRC Clinician Comments
13. Category [This is the Grade – Either Unexpected Grade 4 or Grade 5 should be entered]
14. Additional Information (IRB Reporting)(after discussion with PI or STRC Clinician
    i. Is This Event Related to Protocol Treatment?
    ii. Is Suspension of the Protocol Needed?
    iii. Any Changes to Consent or Protocol Needed?
    iv. Was Nature or Severity of Event Unexpected?
15. Date of the event.
16. Brief description (include brief clinical history relevant to this event, including therapies believed related to event).
17. Date of Last Dose before event
18. Relevant tests/labs.
19. Other Relevant Treatment Information
20. Other Comments/Notes (include regimen of chemo and dates the patient received them if known).
21. Cc (email) (include treating Physician; separate email list with comma",")
22. Your Name
23. Your Email
24. Confirm Your Email

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

Bayard Powell, MD – Director-at-Large, CCCWFU; Chair, PRC; Section Head, Hematology/Oncology. 6-7970 / 6-2701 / Pager 336-806-9308
Antonius Miller, MD – Hematology Oncology 6-7970 / 6-7414 / Pager 704-637-8384
Glenn Lesser, MD – Hematology Oncology 6-9527 / 6-7972 / Pager 336-806-8397
Kathryn Greven, MD – Vice Chair – Radiation Oncology. 3-3600 / 3-6505 / Pager 336-806-8314
Marissa Howard-McNatt, MD – General Surgery 6-0545 / 336-806-6438
Mercedes Porosnicu, MD- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given 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 your STRC notification form. The important criteria is that you have taken reasonable steps to notify and document that you have initiated some type of contact 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 agree with the investigator's assessment if STRC does not agree with the investigator. STRC reserves the right to suspend the trial pending further investigation.
Is there any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report – and if so an immediate suspension of enrollment should take place.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

Acronyms and Definitions

STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
IRB-Institutional Review Board
CCCWFU-Comprehensive Cancer Center Wake Forest University
ORIS-Oncology Research Information System
NCI-National Cancer Institute
CPDM-Clinical Protocol and Data Management
Interventional Trials-Therapeutic Level 1 and Level 2 trials
Therapeutic Level 1-A cancer treatment protocol aimed at directly treating/curing the patient's cancer.
Therapeutic Level 2-A therapeutic protocol not cancer treatment involves clinical activity to treat symptoms, improve the patient's quality of life, or prevent cancer.

Appendix D: Tobacco Use Case Report Form (Baseline)

CASE REPORT STUDY FORM FOR PATIENT TOBACCO USE TO BE USED AT BASELINE

Study Number: _____ PID: _____

Investigator: William J. Petty, M.D. Date: _____

Research Personnel Filling out form_____

Cancer Patient Tobacco Use Questionnaire (C-TUQ)
Baseline

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

☐ Yes
☐ No ➡ **You are finished with this form.**
☐ Don't know/Not sure ➡ **You are finished with this form.**

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

Appendix E: Tobacco Use Case Report Form (Progression)

A CASE REPORT STUDY FORM FOR PATIENT TOBACCO USE TO BE USED AT PROGRESSION

Study Number: _____ PID: _____

Investigator: William J. Petty, M.D. Date: _____

Research Personnel Filling out form_____

Cancer Patient Tobacco Use Questionnaire (C-TUQ)
Follow-up Assessment

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

☐ Yes
☐ No ➡ **You are finished with this form.**
☐ Don't know/Not sure ➡ **You are finished with this form.**

2. 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

Appendix F: Adverse Event Log

WFBCCC Adverse Event (AE) Log

PI: William J. Petty, MD **PID: _____** **MRN: _____**

Cycle Start Date: _____ **Cycle End Date: _____** **Cycle #: _____**

Adverse Event CTC Term	**Value** (-5 if non-numeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	***Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxicity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** 1=IRB 2=STRC 3=FDA 4=Sponsor

*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

Appendix G: RECIST Measurement Form

Instructions: Complete and submit this form as required by the protocol. Do not leave any entries blank. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable or not done. Retain a copy for your records and submit original to the WFBCCC Data Management Center.

WFBCCC Study Number: _____ WFBCCC Patient ID: _____

Patient Name: _____ MRN: _____
WFUHS/Affiliate:

_____
(Specify)

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

Date of Observation (mm/dd/yy)							
Cycle:							
TARGET LESIONS							
Response Status (CR, PR, SD, PD)							
List sites for response:	Means of Evaluation	Measurement	Measurement	Measurement	Measurement	Measurement	Measurement
1.							
2.							
3.							
4.							
5.							
Total sum of LD for all Target Lesions:							
NON-TARGET LESIONS							
Response Status (CR, Incomplete Response/SD, PD):							
List sites for response	Means of Evaluation	Measurement	Measurement	Measurement	Measurement	Measurement	Measurement
1.							
2.							
3.							
4.							
5.							
6.							
7.							
Observer Signature:							

ORIS ID: __ __ __ __ __ __ __ __ Date___ ___ /___ ___ /___ ___

Appendix H:RECIST Data Collection Form

Study Visit:

- ☐ After First Progression
- ☐ Follow-Up (8 Weeks Nivo or 9 Weeks Pembro depending upon treatment)
- ☐ Other visit: (please specify) _____

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

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

Evaluation of Target Lesions

☐ Complete Response (CR)

☐ Partial Response (PR)

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

☐ Stable Disease (SD)

☐ NE

Evaluation of Non-Target Lesions

☐ Complete Response (CR)

☐ Non-CR/Non-PD

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

☐ NE

Overall Response this Visit

☐ Complete Response (CR)

☐ Partial Response (PR)

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

☐ Stable Disease

☐ NE

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

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

Appendix I: Enrollment Mutation Case Report

CASE REPORT STUDY FORM FOR PRIMARY GENETIC DRIVER MUTATION TO BE USED AT ENROLLMENT

Study Number: _____

PID: _____

Investigator: William J. Petty, M.D.

Date: _____

PRIMARY DRIVER MUTATION	
EGFR ☐	BRAF ☐
Alk ☐	V600E ☐
ROS-1 ☐	RET ☐
MET ☐	HER2 ☐

Test Method

FoundationOne Testing ☐ Other ☐

Guardent360 Testing ☐

MEDICATION USE RELATED TO THE DRIVER MUTATION

Gene Targeted Therapy? Yes☐ No ☐

Name of Targeted Therapy_____

Current Dose_____

Person Filling out form_____ Date_____

Physician Signature_____ Date_____

Appendix J: Progression Mutation Case Report

CASE REPORT STUDY FORM FOR SECONDARY DRIVER MUTATION
TO BE USED AT THE POINT OF DISEASE PROGRESSION

Study Number: _____

PID: _____

Investigator: William J. Petty, M.D. Prior Agent _____

Date: _____ Maximum Tolerated Dose_____

PD-L1 STATUS

PD-L1 Score*_____

*If <50% Move to Secondary Driver Mutation section

SECONDARY DRIVER MUTATION

Secondary Driver Mutation Identified? Yes☐ No ☐

Identity of Secondary Driver Mutation_____

Treatment Arm Assigned: Arm 1(≥50% PD-L1) ☐
Arm 2(<50% PD-L1, 2º driver) ☐
Arm 3 (<50% PD-L1, no 2º driver) ☐

Test Method

FoundationOne Testing ☐ Other ☐
Guardent360 Testing ☐

Source Evidence of Secondary Driver Mutation Status

NCCN ☐

Published Paper ☐ Citation_____

Case Study ☐ Citation_____

Other_____

Person filling out form_____ Date_____

Physician Signature_____ Date_____

Appendix K: Plasma/Tissue Collection

CASE REPORT STUDY FORM FOR TISSUE COLLECTION

Study Number: _____

PID: _____

Investigator: William J. Petty, M.D.

Date: _____

All tissues and plasma should be sent to the Tumor Tissue Core.
Wake Forest Cancer Center
Tumor Tissue Core Facility
Care of Dr. Greg Kucera
Hanes Building Rm 4049
Medical Center Blvd
Winston-Salem NC 27157

Baseline

Plasma ☐

Person collecting: _____ Time:_____ Date:_____

Disease Progression

Plasma ☐

Person collecting: _____ Time:_____ Date:_____

Appendix L: Data Collection Form: Performance Status

PID: _____ Date Completed: ____ / ____ / ____

Investigator: William J. Petty, M.D. Study Number: _____

Visit:
☐ Pre-study
☐ First Progression
☐ Other (Specify: _____)

ECOG Performance Status (Date Performed: ____ / ____ / ____)
☐ 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.

Research Personnel Filling out form_____
Date_____