Section of Hematology and Oncology

Single-arm phase II combination study of low-dose paclitaxel with pembrolizumab in platinum-refractory urothelial carcinoma

Informed Consent Form to Participate in Research
Michael M. Goodman, 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 urothelial carcinoma that is either recurrent, meaning you have previously received treatment for your cancer, or metastatic, meaning the cancer has spread to other parts of your body. 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 in combination with low-dose 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. Pembrolizumab had been approved for the treatment of melanoma and is being studied for the treatment of patients with other cancers including urothelial carcinoma. Paclitaxel is already a standard chemotherapy treatment for urothelial carcinoma. Pembrolizumab has been approved by the US Food and Drug Administration (FDA), but it has not been approved for use in this manner, at this dose and for this condition. The goal of this study is to determine if paclitaxel and pembrolizumab together can treat urothelial carcinoma better than paclitaxel alone, as well as determine how well this combination of drugs is tolerated by subjects.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

30 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 include an assessment of your medical history, a physical examination, labs, tumor assessments, and collection of a tumor tissue sample, unless we already have a sample of your tumor stored at the Wake Forest Baptist Health Tumor Bank within the last 6 months. If the results show that you meet the requirements, you will be enrolled in the study.

Intervention

The intervention is: Pembrolizumab (200mg), given once every three weeks as a 30 minute intravenous infusion, followed by standard Paclitaxel (80mg/m^2), given weekly for 2 of every 3 weeks as a 1-hour infusion. As part of standard therapy, you will also be given several medications prior to receiving Paclitaxel for the prevention of symptoms such as nausea, inflammation, allergic reactions, and acid reflux. These "pre-meds" can be given either through your IV or by mouth, according to current institutional guidelines.

Study visits

- The intervention will be given on a 3 week (21 day) cycle. Patients will be seen on day 1 of each cycle for a physical exam, labs, and to receive treatment. Patients will also have labs and treatment on day 8 of each cycle.
- Every 9 weeks, you will have an examination of your tumor(s) by computed tomography (CT) - an X-ray that uses radiation to produce pictures of your body including tumors, or magnetic resonance imaging (MRI) - 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.
- In addition to the intervention, at the initial visit and every 12 weeks thereafter, blood and urine samples will be drawn to examine immune response.

Blood drawing

Samples of your blood and urine will be collected throughout the study. 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 at screening and then every 12 weeks.

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?

This combination intervention will continue for 6 months (24 weeks) unless your cancer progresses, you can no longer tolerate the intervention, 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 intervention on this study, you will have an End of Treatment study visit with a physical exam, labs, and imaging. At this visit, if your cancer has progressed (continued to grow or spread), you will not receive additional treatment as part of this study. Your cancer doctor will discuss other treatment options with you. You will be contacted by a member of your study doctor's research team about every 3 months to see how you are doing and ask for an update on other anti-cancer therapies you have taken. This will likely be done during a routine clinic visit with your doctor but may be done by telephone.

If your cancer is stable but not gone, and your response to the initial therapy was good, you will have the option of remaining on pembrolizumab alone for an additional 18 months or until your disease progresses. If you choose to do this, you will enter a "maintenance phase" where you will be seen every 21 days, given the pembrolizumab only, and have routine blood tests done. Additionally, you will have imaging and thyroid blood tests done every 3 months (+/- 10 days).

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.

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.

Pembrolizumab treatment may result in auto-immune complications, which is when your immune system attacks your normal tissues and organs instead of, or in addition to, the cancer.

Immune-mediated serious (may cause hospitalization and/or death) side effects seen in **1.0% or less** of patients treated with pembrolizumab include the following:

- Inflammation of the skin so you may have widespread peeling of the skin, itching, skin redness. In very rare cases, this can be severe enough to cause hospitalization and/or lead to death.
- Inflammation of the bowels/gut so you may feel stomach pain with loose or watery stools or stools that are black, tarry, sticky or have blood or mucus
- Inflammation of the middle layer of the heart wall (called myocarditis). This can lead to hospitalization and/or death.
- Inflammation of the lungs so you may feel short of breath and cough. This can cause scarring in the lungs or pneumonia and rarely can lead to death.

- Inflammation of the liver that may cause a poor appetite, feeling tired, mild fever, muscle or joint aches, upset stomach and vomiting, bleeding and bruising more easily than normal, stomach pain, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause headaches, upset stomach, changes in behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting. This inflammation of the pituitary gland may cause the adrenal glands (on top of the kidneys) to not make enough hormone causing tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and abdominal aches, nausea, vomiting, diarrhea, fever, salt craving, rapid heart rate, and sometimes darkening of the skin like a suntan.
- Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, increased sweating, weight loss, hair loss, tired, have diarrhea
- Too little thyroid hormone so you may feel tired, gain weight, feel cold, voice gets deeper, hair loss, have infrequent or hard bowel movements
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the muscles so you may feel weak or pain in the muscles
- Inflammation of the pancreas, (a gland in your abdomen that controls sugar levels) so you may have severe upper abdominal pain that may move to the back, sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have redness of the eye, blurred vision, sensitive to light, have eye pain, see floaters or have headaches
- Dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the pancreas (diabetes) so you may have too much sugar in your blood, may need to urinate more often, lose weight, feel thirsty, and may need regular insulin shots
- Inflammation of the nerves that may cause pain, weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness
- Gastrointestinal Bleeding, also known as gastrointestinal hemorrhage: a significant blood loss over a short period of time that can occur from the mouth to the rectum. Symptoms may include vomiting red blood, vomiting black blood, bloody stool, or black stool

Paclitaxel treatment may cause neuropathy, or numbness/tingling of hands and feet. Allergic reactions to paclitaxel are possible and steroids are given prior to each treatment to prevent this. It is possible that the steroids given to prevent allergic reactions may make the pembrolizumab treatment less effective. Furthermore, the exact dosing schedule of paclitaxel used in this study has not been evaluated in patients with urothelial cancer previously.

There may be other treatment-related side effects or risks that are not known at this time.

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 blood tests can result in low iron in your blood (iron deficient anemia).

CT scans: 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: 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.

Fresh Biopsy: If we do not have a sample of tumor tissue stored at the Wake Forest Baptist Health Tumor Bank within the last 6 months, will need to perform a fresh biopsy. A CT scan or ultrasound may be used to guide the doctor to the site of the tumor where the biopsy will be taken. Numbing medicine (local anesthetic) will be injected around the site where a needle-like instrument will be inserted into your tumor and a small piece of tissue will be removed. The site where the needle-like instrument is inserted may need a stitch (or suture) that will later be removed by a nurse or a doctor.

Risks associated with tumor biopsy procedures (s) can be:

Likely: Minor local bleeding, pain at the needle insertion site; a swelling under the skin that contains blood (hematoma); sleepiness, if you choose to receive a 'pain killer' and/or medicine to make you relax

Unlikely but serious: Infection; shortness of breath that sometimes need you to be

admitted to the hospital for observation and a temporary placement of a chest tube to allow you to breath, slow heart rate, and low blood pressure.

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 120 days (approximately 4.5 months) 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.

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 120 days (approximately 4.5 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?

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 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 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.

Your Protected Health Information and other information that identifies you 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; central laboratories, reading centers or analysis centers; 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) or the Office of Human Research Protections (OHRP), 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.

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 optional 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 Michael Goodman, 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:

Michael Goodman, 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. 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.

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. You or your insurance company will be charged for any portion of your care that is considered standard. This includes treatment with the standard chemotherapy drug Paclitaxel and any other preventative medications given to you during your infusion.
The investigational study drug, Pembrolizumab, will be provided by the study sponsor, Merck, at no cost to you. 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.

Your involvement in this research study is voluntary and you will not be paid for your participation. 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.

WILL YOU BE PAID FOR PARTICIPATING?

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

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Merck & Co., Inc. The sponsor is providing 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.

If you are injured, the sponsor 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 sponsor 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 study personnel.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

You may or may not receive any direct benefit from participating in this study. 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.

Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

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, or study personnel.

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.

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:_____ Date:_____ Time:_____ am pm