Informed Consent Form

Immune Checkpoint Inhibitors With or Without Propranolol Hydrochloride In Patients With Urothelial Carcinoma

NCT Number: NCT04848519

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You Are Being Asked to Be in a Research Study

Concise presentation of key concepts

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree to be in the study, you will be one of 24 people who are being studied at Emory Health System, Saint Joseph's Hospital and elsewhere.

Why is this study being done?
This study is being done to answer the question: is low-dose propranolol in addition to the standard of care (ICI) immune checkpoint inhibitors (pembrolizumab, nivolumab, or avelumab) effective and safe in the treatment of muscle invasive and advanced urothelial cancer? You are being asked to be in this research study because you were diagnosed with muscle invasive or advanced urothelial (renal pelvis, ureter, bladder, or urethra) cancer and qualify for treatment with either pembrolizumab, nivolumab, or avelumab depending on your disease stage and prior treatments.

Do you have to be in the study?
It is your choice to join this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. Before you choose, take time to learn about the study.

What do you have to do if you choose to join this study?
If you qualify and choose to join the study, you will participate for up to two years. For this study, you will receive treatment with the ICI (Pembrolizumab, Avelumab or Nivolumab) on Day 1 of each Cycle, combined with taking propranolol 30 mg twice a day OR you will receive the ICI (Pembrolizumab, Avelumab or Nivolumab) alone. You will also come in for physical visits with your doctor, have some blood samples drawn, answer some questionnaires, have an ECG (electrocardiogram), CT scans, and several other assessments throughout your participation in the study. Some of these procedures will be paid for by the study.

How is this study going to help you?
If you are in the study, you will be helping the researchers answer the study question. However, there is no guarantee that enrolling in this study will have any direct benefit. If there are any significant findings while the study is being conducted, you will be provided with and new information that becomes available to your study team. This will be provided via a discussion with your treating physician.

What are the risks or discomforts you should know about before deciding?
The study will take time. The drug combination that is being tested may not work any better than regular care and may even cause harm. All studies have some risks. Some risks are small, like being bored or losing time. Some are more serious. Risks for this study include:

- fatigue, dizziness, cold hands and feet sensation, and constipation
- loss of privacy,
- and breach of confidentiality.

You can find a full list of expected risks, their frequency and severity are in the section titled "What are the possible risks and discomforts?".

Alternatives to Joining This Study
If you do not wish enrolling in this study, your doctor will discuss treating your advanced bladder cancer with pembrolizumab, nivolumab, or avelumab alone, as a standard of care and outside the setting of a clinical trial.

Nivolumab is approved for treatment of high-risk muscle-invasive disease after radical surgery. Avelumab is approved for treatment in metastatic disease as maintenance in patients who received platinum-based chemotherapy and had no disease progression. Pembrolizumab is approved in patients with advanced or metastatic disease who cannot receive platinum-based chemotherapy or who have had disease progression on prior platinum-based chemotherapy.

Costs
The study sponsor will pay for certain items and services that you may receive if you take part in this study. You WILL have to pay for the items or services for which the study sponsor does not pay. These are including some of the study procedures, in particular those that are not covered by your medical insurance. The sponsor will not pay for your regular medical care.

The study team can help you work out how much you might have to pay. There is more information in the "Costs" section further below.

What Should I Do Next?
Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions such as how much time you will have to spend on the study, any words you do not understand and more details about study procedures. Make sure you understand which parts of the study are research and which are standard care that you would have even if you did not join the study. 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: Immune Checkpoint Inhibitors With or Without Propranolol Hydrochloride In Patients with Urothelial Carcinoma

IRB #: STUDY00002186

Principal Investigator: Bassel Nazha, MD, MPH

Study-Supporter: Morningside Center for Innovative and Affordable Medicine

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 choose if you want to be a part of the study. It is entirely your choice. If you choose 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 choose not to join this study, your doctor will still treat you.

Before making you decide:

- 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 will get a copy of this form. 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 evaluate whether low-dose propranolol in addition to the standard of care immune checkpoint inhibitors (pembrolizumab, nivolumab, or avelumab) is effective and safe in the treatment of muscle-invasive or advanced urothelial cancer.

What will I be asked to do?

This study asks you to do several things, most of them would be done as standard of care if you were not on this study.

This study has 3 different Arms or regimens that will be used in this research. They will be determined based off the clinical treatment decision that you have discussed with your physician, the cancer stage, and prior treatment history. You will be assigned once you are found eligible for the study.

Here are the study treatment Arm descriptions:

Subjects receiving Pembrolizumab

Arm	Regimen Description				
	Agent	Dose	Route	Schedule	Cycle Length
ICI plus propranolol	Pembrolizumab	200 mg	IV infusion over 30 min	Every 3 weeks	42 days (6 weeks)
	Propranolol hydrochloride	30mg	Oral	Twice a day, continuous	
ICI Alone	Pembrolizumab	200mg	IV infusion over 30 min	Every 3 weeks	

Subjects receiving Avelumab

Arm	Regimen Description				
	Agent	Dose	Route	Schedule	Cycle Length
ICI plus propranolol	Avelumab	10mg/kg	IV infusion over 60 min	Every 2 weeks	42 days (6 weeks)
	Propranolol hydrochloride	30mg	Oral	Twice a day, continuous	
ICI Alone	Avelumab	10mg/kg	IV infusion over 60 min	Every 2 weeks	

Subjects receiving Nivolumab

Arm	Regimen Description				
	Agent	Dose	Route	Schedule	Cycle Length
ICI plus propranolol	Nivolumab	480mg	IV infusion over 30 min	Every 4 weeks	28 days (4 weeks)
	Propranolol hydrochloride	30mg	Oral	BID, Continuous	
ICI Alone	Nivolumab	480mg	IV infusion over 30 min	Every 4 weeks	

First, once all your questions have been answered and you feel comfortable that you understand what this study involves, you will need to sign this informed consent.

Screening

To find out if you can take part in this study, you will go through a Screening process. In this process, you will be asked about your general health and your medical history. You will also be

asked about medicines, prescriptions and any over-the-counter drugs and supplements you are taking right now or have taken within 28 days prior to the first dose of study drug.

If any of the tests required at screening were performed prior to signing consent (within 28 days), as part of your routine care, and if they fall within the time allowed by the study, they may be used and need not be repeated.

This screening evaluation process may take up to a maximum of 28 days prior to starting the study and will include the following:

- Obtain Informed Consent
- Review your current condition, your medical history, and any medications you may be taking.
- A physical examination (including Performance assessment, vitals (including your height and weight)
- Obtaining an electrocardiogram (to record the rhythms and electrical activity of your heart).
- Approximately one tablespoon of blood will be drawn for blood tests (electrolytes, kidney function, liver function) and for a complete blood count (white blood cells, red blood cells, and platelets)
- We will perform a pregnancy test if you are a woman who could have children. You must not be pregnant, breastfeeding, or planning to have children (male patients included) in order to join the study.
- You will be asked to fill a one-page questionnaire about your health and feelings.
- Radiologic imaging studies to evaluate tumor status: Have a computerized tomography (CT) scan or magnetic resonance imaging (MRI) to see tumor. A CT scanner is used to take a series of X-rays of your body at slightly different angles. A computer puts these together to produce a very detailed picture of the inside of your body. Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to produce detailed pictures of the inside of your body. The pictures produced by the CT scans and the MRIs provide doctors with information to help them assess the extent of your cancer. CTs will be performed with intravenous (IV) contrast; MRIs will be performed with IV contrast. This means that you may have to receive a special dye by injection into a vein that will highlight areas of disease involvement more easily for a doctor who is reviewing your scans.
- A stool sample for research purposes.
- A blood sample of 60mL for research purposes.

If you are found to be eligible for the study, and agree to participate, you will be assigned to one of the 3 Arms described in the tables above.

Treatment schedule

If you are found to be eligible for the study, and agree to participate, you will be started on the 1st treatment. Depending on the Arm you get assigned to, the “treatment cycle” will either be 28 days (4 weeks) or 42 days (6 weeks).

- On Day 1 of each cycle of treatment, (until discontinuation of study treatment)) you will receive either:
    - pembrolizumab (200 mg) will be administered on Day 1 into the vein of your arm or in the chemotherapy port at the infusion center, with or without propranolol hydrochloride (orally 30mg twice a day) which you would continue taking daily at home thereafter.

        - You will be requested to maintain a diary for each dose of propranolol hydrochloride.
    - Avelumab (10mg/kg) will be administered on Day 1 into the vein of your arm or in the chemotherapy port at the infusion center, with or without propranolol hydrochloride (orally 30mg twice a day) which you would continue taking daily at home thereafter.
        - You will be requested to maintain a diary for each dose of propranolol hydrochloride.
    - Nivolumab (480mg) will be administered on Day 1 into the vein of your arm or in the chemotherapy port at the infusion center, with or without propranolol hydrochloride (orally 30mg twice a day) which you would continue taking daily at home thereafter.
        - You will be requested to maintain a diary for each dose of propranolol hydrochloride.

During every cycle (and at the time of discontinuation of study treatment), you will have several of the following assessments before receiving your treatment. Some of these will not be done each time so please refer to the detailed Assessments sections below.

Physical Exams with Vitals and Medication Review
At the start of each cycle (Day 1) and at study discontinuation, you will have a physical examination. This will include a Performance assessment and collection of vitals (including your height and weight). Your treating physician and study team will review any medications you may be taking. At every clinic visit, we will be assessing for side effects. If the side effects are severe and do not come under control, you may be withdrawn from the study if the study doctor feels this is in your best interests.

Standard of Care Labs
Approximately one tablespoon of blood will be drawn for blood tests (electrolytes, kidney function, liver function) and for a complete blood count (white blood cells, red blood cells, and platelets). This will be completed Day 1 of treatment and at Study Discontinuation.

Patient-reported outcome questionnaire
You will be asked to fill a one-page questionnaire about your health and feelings at the first day of every cycle, and at study discontinuation.

Research blood samples
Your blood samples will be used to study cells, genes and proteins present in the liquid portion of the blood (serum). This study will attempt to find differences in the blood between patients and before and after treatment. It might help us understand changes in biomarkers induced by the treatment. Each sample will be of 60 mL. Those samples are for research purposes and are not part of your standard clinical care.
Samples will be collected:

- Cycle 1 Day 1, Day 8 and Cycle 2 Day 1 for subjects receiving avelumab or pembrolizumab.
- Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 15 for subjects receiving nivolumab.

Research Tissue Sample
If you agree to participate, a piece of your surgical tumor sample (used for your cancer

diagnosis) will be used and archived for Research purposes. Tissue will be preserved for future exploratory studies including genomic profiling.

Research stool sample
Along with being collected at Screening (baseline), a research stool sample will be collected at the beginning of Cycle 4 (Day 1 of Cycle 4) to study the treatment effect on gut microbiome.

Imaging studies (CT or MRI)
Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis.

- Baseline imaging studies must be performed within 4 weeks of study start
- Radiologic imaging studies every 12 weeks to evaluate your tumor status. This will continue until you a) withdraw consent or b) you start a new treatment.

Study Discontinuation Visit
Whether you are taken off study treatment early for safety / toxicity reasons, for disease progression or you complete the full 2 years of study treatment, you will have the following assessments (regardless of the treatment Arm you were on):

- Physical Exams with Vitals and Medication Review you will have a physical examination. This will include a Performance assessment and collection of vitals (including your height and weight).
- Review your current condition to assess for any new or ongoing side effects.
- Approximately one tablespoon of blood will be drawn for blood tests (electrolytes, kidney function, liver function) and for a complete blood count (white blood cells, red blood cells, and platelets)
- You will be asked to fill a one-page questionnaire about your health and feelings.
- Radiologic imaging studies are required every 12 weeks to evaluate tumor status. If this discontinuation visit falls on or around this timepoint, you will have an appointment scheduled for you.
- A blood sample of 60mL for research purposes.

Duration of Study Follow-up
Patients will be followed for approximately 28 days (Safety Follow-up) after the last dose of study drug. At this point you will have

- Physical Exams with Vitals and Medication Review you will have a physical examination. This will include a Performance assessment and collection of vitals (including your height and weight).
- Review your current condition to assess for any new or ongoing side effects.
- Approximately one tablespoon of blood will be drawn for blood tests (electrolytes, kidney function, liver function) and for a complete blood count (white blood cells, red blood cells, and platelets)

Long-term (Survival) follow-up
Long-term Follow up will continue every 12 weeks up to 2 years post last dose of study drug. During this time, or until you withdraw your consent:

- Your study team will check up on you for survival status.
- Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

How will your study drug be provided?
The study drug 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 study drug to you. If you have questions about the study drug, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the study drug. The number for the pharmacy is included on your study drug package.

Who owns your study data and samples?
If you join this study, you will be donating your samples and data. You will not be paid if your samples or data are used to make a new product. If you withdraw from the study, data and samples that were already collected may still be used for this study. All study samples will be maintained in the laboratory to which it was sent initially for analysis. If you request destruction of your samples, you will be informed of compliance with such request.

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.

Propranolol
The most common risks and discomforts expected in this study (frequency of 1 to 10%) are: dizziness or lightheadedness (4 to 7%), unusually slow pulse, constipation (1 to 3%), unusual tiredness (5 to 7%) or cold hands and feet.

The less common risks and discomforts expected in this study (frequency <1%) are: mental confusion, low blood pressure, swelling of ankles, feet and lower legs; anxiety and / or nervousness, sexual problems such as erectile dysfunction or reduced sex drive, headache, nightmares, trouble sleeping, feeling of sadness and other symptoms of depression.

Rare but possible risks include: Severe allergic reaction with skin rash, pins and needles sensations, hallucinations, and breathing difficulty or wheezing.

Immune checkpoint Inhibitor (Pembrolizumab, Nivolumab or Avelumab)
An immune checkpoint inhibitor (ICI) works by helping your immune system to fight your cancer. However, ICI 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. These may become serious (i.e., causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking ICI. These side effects can affect more than one of your normal organs and tissues at the same time.

VERY COMMON
Out of 100 people who receive ICI, 20 or more people may have the following:
- Itching of the skin
- Loose or watery stools
- Cough

COMMON
Out of 100 people who receive ICI, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

UNCOMMON

Out of 100 people who receive ICI, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough.
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection.

RARE

Out of 100 people who receive ICI, less than 1 person may have the following:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis.
- Inflammation of the muscles so you may feel weak or have pain in the muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly

aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan.
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing.
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs.
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation
- Inflammation of the blood vessels
- The loss of fat tissue from your body or the redistribution of fat tissue to atypical areas of your body. This could be accompanied by metabolic abnormalities such as diabetes mellitus, high triglycerides or fat accumulation in the liver (leading to inflammation of the liver)

In addition to the above, since ICI were approved, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:
- Inflammation of the joints which may include join pain, stiffness and/or swelling.
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving ICI. Sometimes this condition can lead to death.

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.

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 2 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.

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. Congenital abnormalities have been reported following maternal use of propranolol. Exposure to propranolol during pregnancy may also increase the risk for other adverse events in the embryo or fetus. Based on their mechanism of action, immune checkpoint inhibitors (ICI) (Pembrolizumab, Nivolumab, or Avelumab) may cause harm to a fetus when given to a pregnant woman. The potential risks of receiving any of these drugs while pregnant include an increased risk of abortion or stillbirth. If you are a woman of childbearing ability, you and the study doctor must agree on an adequate method of birth control or abstinence for the duration of the study. 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, you should not get a sexual partner pregnant while taking the study drug

and for 3 months after the last dose. You and the study doctor should agree on an adequate method of birth control or abstinence for the duration of 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.

Researchers may learn something new during the study that may affect your choice to be in the study. If this happens, they will tell you about it. Then you can choose if you want to stay in this study or not. You may be asked to sign a new consent form that includes the new information if you choose to stay in the study.

Will I benefit directly from the study?
You may not benefit from joining the study. Your condition may improve while you are in this study or it may get worse. This study is designed to learn more about whether the addition of propranolol to pembrolizumab, avelumab or nivolumab could enhance its effects on the cancer cells. If the treatment being studied (i.e. propranolol plus pembrolizumab, propranolol plus avelumab, or propranolol plus nivolumab) is more effective than the standard treatment alone (i.e. pembrolizumab alone, avelumab alone, or nivolumab alone), you may be among the first to benefit. The study results may also 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 choose not to join this study, there is care available to you outside of this research study. The standard care option would be either pembrolizumab, avelumab, or nivolumab. The study doctor will discuss this with you. You do not have to be in this study to be treated for bladder cancer.

If you choose to join this study, however, you may not be able to participate in other research studies, if they exclude people who have taken certain treatments. Discuss this with the researchers if you have concerns. You may wish to look on websites such asclinicaltrials.gov and ResearchMatch.org for other research studies you may want to join.

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
We will store all the data and specimens that you provide using a code. We need this code so that we can keep track of your data over time. This code will not include information that can identify you (identifiers). Specifically, it will not include your name, initials, date of birth, or medical record number. We will keep a file that links this code to your identifiers in a secure location separate from the data.

We will not allow your name and any other fact that might point to you to appear when we present or publish the results of this study.

Your data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, we may share the data and/or specimens, linked by the study code, with other researchers at Emory, or with researchers at other institutions that maintain at least eh same level of data security that we maintain at Emory. We will not share the link between the study code and your identity.

We may also place data in public databases accessible to researchers who agree to maintain confidentiality (by signing a data use agreement) if we remove the study code and make sure that the data are anonymized to a level that we believe that is highly unlikely that anyone could identify you. Despite these measures, we cannot guarantee anonymity of your personal data. Once the study has been completed, we will send you a summary of all of the results of the study and what they mean. We will not send you your individual results from this study.

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 of the study tests and procedures will be used only for research purposes and will not be placed in your Emory and Saint Joseph's Hospital medical record. Tests and procedures done at non-Emory places may not become part of your Emory and Saint Joseph's 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 believe you have become ill or injured from this research, you should contact Dr. Bassel Nazha at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory and Saint Joseph's will help you to get medical treatment. Neither Emory, Saint Joseph's nor the sponsor have set aside money to pay for this medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

For Emory and Saint Joseph's, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory or Saint Joseph's employee. "Negligence" is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

Costs
The study sponsor will pay for certain items and services that you may receive if you take part in this study.

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.

<u>Withdrawal from the Study</u>
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 complete some of the final steps such as lab work or imaging as applicable.

The researchers also have the right to stop your participation in this study without your consent for any reason. They may do this if they believe it is in your best interest or if you do not agree to changes that may be made in the study.

These are the expected reasons why the researchers may stop your participation:

- If you develop a serious side effect from your treatment
- If your clinical assessment or imaging scans suggest that your cancer is not responding to treatment
- If you choose to receive care at another institution

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 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 disclose your PHI to provide you with study related treatment and for payment for such treatment. We will also use and disclose your PHI to conduct normal business operations. We may disclose 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 disclose your PHI as described in this document. You do not have to sign this form. If you do not sign this form, 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.
- 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. 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 Healthcare 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-supporter: Morningside Center for Innovative and Affordable Medicine

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:

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

At that point, we will not collect any more of your PHI. We may use or disclose the PHI already collected so we 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 PHI to people who are not covered by the Privacy Rules, then your PHI will not 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.

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

If you have questions about the study procedures, appointments, research-related injuries or bad reactions, or other questions or concerns about the research or your part in it, contact Dr. Bassel Nazha at [redacted]:

This study has been reviewed by an ethics committee to ensure the protection of research participants. If you have questions about your **rights as a research participant**, or if you have **complaints** about the research or an issue you would rather discuss with someone outside the research team, contact the Emory Institutional Review Board at [redacted]:

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you choose to be in this research study. You will not give up any of your legal rights by signing this form. 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)**