Informed Consent Form

Phase II trial of Nivolumab and Metformin in patients with treatment refractory MSS metastatic Colorectal Cancer

NCT Number: NCT03800602

Document IRB Approval Date: 1/15/2020

EMORY | WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

You Are Being Asked to Be in a Research Study

What Is a Research Study?

The main purpose of research studies is to gain knowledge. This knowledge may be used to help others. Research studies are not intended to benefit you directly, though some might.

Do I Have to Do This?

No. Being in this study is entirely your choice. If you decide to join this study, you can change your mind later on and withdraw from the research study.

Taking part in a study is separate from medical care. The decision to join or not join the research study will not affect your status as a patient.

What Is This Document?

This form is an informed consent document. It will describe the study risks, procedures, and any costs to you.

This form is also a HIPAA Authorization document. It will describe how your health information will be used and by whom.

Signing this form indicates you are willing to take part in the study and allow your health information to be used.

What Should I Do Next?

1. Read this form, or have it read to you.
2. Make sure the study doctor or study staff explains the study to you.
3. Ask questions (e.g., time commitment, unfamiliar words, specific procedures, etc.)
4. If there will be medical treatment, know which parts are research and which are standard care.
5. Take time to consider this, and talk about it with your family and friends.

Emory University and Saint Joseph's Hospital
Consent to be a Research Subject / HIPAA Authorization

Title: Winship 4494-18: Phase II trial of Nivolumab and Metformin in patients with treatment refractory MSS metastatic Colorectal Cancer

Principal Investigator: Mehmet Akce, MD

Investigator-Sponsor: Mehmet Akce, MD

Study-Supporter: Bristol-Myers Squibb (BMS)

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

What is the purpose of this study?

The purpose of this study is to determine the effectiveness of combining metformin with nivolumab in microsatellite stable metastatic colorectal cancer. Metformin is an antidiabetic drug and is widely used in diabetes. Metformin is not approved for cancer treatment by the U.S. Food and Drug administration (FDA) however it is being studied in several other clinical trials for its potential for cancer treatment in combination with

different cancer drugs. Nivolumab is approved for treatment of certain cancers such as melanoma, , hepatocellular carcinoma, microsatellite instability high (MSI-H) metastatic colorectal cancer by the U.S. Food and Drug administration (FDA). Only 5% of metastatic colorectal cancers are microsatellite instability high (MSI-H) and rest is microsatellite stable (MSS) and MSS colon cancer do not respond to nivolumab therapy.
Tumor biopsies are required for participation and will be performed twice at different time points for each patient from the most accessible tumor site. Biopsies are important to understand whether metformin is affecting the tumor microenvironment.

We plan to enroll approximately 31 patients on this trial.

Patients will be started on metformin only by mouth twice daily for the first two weeks of the study as outlined in the table below. After 2 weeks of metformin only treatment patients will be started on nivolumab 480 mg intravenously every 4 weeks along with twice daily administration of metformin by mouth (Cycle 1 Day 1 of the study, each cycle is 4 weeks). The doses of drugs you start could be lowered of held if you experience serious side effects.

Metformin dosing in the first two weeks of the study (first 14 days of study (-14 through -1)
500 mg by mouth twice daily on days -14 through -12
500 mg by mouth in the morning, 1000 mg by mouth in the evening on days -11 through -8
1000 mg by mouth in the morning, 1000 mg by mouth in the evening on days -7 through -1
Patients with diabetes mellitus will be asked to keep a blood glucose level log at home for the first 4 weeks of the trial.

What will I be asked to do?

All subjects must sign an informed consent document prior to initiation of any study related procedures. The informed consent document must be signed within 28 days of first dose of study treatment.

Screening procedures are to be conducted within 28 days of starting the study.

- Medical History
- Record concomitant medications taken up to 28 days prior to day 1 cycle 1
- Vitals [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)]
- Physical Examination, including height and weight
- Collect samples for

  - Safety tests- thyroid function, blood counts, triglycerides, cholesterol, blood sugar, liver and kidney functions
  - Serum or urine pregnancy test for women of childbearing potential within 72 hours of study drug.
  - HIV, HBsAg, HCV RNA if clinically indicated and urinalysis
- 12-lead ECG
- Radiologic imaging studies to evaluate tumor status. Contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen and pelvis.
- Research blood samples (20 cc) and paired biopsy after the consent is signed and before the trial treatment is started. Biopsy of an organ where the cancer is evident and is deemed most accessible and feasible for biopsy.

Treatment procedures

Cycle 1 D -14

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- Assessment of side effects
- Laboratory assessments
  - Blood tests-routine-blood counts, liver and kidney function
  - Tumor marker in the blood
- Metformin taken by mouth

Cycle 1 Day -7

- Metformin taken by mouth
- Review of adverse events, dosing and compliance and concomitant medication (by clinical trial coordinator via phone call)

Cycle 1 Day 1

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- Assessment of side effects
- Laboratory assessments

  - Blood tests-routine-blood counts, liver and kidney function
  - Tumor marker in the blood
  - Blood sample 20 cc for research
- Metformin taken by mouth
- **Subject #1-9, 19-23 (14 patients in total)** will get research biopsy#2 of paired biopsy (same day of up to 5 days later)
- Nivolumab 480 mg will be administered as a 30-minute intravenous infusion in the infusion center after biopsy#2 (same day or up to 5 days later)

Cycle 1 Day 15

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- Assessment of side effects
- Laboratory assessments
  - Blood tests-routine-blood counts, liver and kidney function
  - Tumor marker in the blood
  - Blood sample 20 cc for research
- Metformin taken by mouth
- **Subject #10-18, 24--31 (14 patients in total)** will get research biopsy#2 of paired biopsy (same day of up to 5 days later)
- Nivolumab 480 mg will be administered as a 30-minute intravenous infusion in the infusion center after biopsy#2 (same day or up to 5 days later)

Cycle 2 Day 1

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- Assessment of side effects
- Laboratory assessments
  - Blood tests-routine-blood counts, liver and kidney function
  - Tumor marker in the blood- CEA (every 2 cycles after cycle 2)
  - Thyroid function tests at cycle 2 and then every 3 cycles
- Metformin taken by mouth

- Nivolumab 480 mg will be administered as a 30-minute intravenous infusion in the infusion center
- Cross sectional imaging (CT or MRI) for restaging at the end of Cycle 2 (± 3 days), then repeat every 2 cycles (every 8 weeks)

Cycle 3 Day 1 and Day 1 of each subsequent cycle

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- Assessment of side effects
- Laboratory assessments
  - Blood tests-routine-blood counts, liver and kidney function
  - Tumor marker in the blood- CEA (every 2 cycles after cycle 2)
  - Fasting triglycerides, cholesterol and glucose (cycle#3 and every 3 cycles)
  - Urinalysis (Cycle 3 and every 3 cycles)
  - Blood sample 20 cc for research
- Metformin taken by mouth
- Nivolumab 480 mg will be administered as a 30-minute intravenous infusion in the infusion center

End of treatment visit

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- Assessment of side effects
- Laboratory assessments
  - Blood tests-routine-blood counts, liver and kidney function
  - Tumor marker in the blood- CEA
  - Thyroid function tests
  - Urinalysis
  - Blood sample 20 cc for research

Subjects will stay on the trial until either cancer gets worse (disease progression), significant side effects (toxicity) or withdrawal of consent.

Safety Follow up Visit
You will be followed for at least 30 days after the last dose of study drug or until you start a new cancer treatment, whichever happens first.

After you complete the 30-day follow-up you will enter the post-treatment follow-up period. The study doctor or staff will discuss with you when and on which days to report to the clinic for the follow-up visits.

If you stop taking the study drug before your cancer gets worse you will continue to come in for a follow-up visit every 8 weeks (± 7 days) with clinic visit and imaging until your cancer gets worse or you start a new treatment for your cancer. After 1 year, the imaging time will occur every 9 weeks (± 7 days).

If at any time after you complete your treatment your cancer gets worse, or you start a new cancer treatment, you will be contacted by telephone every 12 weeks for survival follow-up until the study ends.

Subjects who are eligible for retreatment with metformin/ nivolumab may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

How will my medicine be provided?
The medicine that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the medicine to you. If you have questions about the medicine, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the medicine. The number for the pharmacy is included on your medicine package.

Who owns my study information and samples?
If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study.

What are the possible risks and discomforts?
There may be side effects from the study drug or procedures that are not known at this time.

Seville orange, star fruit, grapefruit and their juices can affect the activity and concomitant use with the study drugs should be avoided.

Side effects of metformin include:

The most common risks and discomforts expected in this study are:

- Diarrhea
- Feeling tired
- Feeling sick to your stomach
- Heartburn
- Dizziness
- Weakness
- Throwing up
- Decreased appetite
- Abdominal pain

Rare but SERIOUS possible risks include: Kidney dysfunction and lactic acidosis measured by blood tests

Side effects of nivolumab include:

Nivolumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer.

Nivolumab works by helping your immune system to fight your cancer.

However, Nivolumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or life-threatening, and in some cases, may lead to death.

VERY COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening or where noted, may cause death)
Out of 100 people who receive nivolumab, 10 or more people may have the following:

- Rash
- Itching of the skin
- Nausea
- Diarrhea
- Fatigue
- Low white blood cells

COMMON, SOME MAYBE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)
Out of 100 people who receive nivolumab, at least 1 but less than 10 people may have the following:

- Upper respiratory tract infection
- Allergic reaction during nivolumab infusion related reaction

- Thyroid gland function increased
- Thyroid gland function decreased
- Decreased appetite
- Headache
- Dizziness
- Peripheral nerve damage, which is characterized with burning, tingling, numbness or weakness in hands, feet or legs
- High blood pressure
- Cough
- Shortness of breath
- **Lung inflammation (pneumonitis)**: Nivolumab might cause inflammation of the tissues of the lung. While many patients with x-ray or CT scan abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and, in rare cases, death has occurred as a result of lung inflammation. Signs and symptoms of lung inflammation may include the following: difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, rapid breathing, fever, low blood oxygen levels, or fatigue. During the study, your study doctor, nurse, and study team are trained to routinely ask about and check for signs and symptoms of lung inflammation mentioned above. They do this by talking with you about your symptoms and by performing regular tests.
- Vomiting
- Belly pain
- Constipation
- Dry mouth
- Mouth inflammation and pain
- Bowel inflammation
- Vitiligo, lightening of the skin color
- Dry skin
- Erythema, redness of skin
- Hair loss
- Joint pain
- Musculoskeletal pain
- Swelling in hands or feet
- Fever
- Blood chemistry and or liver function abnormalities
- Weight loss

UNCOMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)
Out of 1000 people who receive nivolumab, at least 1 but less than 10 people may have the following:

- Lung infection
- Inflammation of airways, bronchitis
- Abnormal blood cell production
- Adrenal insufficiency
- Pituitary gland inflammation
- Inflammation of thyroid gland
- High blood sugar
- Dehydration
- Liver inflammation
- Inflammation of the peripheral nerves
- Inflammation of the eye
- Blurred vision
- Dry eye
- Increased heart rate
- Fluid accumulation in the lungs
- Inflammation of pancreas
- Inflammation of stomach
- Erythema multiforme: Skin inflammation
- Psoriasis characterized with scaly skin
- Hives
- Rosacea, acne like skin condition characterized with redness of face
- Joint inflammation
- Polymyalgia rheumatic, inflammatory disorder causing muscle pain and stiffness
- Kidney failure or kidney damage
- Chest pain

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)
Out of 10,000 people who receive nivolumab, at least 1 but less than 10 people may have the following:

- Anaphylactic reaction, characterized with severe and potentially life threatening allergic reaction
- Excess blood acids and coma due to diabetes complications
- Guillain-Barre syndrome, which is characterized with weakness and tingling starting in legs and feet and spreading to arms and upper body, which can result in severe muscles weakness and paralysis
- Inflammation of the covering of the nerves
- Myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles
- Inflammation of brain, potentially life threatening
- Abnormal heart rhythm
- Inflammation of heart

- Lung infiltration
- Blood vessel inflammation
- Duodenal ulcer
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn, has occurred in patients who received nivolumab.
- Stevens-Johnson syndrome, which results in blistering and shedding of skin due to severe skin and mucous membrane inflammation
- Sjogren`s syndrome, which is characterized with dry eyes and dry mouth
- Myopathy, which is damage to muscles
- Myositis, which is chronic muscles inflammation with muscle weakness
- Rhabdomyolysis, which is muscle inflammation with muscle fiber contents released into blood stream which could damage kidneys
- Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), lymph node disorder with painful and inflamed lymph nodes most affecting lymph nodes of neck and associated with fever and joint/muscle pain
- In addition to the above, complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplant (HSCT) before or after nivolumab. Complications, including rejection, have also been reported in patients who have received an organ or tissue transplant.

What effects could the tests have on me?

Risk of blood drawing and intravenous access: Putting a tube or needle in your vein to draw blood or give you drugs may hurt when the needle is put in. There is a risk of continued pain, bruising, dizziness, fainting or infection, which although rare, can occur.

Electrocardiogram (ECG): Small pads are attached to your skin in order to record the electrical activity of your heart. The ECG itself is painless, however it may cause minimal discomforts during the attachment and removal of the ECG leads to and from the skin. Sometimes it may be necessary to shave small areas of the chest in male patients in order to attach the ECG leads.

Contrast Agents: Your CT or MRI procedure will require the use of a “contrast agent.” The contrast agent is a substance that helps the radiologist interpret the images. The contrast agent will be injected by either a hand-held needle or a machine that does the injection. Most contrast agents stay in your body for only a few minutes, but some of them can remain for a few hours or days without any harm to you or anyone near you. Contrast agents are generally quite safe, but any injection involves some risks. The injection could harm a nerve, artery or vein, or cause infection. The contrast agent could affect kidney function or cause an allergic reaction, though these outcomes are rare. The contrast agent could also leak from your veins a little causing swelling and discomfort, that is typically treated with ice packs.

Magnetic Resonance Imaging (MRI): MRI exams use powerful magnets to create images of the body. In addition to the possible reactions to contrast materials, you may feel claustrophobic while in the magnet, and will hear loud beeping or hammering noises. If you have tattoos or any metal items in your body such as implants, pacemakers, clips or shrapnel, we will do special screening to make sure your MRI scan is done safely.

Radiation-Related Risks: You will be exposed to radiation from CT scans. These procedures are necessary for your medical care and will occur even if you do not participate in this study. The radiation dose estimate that you will receive is equal to or less than the radiation exposure allowed to be received by a radiation worker for 5 years. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. Although the risk from radiation is cumulative it is not expected to adversely affect your condition or treatment. The Emory University Radiation Safety Committee has reviewed and approved the use of radiation in this research study.

Tumor Biopsy: Having biopsies performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling and/or infection at the site of the biopsy, perforation of gastric wall/esophagus and rarely, death. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site. Other potential risks will be described to you and discussed with you by physicians who conduct these biopsies. The tumor biopsies will be performed by interventional radiology at Emory University.

If you are a woman: to protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. If you become pregnant, there may be risks to you, the embryo, or fetus. These risks are not yet known. If you are a woman of childbearing ability, you and the study doctor must agree on a method of birth control to use or abstinence throughout the study and for 120 days after the last dose of study medicine. If you think that you have gotten pregnant during the study, you must tell the study doctor immediately. Pregnant women will be taken out of the study.

If you are a man: the effect of the study drug on sperm is not known. To protect against possible side effects, if you are a man you should not get a sexual partner pregnant while taking the study drug and for 4 months after the last dose. You and the study doctor should agree on a method of birth control to use throughout the study.

If you will be taking the study drug home, keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?
Your cancer may improve while you are in this study, but it may not, and it may even get worse. This study is designed to learn more about the effects of combination of nivolumab and metformin. The study results may be used to help others in the future.

Will I be compensated for my time and effort?
You will not be offered compensation for being in this study.

What are my other options?
If you decide not to enter this study, there is care available to you outside of this research study. These options include other clinical trials or standard chemotherapy drugs including regorafenib and TAS-102 (if you have not been treated with these drugs already). The study doctor will discuss these with you. You do not have to be in this study to be treated for your cancer.

Taking part in this study, however, may make you unable to participate in some other research studies, if they exclude people who have taken certain treatments. You should discuss this with the researchers if you have concerns. You may wish to research other study options at websites like clinicaltrials.gov and ResearchMatch.org.

How will you protect my private information that you collect in this study?
Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

Storing and Sharing your Information
De-identified data from this study, may be shared with the research community at large to advance science and health. Data from this study may be placed into public databases where, in addition to having no direct identifiers, researchers will need to sign data use agreements before accessing the data. We will remove or code any personal information that could identify you before your information is shared. This will ensure that, by current scientific standards and known methods, it is extremely unlikely that anyone would be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Medical Record

If you have been an Emory and Saint Joseph's Hospital patient before, then you already have an Emory and Saint Joseph's Hospital medical record. If you have never been an Emory and Saint Joseph's Hospital patient, you do not have one. An Emory and Saint Joseph's Hospital medical record will be made for you if an Emory and Saint Joseph's Hospital provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory and Saint Joseph's Hospital medical record you have now or any time during the study.

Emory and Saint Joseph's Hospital may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory and Saint Joseph's Hospital medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include: results on the correlative blood samples and results on the analysis of tumor biopsy specimens.

Tests and procedures done at non-Emory and Saint Joseph's Hospital places may not become part of your Emory and Saint Joseph's Hospital medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you get ill or injured from being in the study, Emory and Saint Joseph's Hospital will help you to get medical treatment. Emory and Saint Joseph's Hospital and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory and Saint Joseph's Hospital or sponsor employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact Dr. Mehmet Akce at telephone number [redacted] You should also let any health care provider who treats you know that you are in a research study.

Costs

Nivolumab and metformin will be free of charge.

Any costs associated with the tumor biopsies will be paid for by the study and no cost to the patient.

You will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for your regular medical care. If you have insurance, Emory and Saint Joseph's Hospital will submit claims to your insurance for items and services that the sponsor does not cover. Emory and Saint Joseph's Hospital will send in only those claims for items and services that it reasonably believes your insurance will pay and that the sponsor has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Emory and Saint Joseph's Hospital and the sponsor will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

If you do not have insurance, Emory and Saint Joseph's Hospital will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Withdrawal from the Study

You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Human Biological Samples

While you are in this study, you will have blood (serum/plasma) and biopsy samples collected to be used for the current study analysis, including re-running study tests, if

necessary, and storing samples for future research. The purpose of storing these samples is to make them available to scientists who are trying to develop new tests, treatments, and ways to prevent diseases. We hope that these samples and images will provide information that will help researchers in the future. The samples will be labeled with an identification code. Your samples and images will never be labeled with your name and will remain separate from the files linked to your name.

Successful research using the samples or other parts of the samples could result in a commercial or therapeutic product with significant value, such as a product for the medical treatment or diagnosis of cancer or other disorders. You will not share in any financial benefits of these uses.

Your samples will only be used for research and will not be sold. These samples may be utilized by Emory and Saint Joseph's Hospital for further or additional analyses to answer scientific or medical questions, but if your samples or images are given to other researchers (other than Emory and Saint Joseph's Hospital) your samples would only be given to researchers who have had their research reviewed by an Institutional Review Board (IRB), which is a committee that protects the rights and privacy of study subjects.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study and for any optional studies in which you may choose to participate.

PHI that Will be Used/Disclosed:
The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data

monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory and Saint Joseph's Hospital may use and disclose your PHI to get payment for study related treatment and to run normal business operations. c
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- Dr. Mehmet Akce is the Sponsor of the study. The Sponsor may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory and Saint Joseph's Hospital offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including: Food and Drug Administration

- Public health agencies.
- Research monitors and reviewer.
- Accreditation agencies.
- Study supported: Bristol-Myers Squibb (BMS)

- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

Mehmet Akce, MD
Winship Cancer Institute, Emory University
1365-C Clifton Road NE
Atlanta, GA 30322

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. The Sponsor, and people and companies working with the Sponsor on this study are not covered by the Privacy Rules. They will only use and disclose your information as described in this Consent and Authorization.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions

about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information

Contact Mehmet Akce, MD at [redacted]

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at [redacted]

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in the main study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

_____

Name of Subject

_____ _____ _____**am / pm**

Signature of Subject (18 or older and able to consent) Date Time(please circle)

TO BE FILLED OUT BY STUDY TEAM ONLY

Name of Person Conducting Informed Consent Discussion

_____ _____ _____**am / pm**

Signature of Person Conducting Informed Consent Discussion **Date** **Time (please circle)**