Section of Hematology and Oncology

IMMUNE RESPONSE IN PATIENTS WITH RECURRENT OR METASTATIC NON-SMALL CELL LUNG CANCER AND PERFORMANCE STATUS OF 2 TREATED WITH A COMBINATION OF PEMBROLIZUMAB AND LOW DOSE WEEKLY CARBOPLATIN/PACLITAXEL

Informed Consent Form to Participate in Research
W. Jeff Petty, MD, 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 a type of cancer called non-small cell carcinoma of the lung (NSCLC) that is either recurrent, meaning you have previously received treatment for your NSCLC, or metastatic, meaning the cancer has spread to other parts of your body, and you have a performance status of 2, meaning that you are ambulatory, capable of all self-care, up and about more than 50% of waking hours, but unable to carry out any work. 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 compare the effects (good and bad) of pembrolizumab given every three weeks with or without low dose carboplatin and paclitaxel. The drug pembrolizumab is in a class of medications called monoclonal antibodies. It works by helping your immune system to slow or stop the growth of cancer cells. Carboplatin and paclitaxel are chemotherapy drugs approved by the US Food and Drug Administration (FDA) for treatment of your disease. Pembrolizumab has been approved for the treatment of melanomas and, as of October 2016, for the treatment of patients with NSCLC. The goal of this study is to determine if carboplatin and paclitaxel can improve the anti-tumor activity of pembrolizumab by improving the activity of your immune system against the tumor, and if it is useful for the treatment of patients with lung cancer who have a performance status of 2.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

43 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Screening

During the first study visit, called a screening visit, you will have medical tests and procedures performed to help the study doctor decide if you meet the requirements to be in the study. These are all considered routine-care procedures (meaning they would be done regardless of your participation in this research study) and include:

- An assessment of your medical history,
- A physical examination,
- Blood chemistry lab tests measuring your red and white blood cells, platelets, liver and thyroid functions,
- A routine-care tumor biopsy, done at or within 12 weeks (84 days) of screening for this study (and with your consent to have your leftover tumor samples stored for future research at the Wake Forest Baptist Health Tumor Tissue Bank.) A portion of your tumor will be collected and checked for different types of immune cell markers to determine your eligibility for study entry.
    - If you already have a sample of tumor tissue stored at the Wake Forest Baptist Health Tumor Tissue Bank that is older than 12 weeks (84 days) at the time of this screening, you will be able to participate only if the sponsor considers that your 'archived' biopsied tumor tissue sample is useful for specific immune staining.
- Tumor assessments, which will be done by imaging studies such as computerized tomography (CT) or Positron emission tomography–computed tomography (PET/CT) and magnetic resonance imaging (MRI scan).

Before your treatment begins, you will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group.

Treatment

The two treatment groups are:

- Single agent treatment: Pembrolizumab every three weeks as 30 minute intravenous infusion
  or
- Combination agent treatment: Pembrolizumab every three weeks as a 30 minute intravenous infusion **plus** low-dose weekly carboplatin and paclitaxel administered as 1-hour intravenous infusions.

Study visits

- Patients in the combination agent treatment group will be seen on a weekly basis for a physical exam, labs, and to receive treatment. Patients in the single agent treatment group will be seen every 3 weeks for a physical exam, labs, and to receive treatment.
- At the initial visit, at 8 weeks after you started treatment, and then every 12 weeks thereafter you will have an examination of your tumor(s) by computed tomography (CT)—like an x ray that uses radiation to produce pictures of your body, including

tumors, or magnetic resonance imaging (MRI)—which uses a magnetic field to produce an image of your body, including tumors. Your study doctor will determine which type of test (either CT or MRI) is best to assess your cancer.

- Prior to your first treatment with pembrolizumab (Cycle 1, Day 1), then again on Day 1 of Cycles 2 and 3 of pembrolizumab, and at the end-of-treatment visit (EOT), blood samples will be drawn to examine immune response.
- At the initial visit and then every 12 weeks you will complete a study questionnaire asking about how you are feeling.

Tumor Assessments

Tumor size assessment by imaging studies such as computerized tomography (CT scan), magnetic resonance imaging (MRI scan), or other methods (x-rays or physical exam) will be 8 weeks after you started treatment and then approximately every 12 weeks thereafter. It is possible that you will receive contrast dye injections during these time points, unless you are allergic to it.

Blood drawing

Samples of your blood and urine will be collected throughout the study. In the combination agent treatment group, these samples will be taken once a week. In the single agent treatment group, blood and urine samples will be taken every three weeks. Blood will be taken from a vein in your arm using a needle. For the immune studies, about 2 tablespoons of blood will be collected on the day you receive your first treatment (Cycle 1 Day 1), after 3 weeks (Cycle 2 Day 1 of pembrolizumab), after 6 weeks (Cycle 3 Day 1 of pembrolizumab), and then at the End of Treatment Visit.

Study participant responsibilities

If you agree to participate in this study, you have certain responsibilities to help ensure your safety. These responsibilities are listed below.

- Complete all required visits
- Take the study medications as prescribed
- Report all side effects and medical problems to the study personnel
- Inform the study doctor or staff if you decide to discontinue your participation. You will be asked to complete an end of treatment visit

HOW LONG WILL I BE IN THE STUDY?

The active chemotherapy treatment period for this study can be up to 2 years. However, we will cap your treatment with carboplatin at 12 weeks (~3 months) if you are still getting treatment on the study at that time. You may continue to receive treatment with pembrolizumab and paclitaxel until your cancer progresses (gets worse), you can no longer tolerate the treatment, your doctor believes it is no longer in your best interest to continue the study treatment, or you decide to withdraw from the study. After you finish receiving treatment on this study, you will have an End of Treatment study visit with a physical exam, blood chemistry lab tests measuring your red and white blood cells, platelets, liver and thyroid functions, and a tumor biopsy. You will be contacted by a member of your study doctor's research team about every 8 weeks to see how you

are doing and ask for an update on other anti-cancer therapies you have taken. This will most likely be done by telephone, but may also overlap with a routine clinic visit with your doctor.

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. If you decide to stop participating in the study please contact Dr. Petty at [redacted]

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. One risk is that you may get a drug or dose of a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects. Risks and side effects related to the drugs we are studying include: fatigue, cough, nausea/vomiting, itchy skin, rash, decreased appetite, constipation, muscle aches, diarrhea, mouth sores, hair loss, and low blood counts. Uncommon adverse effects include pain with breathing, pneumonia, infections, and kidney dysfunction.

Pembrolizumab: Most common adverse reactions (reported in ≥20% of patients) included fatigue, fever, cough, dyspnea (shortness of breath), nausea and/or vomiting, skin rash or itching, muscle aches, back pain, decreased appetite, constipation, and diarrhea.

Uncommon but serious adverse drug reactions (reported in 2% -10% of patients) were hyperthyroidism (overactive thyroid), and inflammation in the lungs (pneumonitis) or skin (cellulitis). Most of the reported side effects are reversible with steroids or hormone therapy, and no deaths due to undesirable effects of the drug have been reported with the use of Pembrolizumab for the treatment of lung cancer patients.

Very rarely (less than 2% of patients), and reported in other clinical studies involving Pembrolizumab, serious adverse reactions have included inflammations in various areas of the body including the colon, liver, pituitary gland, kidneys, heart wall, even a severe skin inflammation known as Stevens-Johnsons syndrome, which includes painful blistering and peeling of the skin and can give you flu-like symptoms. These inflammation disorders have been reported to cause hospitalization and, in one extreme case, reported to lead to death. The study sponsor, Merck, continues to monitor the safety profile of this drug and inform all study doctors of new risks.

Paclitaxel: The most common adverse reactions (incidence ≥25%) include bone marrow suppression and overall low blood counts (neutropenia, leukopenia, anemia, thrombocytopenia), blood/bone marrow infections, bleeding, increased need for blood transfusions, hypersensitivity reactions, abnormal ECG, other heart problems, low blood pressure, nerve pain, joint pain, nausea/vomiting, diarrhea, mouth inflammation, hair loss, liver dysfunction, and injection site reactions.

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

were the same as for paclitaxel described above, but to include kidney dysfunctions as seen in rising creatinine or blood urea elevation, electrolyte depletion, and generalized pain. There is also a risk of allergic reaction to carboplatin.

Regarding the combination of pembrolizumab with low dose carboplatin and paclitaxel, we do not anticipate any potentiation of side effects. Studies done with similar drug combinations, confirm that the treatment seems to be tolerable with manageable toxicity. If you are randomized to the combination treatment, the study team will perform weekly physical exams and blood tests to monitor your tolerance to the treatment.

Possible risks from study procedures

Blood tests: 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).

Tumor Biopsy (Standard of Care): The possible risks associated with removal of a piece of your cancer (a biopsy) depend on the part of the body where the biopsy will be performed. You may experience pain from the biopsy and you may have bruising, soreness or scarring at the biopsy site. Rarely, a patient who has had a biopsy may experience infection and/or internal bleeding and depending on the location of the biopsy, 'punctured lung' and/or 'collapsed lung' (due to an abnormal collection of air or gas in the space that separates the lung from the chest).

CT scans (Standard of Care): Participation in this research study will involve exposure to radiation from the CT scan. The amount of radiation exposure that you will receive from each CT scan is considered minimal. The more radiation received over the course of your life increases the risk of cell changes in your body or having cancerous tumors. The radiation from this study is not expected to greatly increase these risks, but the exact increase of such risks is unknown.

Some CT scans require you to take a "contrast solution" either by mouth, enema, or injection into a vein. Although rare, the contrast solution may cause an allergic reaction such as nausea, vomiting, itching, skin rash, or in very rare instances a swelling of the throat and difficulty in breathing. If you feel any of these symptoms of an allergic reaction you must tell the staff immediately so that you can be treated without delay. In addition, because you must lie with your head and neck inside the narrow scanner tube, you may become anxious and frightened inside the enclosed space (claustrophobic).

MRI (Standard of Care): When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your study doctor. Your study doctor may give you a medication to make you feel more comfortable in a confined space. MRIs use powerful magnets to make images. Therefore, persons with certain metal implants,

such as pacemakers, should not have an MRI. If you have an implant or any metal in your body, please check with your study doctor to see whether you can have an MRI or not. For people without metal implants, there are no known health risks associated with exposure to the magnet. As images are taken, a loud banging noise will be produced. Earplugs or headphones may be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Taking part in this research study may involve providing information that you consider confidential or private. We will do our best to protect your confidential information. 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. 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.

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential and men whose female partner can have children must use a reliable method of birth control while participating in this study and for 4 weeks after your last dose of study drug. 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. If you suspect that you or your partner may have become pregnant during the study, contact the study doctor immediately. Your study doctor will want to follow you and the progress of your pregnancy until the baby is born. 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 prior to study entry, if you are a sexually active woman of childbearing potential.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may not receive any direct benefit from participating in this study. In some patients, the cancer may stop spreading, may shrink in size, or may become undetectable. Even if you do not receive any personal benefit from this study, your participation may benefit future patients by helping develop a new therapy for others with similar conditions.

WHAT OTHER CHOICES ARE THERE?

If you do not wish to participate in this study, you may continue to be treated by your doctor and your care will not be jeopardized in any way. Your doctor will discuss other treatment options available to you. For example, you may receive the treatment weekly carboplatin and paclitaxel without participating in this study.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or 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 results from your blood tests, physical examinations, gender, demographics, and other tests. It also includes identifying information such as your name and date of birth.

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. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

3) Federal agencies with regulatory oversight, such as the FDA and the Department of Health and Human Services (DHHS)

4) 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.

5) The study sponsor and those that they have designated to work on this research study

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 an indeterminate period of time. This authorization does not expire. 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. The results of this study may be presented at meetings or in publications; however, your identity will not be disclosed in these presentations. Individual results from tumor biopsy analysis will not be provided to you or

your study doctor and will not be placed in your medical chart considering that all this data is still investigational and not part of the standard of care procedures.

You can tell W. Jeff Petty, MD 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:

W. Jeff Petty, MD
Wake Forest Baptist Health
Section on Hematology and Oncology
Medical Center Blvd.
Winston-Salem, NC 27157

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.

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.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. You or your insurance company will be charged for any portion of your care that is considered standard. You will not need to pay for any tests or procedures that are done for the sole purpose of this study. You may be responsible for any co-payments and deductibles that are standard for your insurance coverage. There will be no additional cost to you to participate in this research study. All study costs, including Pembrolizumab and procedures related directly to the study will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

Your involvement in this research study is voluntary and you will not be paid for your participation. Parking validation will be provided for all study-related visits.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

Merck & Co., Inc. is providing investigational drug, money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

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, [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 Dr. Petty, or study personnel [redacted].

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. To ensure your safety, you will be asked to undergo a final evaluation visit.

The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped.

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, Dr. Petty, or study personnel [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 [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