Department of Comprehensive Cancer Center/Section of Hematology Oncology

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

Informed Consent Form to Participate in Research

William J. Petty, M.D., Principal Investigator

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have non-small cell lung cancer that results from a genetic change called a "driver mutation". Also, you are either being treated for this type of cancer now or will be starting this treatment with a special targeting treatment toward this mutation. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to find out what other treatment options work when a patient has cancer caused by a driver mutation and the treatment that targets that mutation stops working. The study is being done to find out what effects (good and bad) giving drugs that target other genetic mutations or other specific proteins that could contribute to your cancer progressing has on you and your condition.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

75 people at Wake Forest School of Medicine will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you qualify for this study, you will be asked to sign this form. Study staff will ask you for your medical history, you will receive a physical exam, your vital signs will be taken, your performance status will be determined (this will help indicate how the cancer is effecting your everyday functioning), and you will have approximately 3 teaspoons of your blood drawn. You will have periodic blood draws throughout the study as part of your normal care and for research purposes. You will continue or begin targeted treatment of your cancer until or if your cancer progresses. If your cancer progresses, then you will give approximately 3 teaspoons of blood to determine if you qualify for therapy that stimulates your immune system, or have a biopsy of your tumor or give blood for genetic testing to determine if there is a second genetic mutation that can be targeted for treatment. Then you will be treated with these therapies (second line therapies) for approximately 3 weeks or as long as your doctor thinks is best.

Drugs used in this study are FDA approved.

If you take part in this study, you will or may have the following tests and procedures:

Blood drawing
You will have approximately 3 teaspoons of blood withdrawn from a vein at every blood draw. At the start of the study you will have a blood draw for research purposes and for your standard of care. Then you will have a blood draw every 3 months or more until if/when your cancer progresses. At this point you will have another blood draw*. After you start the second line of chemotherapy for your cancer relapse or progression, you will have a blood draw 4 weeks later. After that you will have a blood draw again every 3 months until if/when your cancer progresses. The total amount of blood withdrawn during the study will depend on how long you will be in the study. This is a part of your normal care (standard of care) and a part of the research.

*For research, this blood draw will be performed specifically for genetic testing and for testing of a particular marker that is involved in preventing your immune system from fighting your cancer.

CT Scans
A CT scan may be performed if your doctor suggests it. A CT scan allows your doctor to look at your cancer to determine the size of the cancer. This would be a part of your standard of care.

Tissue Biopsy of your Cancer
To determine if your cancer has specific genetic mutations that cause it to progress a tissue biopsy may be performed if requested by your doctor. This is a part of the research purpose of the study.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

As part of this study, a blood sample and/or tumor sample will be obtained and DNA from your blood or tumor sample will be purified. DNA, or deoxyribonucleic acid, stores and transmits inherited traits, such as eye color or blood type. As part of this research project, your DNA will be studied in an effort to find out if there are genes that contribute to medical conditions that are part of this study. We will only be looking at genes that are known to be involved in cancer. Once we know what genes that may be involved from your sample, we would attempt to treat your cancer in a way that would target those genes. These results will be placed in your medical records as they would directly influence your care and cancer treatment.

Storage of Biological Tissue

If you agree to participate in this study, we would like to use a portion of your blood **or a portion of the tissue from your tumor** biopsy to use for future research. This sample will be kept and may be used in

future research to learn more about other diseases. Your sample will be obtained **at the Comprehensive Cancer Center** at Wake Forest Baptist Medical Center. The sample will be stored **in the Tumor Tissue and Pathology Shared Resource** at Wake Forest Baptist Medical Center and it will be used only by researchers approved by the Principal Investigator of this study, William J. Petty, M.D. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. You do not have to allow a portion of the blood or tissue for future research outside of this study in order to participate in this study.

If you would like to allow a portion of the blood or tumor tissue for future research, please indicate your wishes below:
____Yes, you may use a portion of my blood and tumor tissue for future research
____No, you may NOT use a portion of my blood and tumor tissue for future research

Print Name_____

Sign Name_____ Date_____

Your blood/tissue sample will be stored de-identified, which means that no identifying information will be stored with it. Researchers will not know the name, date of birth, medical record number, social security number, etc., of the person who donated the sample.

The research that may be performed with your blood/tissue sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood /tissue will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood/tissue sample will not affect your care.

Your blood/tissue sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for up to 3 years or until if your doctor believes you should no longer be in the study depending on the status of your condition.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the procedures, nivolumab, pembrolizumab, and targeted treatment drugs we are studying include:

Risks of Targeted Treatment Drugs

In this study you will be tested for genetic changes that likely contribute to your cancer. Many genetic changes may be involved. There may be special drugs that can be used to treat these genetic changes. However, it is impossible to predict exactly which mutations and drugs will be used at this time. Therefore, if you have a genetic change that can be treated with a drug, your research staff will communicate the appropriate risks about the drugs before administering the drugs.

Risks of Nivolumab

Most common adverse reactions have included fatigue, cough, nausea, pruritus (itching), rash, decreased appetite, constipation, arthralgia (joint pain), thyroid function abnormalities, and diarrhea. The most frequent serious adverse drug reactions were renal failure, dyspnea (difficulty breathing), and pneumonitis. Additional AEs are listed below:

Adverse Effects

>10% (All grades)

NSCLC (Non-Small Cell Lung Cancer)

- Fatigue (50%)
- Lymphopenia: low lymphocytes, a white blood cell (47%)
- Dyspnea (difficulty breathing), hyponatremia (low blood sodium levels) (38%)
- Musculoskeletal pain (36%)
- Cough (32%)
- Nausea (29%), anemia (low red blood cells) (28%), constipation (24%)
- Increases creatinine (22%)
- Hypercalcemia (high blood calcium), hypokalemia (low potassium in the blood), hypomagnesemia (low magnesium in the blood) (20%)
- Vomiting, asthenia (weakness, lack of energy) (19%)
- Diarrhea (18%)
- Edema (swelling), fever (17%)
- Abdominal pain, rash, increased AST (liver enzyme associated with damage) (16%)
- Increased alkaline phosphatase, thrombocytopenia (low level of blood platelets) (14%)
- Chest pain, arthralgia (joint pain), decreased appetite and weight (13%)
- Increased ALT (liver enzyme associated with damage) (12%), pruritus (itchy skin) (11%)

1-10% (all grades)

NSCLC

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

1-10% (grades 3-4)

NSCLC

- Dyspnea (difficulty breathing) (9%)
- Fatigue (7%)
- Musculoskeletal pain (6%)

- Pneumonia (5%)
- Decreased appetite (2.6%)
- Pain (2.6%)
- Nausea (1.7%)
- Abdominal pain (1.7%)
- Asthenia (weakness, lack of energy) (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

Risks of Pembrolizumab

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

- NSCLC included fatigue, decreased appetite, dyspnea (difficulty breathing) and cough.

Other risks include:

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 (fever)	12	1
Peripheral Edema (swelling from fluid)	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	25	1
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea (difficulty breathing)	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 (joint pain)	15	1
Back pain	10	2
Blood and Lymphatic System Disorders		
Anemia	12	2
Skin and Subcutaneous Tissue Disorders		

Pruritus (itchy skin)	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

Risks of Biopsy

An open or thoracoscopic lung biopsy is a surgical procedure that is performed under general anesthesia. As with any surgical procedure, complications may occur. Some possible complications may include, but are not limited to, the following:

- Blood loss or clots
- Pain or discomfort
- Infection
- Pneumonia

A needle or transbronchial lung biopsy is performed under light sedation and/or local anesthesia. Some possible complications of these procedures may include, but are not limited to, the following:

- Pneumothorax is when air becomes trapped in the pleural space causing the lung to collapse
- Bleeding in the lung
- Infection

Risks of Local Anesthesia

There may be some tingling and pain when the drug is administered, and when it is wearing off, and there may be some bruising, but these are usually minor.
Temporary adverse effects that affect some people include:

- blurred vision, dizziness, and vomiting
- headache
- muscle twitching
- continuing numbness, weakness, or tingling

An allergic reaction could develop hives, itching, and breathing difficulties.

If you are pregnant, or suspect that you may be pregnant, you should notify your doctor.

If the biopsy is performed using an X-ray (CT or fluoroscopy), the amount of radiation used during the procedure is considered minimal; therefore, the risk for radiation exposure is very low.

There may be other risks depending on your specific medical condition. Be sure to discuss any concerns with your doctor prior to the procedure.

Risks of Blood Draws

You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare

occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Other Risks

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

Reproductive Risks and other Issues to Participating in Research

Due to known risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

Contraceptive Measures for Males

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for 2 years months afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: decreased or stabilized tumor size.

Based on experience with nivolumab, pembrolizumab and other targeted therapies in patients

with similar cancers, researchers believe it may be of benefit to subjects with your condition. However, because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:

- Other chemotherapies
- Comfort care, which is an option if you decide that you do not want any more active treatment for your cancer. Comfort care includes pain medication and other types of support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends, and your doctor.

You could be treated with nivolumab or pembrolizumab even if you do not take part in the study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. We will give you an estimate of what the added cost may be based on your particular situation and insurance coverage.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and/or effectiveness of nivolumab, pembrolizumab and other targeted chemotherapy drugs; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a research study. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study. Parking will be validated for study-related visits.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest Baptist Medical Center Comprehensive Cancer Center. The sponsor is providing money or other support to Wake Forest Health Sciences to help conduct this study.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call William J. Petty, M.D. at [redacted]

What About My Health Information?

In this research study, any new information we collect from you and information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** your health history, how you respond to study procedures, laboratory and other test results, and physical examinations.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store

records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA), and the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

1) Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

2) Representatives from government agencies such as the US Food and Drug Administration (FDA).

3) The study Principal Investigator, his staff and approved members of the laboratory and study team at Wake Forest Baptist Health and Wake Forest Health Sciences or individuals of other laboratories performing work on the project on behalf of Wake Forest Health Sciences and Wake Forest Baptist Medical Center.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified and any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of

your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell William J. Petty, M.D. that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

William J. Petty, M.D.
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time. Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study

at any time. This could be for any reason (scientific or clinical) that the Investigator feels necessary in relation to your condition and the study.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, William J. Petty, M.D. at [redacted]

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm