THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Phase II Study of NBTXR3 Activated by Radiation and Combined with Pembrolizumab for Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma Refractory to PD-1 Blockade

2020-0541

Study Chair: Jay Reddy, MD, PhD

_____ _____
Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

This research has been reviewed and approved by an Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

The goal of this clinical research study is to learn if NBTXR3 activated by radiation can help to control head and neck squamous cell carcinoma (HNSCC) when given in combination with pembrolizumab. The safety of this treatment will also be studied.

This is an investigational study. NBTXR3 is not FDA approved or commercially available. It is currently being used for research purposes only. Radiation therapy is delivered using FDA-approved and commercially available methods. Pembrolizumab is FDA approved and commercially available for the treatment of recurrent (has come back) or metastatic (has spread) head and neck cancer after platinum chemotherapy. Continued treatment with anti-PD-1/antiPDL-1 therapy following clear evidence of progression is not a standard of care approach. The use of NBTXR3 activated by radiation therapy and combined with pembrolizumab is investigational.

The study doctor can explain how the study drugs and radiation therapy are designed to work.

The study drugs and radiation therapy may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment.

You can read a list of potential side effects below in the Possible Risks section of this consent.

You may receive 1 dose of NBTXR3 injected into the tumor(s) and/or lymph node(s). You may receive radiation therapy for up to 1½ weeks. Pembrolizumab may be given as part of standard of care for up to 2 years.

NBTXR3 will be provided at no cost to you. You and/or your insurance provider will be responsible for the costs of radiation therapy and pembrolizumab.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive radiation therapy and/or pembrolizumab without NBTXR3 or other standard of care treatment. Please talk with your doctor about what may be the right treatment option for you. The study doctor will discuss with you the risk and benefits of these alternate treatments. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening

Signing this consent form does not mean that you will be able to take part in this study. The following screening tests will help the doctor decide if you are eligible:

- You will have a physical exam. If the study doctor thinks it is needed, this will include taking photographs of any mouth blisters and sores. Your face will not be shown in the photograph.
- You will have an EKG to check your heart function.
- Blood (about 4 tablespoons) will be drawn for routine testing and to test for infectious viruses (hepatitis B and C).
- You will have a CT scan to measure the size of the tumor(s) and to help plan study treatment and radiation therapy.
- You will have a PET-CT or CT scan to check the status of the disease and to help plan study treatment and radiation therapy.
- If the study doctor thinks it is needed, you will also have an MRI of your brain.
- If you can become pregnant, urine will be collected for a pregnancy test. If the urine test is positive or cannot be confirmed negative, blood (about ½ tablespoon) will be drawn. To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Groups

If you are found to be eligible to take part in this study, you will be assigned to 1 of 2 study groups (Groups 1 and 2) based on if you received anti-PD-1 immunotherapy, for example pembrolizumab or nivolumab, before taking part in this study. The study doctor will tell you what group you are in.

Up to 20 participants will be enrolled in this study. All participants will be treated at MD Anderson.

Study Drug Administration

About twelve (12) and 2 hours before the NBTXR3 injection, you will receive prednisone to help decrease the risk of side effects. You may ask the study staff for information about how the drug is given and its risks.

You will receive NBTXR3 on Day 1 of the study. One (1) dose of NBTXR3 will be given as an injection directly into 1-3 selected tumor(s) and/or lymph nodes. The study doctor will tell you where you will receive the injection. You will have an image-guided biopsy prior to the NBTXR3 injection. The NBTXR3 injection will also be image-guided (the study doctor can explain this in more detail), and the selected injection procedure will be based of the location of your tumor(s) and/or lymph nodes, which can be either in the head and neck, lungs, or liver. For the image-guided procedures, either the area will be numbed with anesthetic or you will receive general anesthesia. Your doctor can explain this in more detail.

For lung tumors, the injection will be given through the chest wall or with a bronchoscopy. If you have a bronchoscopy, you will be given drugs to relax, and then a local anesthetic will be sprayed into your nose and throat to numb those areas. A slim, flexible tube with a light will be placed through your nose or mouth and into your lungs. A small brush will be fed through the tube and into your lungs. The brush will gently scrape off a sample of lung tissue. Tweezers will then be fed through the tube to collect the tissue samples. A small amount of water will be sprayed into your lungs and then suctioned out through the tube to collect additional tissue samples and mucus samples.

After the injection, you will stay in the clinic for at least 2 hours, so that you can be watched for side effects. If the study doctor thinks it is needed, you may stay in the hospital overnight. This will be discussed with you.

Within 8 days after the NBTXR3 injection, you will start radiation therapy and receive it for about 1 to 1½ weeks. The study doctor will explain your radiation therapy schedule.

Starting the day after your last radiation therapy treatment, you will receive pembrolizumab by vein (intravenous injection or "IV") over about 30 minutes . Pembrolizumab will be given every 3 weeks during the study. You may continue receiving pembrolizumab during follow-up (up to 2 years after your first start taking the study drug). At that time, you may receive a smaller dose every 3 weeks or a larger dose every 6 weeks.

You will no longer be able to take the study drug(s) if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Study Visits

On **Day 1**:

- You will receive premedication with corticosteroids (e.g., prednisone) prior to NBTXR3 injection.
- You will have a physical exam. If the study doctor thinks it is needed, this will include taking photographs of any mouth blisters and sores.
- Blood (about 4 tablespoons) will be drawn for routine and biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug.
- You will have an image-guided biopsy to check the status of the disease and for immune system and biomarker testing. To perform an image-guided biopsy, a needle is inserted into the affected area using imaging such as CT, ultrasound, or MRI to collect cells or tissue from the suspected tumor. The doctor will use the imaging to guide the needle into the area. Two (2) types of samples may be collected. It will either be a fine needle aspirate (FNA) that collects cells and/or a core biopsy that collects a small piece of tissue.
- You will receive NBTXR3 injection directly into your tumor(s) and/or lymph nodes under image-guidance.
- You will be observed at least 2 hours after the injection. Blood (about 2 tablespoons) will be drawn for routine testing prior to your discharge.

Between Days 3 and 8, you will have a CT scan to plan for radiation therapy planning and to check the status of the disease.

During the time you receive radiation therapy:

- At least 1 time each week, you will have a physical exam. If the study doctor thinks it is needed, this will include taking photographs of any mouth blisters and sores.
- One (1) time each week, blood (about 4 tablespoons) will be drawn for routine tests.

At any time during this study, if the study doctor thinks it is needed:

- Blood (about 4 tablespoons) may be drawn for routine testing.
- You may have an EKG to check your heart function.

End of Treatment Visit

About 6 weeks after you complete radiation therapy:

- You will have a physical exam. If the study doctor thinks it is needed, this will include taking photographs of any mouth blisters and sores.
- You will have a CT and/or an MRI to measure the size of the tumor and check the status of the disease.
- Blood (about 4 tablespoons) will be drawn for routine and biomarker testing.
- You will have an image-guided biopsy to check the status of the disease and for immune system and biomarker testing.

Follow-Up

Every 6 weeks after the End of Treatment Visit for 2 years:

- You will have a physical exam. If the study doctor thinks it is needed, this will include taking photographs of any mouth blisters and sores.
- Until the end of study, blood (about 4 tablespoons) will be drawn for routine testing. On your 3 month visit only, blood (about 4 tablespoons) will also be drawn for biomarker testing.
- You will have CT, PET/CT, and/or MRI scans to check the size of the tumor and to check the status of the disease.
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Every 6 weeks until the end of the study, the study staff will ask you about your health and any side effects you may be having. This will be done at your follow-up visits or by phone call. The phone call may last about 5 to 15 minutes.

End of Study Visit

Two (2) years after the End of Treatment visit:

- You will have a physical exam. If the study doctor thinks it is needed, this will include taking photographs of any mouth blisters and sores.
- Blood (about 4 tablespoons) will be drawn for routine.
- If the doctor thinks it is needed, you will have a CT or MRI scan to measure the size of the tumor(s) and a PET-CT, or TAP-CT to check the status of the disease.

Other Information

The study doctor will discuss the following with you:

- While taking part in this study, you cannot receive other investigational drugs, anticancer therapies, or immunotherapy outside of this study.
- Tell the study doctor about all herbal remedies you are taking or plan to take during the study. Some remedies are not allowed on this study.
- Do not receive a live-virus vaccine within 28 days before receiving the study drug or during this study. Live-virus vaccines include the measles, mumps, rubella, varicella/zoster, yellow fever, rabies, and the typhoid vaccine.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Side effects will vary from person to person, and some may occur after you have stopped receiving treatment. Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs/procedures.

NBTXR3 Side Effects

This is an early study of NBTXR3, so the side effects are not well known. Based on early human studies, NBTXR3 may cause the following side effects:

• chest pain • high blood pressure • low blood pressure (possible dizziness/fainting) • dizziness • stroke • feeling hot • fever • headache • fatigue • skin damage related to radiation • skin infection • skin redness • swelling • night sweats • abnormal sensation (such as pins and needles) • flushing • increased sweating • inflammation of the fatty layer under the skin • abnormal blood test • body-wide inflammation	• weight loss • vomiting • nausea • swollen tongue • tongue pain • abdominal pain • diarrhea • difficulty swallowing • mouth and throat pain, inflammation, and/or bleeding • mouth blisters/sores (possible difficulty swallowing) • lip cracking • inability to urinate • frequent urination • loss of bladder control • bleeding • abnormal blood test (possible inflammation and/or clotting) • increase in infection-fighting cells • abnormal liver tests (possible liver damage and/or	• arm/leg pain • abnormal kidney test (possible kidney damage) • wheezing • cough • coughing up blood • difficulty breathing (possibly due to lung damage) • lung congestion (possible difficulty breathing) • lung inflammation (possible difficulty breathing) • lung inflammation causing chest pain • interrupted breathing • bleeding in or from the tumor • injection site infection, swelling, pain, and/or heat • drug leakage from the injection site • pain at the tumor site • postoperative wound complication,

• high blood sugar (possible diabetes) • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	yellowing of the skin and/or eyes) • muscle and/or bone stiffness • musculoskeletal chest pain • neck pain • weakness of an arm or leg • weakness • fluid in the joints • facial pain • numbness	infection, or discharge • wound healing problems • allergic reaction • severe life-threatening infection (possible difficulty breathing, low blood pressure, and/or organ failure)

NBTXR3 may cause cytokine release syndrome. This involves a release of a large amount of proteins into the blood stream. This may cause changes in blood pressure and heartbeat, flu-like symptoms (nausea, fever, and chills), and/or affect your lung/liver/kidney function. It may also cause certain brain-related symptoms, such as dizziness, weakness, confusion, difficulty speaking, and/or decreased brain function (possible paralysis and/or coma).

NBTXR3 may cause low blood cell counts (red blood cells and white blood cells).

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Radiation Therapy Side Effects

It is not known how often the side effects of radiation therapy may occur.

• swelling • swelling of the arms or torso • heart damage (possible high blood pressure, irregular heartbeats, narrowing or blockage of arteries that supply blood to your heart) • heart attack • damage to the spinal cord due to radiation (possible paralysis, weakness, and/or abnormal sensation) • fatigue • skin changes (possible dryness, itching, peeling, scaling, scarring and/or blistering) • hair loss at the treatment site	• jaw tightness • mouth problems • inflammation/sores of the esophagus, stomach, mouth, or airways • blockage of the esophagus • trouble swallowing • nausea/vomiting • diarrhea • bleeding of the mouth, trachea, esophagus, lungs, or liver • abnormal connections or passageways between the lungs, esophagus, and /or trachea. • weight loss • abnormal taste • urinary and/or bladder changes • sexual changes	• inability to produce children • joint problems • pain • decreased movement or feeling in the arm and hand • loss of feeling or movement due to spinal cord inflammation or nerve damage • inflammation, ulcers, thickening, and/or scarring of the lung or airways (possible bleeding, difficulty breathing, cough, and pain) • cough with or without blood • secondary cancers • tissue death (bone)

Radiation therapy may cause low blood cell counts (platelet and/or white blood cells):

- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Radiation therapy may cause you to develop another type of cancer. Side effects may not occur for up to 6 months after radiation therapy is over. Side effects will vary depending on what part of the body is receiving radiation therapy.

Pembrolizumab Side Effects

Common (occurring in more than 20% of patients)

• fatigue • fever • skin rash and/or itching • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• high blood sugar (possible diabetes) • high blood levels of fat (possible heart disease and/or stroke) • loss of appetite • nausea • constipation • diarrhea • abdominal pain • low blood cell count (white/red/platelets)	• abnormal liver test (possible liver damage) • pain • abnormal kidney test (possible kidney damage) • cough • difficulty breathing

Pembrolizumab may cause low blood cell counts (red, white, and/or platelets):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.

If you have a stem cell transplant from a donor after you receive pembrolizumab, you may have an increased risk of complications, such as severe graft-versus-host disease (when transplanted donor tissue attacks the recipient's organs such as skin, liver, and/or intestines) and/or clotting of blood within the liver. Deaths have been reported in patients who received a stem cell transplant from a donor after pembrolizumab therapy. If you decide to receive a stem cell transplant from a donor, please tell your transplant doctor that you received pembrolizumab in the past.

Occasional (occurring in 3-20% of patients)

• swelling (face/arm/leg) • inflammation of the tissue around the heart (possible chest pain) • irregular heartbeat • headache • confusion • patches of skin color loss • underactive thyroid gland (possible weight gain,	• low blood sugar • weight loss • fluid in the abdomen • blood in the urine • vomiting • abnormal liver test (possible yellowing of the skin and/or eyes) • weakness	• nerve damage (possible numbness, pain, and/or loss of motor function) • difficulty breathing (possibly due to lung inflammation) • flu-like symptoms • infusion reaction (possible dizziness,

heart failure, and/or constipation) • overactive thyroid gland (possible weight loss, diarrhea, mood swings, difficulty sleeping, heart rate changes, and/or sweating)		low blood pressure, nausea, pain, and/or difficulty breathing

Frequency Unknown

• heart failure • heart attack • build-up of fluid around the heart (possible heart failure)	• abnormal connections or passageways between organs or vessels • bleeding in the rectum and/or uterus	• blockage in the lung (possible pain and/or shortness of breath) • nosebleed • coughing up blood

Rare but serious (occurring in fewer than 3% of patients)

• low blood pressure (possible dizziness/fainting) • heart inflammation • build-up of fluid in the tissue around the heart • blood vessel inflammation (possible bleeding and/or bruising) • seizure • immune system damage to the nervous system (causing muscle weakness, numbness and/or paralysis) • spinal cord inflammation (possible pain, weakness, loss of feeling or movement, and/or paralysis) • brain inflammation (possible paralysis and/or coma) • shedding, scaling and/or inflammation of the skin (possible fatal loss of bodily fluids) • large skin blisters • very severe blistering skin disease (loss of large portion of skin and/or with ulcers of the skin and digestive tract)	• hormonal deficiency that affects the body's ability to control blood pressure and react to stress • pituitary gland inflammation (possible headaches) • inflammation of the thyroid gland (possible tenderness in the neck) • diabetes requiring insulin • severe high blood sugar due to uncontrolled diabetes • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • inflammation of the pancreas (possible abdominal pain) • anemia due to destruction of red blood cells • liver damage (hepatitis)	• inflammation inside the eye (possible vision problems) • kidney inflammation (possible kidney damage/failure) • kidney failure • build-up of fluid around the lungs • immune response that causes the body to attack itself (possible organ damage) • multi-organ disease causing lesions, most often in the lungs (sarcoidosis) • immune response (causing muscle weakness) • immune system reaction (possible fever, jaundice, liver/spleen enlargement, irritability, and/or seizures) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • Vogt Koyanagi Harada syndrome -- pigmented tissue (possible eye pain/swelling and changes in vision, hearing loss, and/or white patches on the skin)

If you have a solid tumor type and you have an organ transplant, pembrolizumab may increase your risk for the transplant to be rejected by your body.

Pembrolizumab works by boosting the immune system. This may cause unknown side effects resulting from your immune system attacking your organs. This may cause inflammation and inflammation-related side effects in any organ or tissue. These side effects can affect more than one of your normal organs and tissues at the same time.

Prednisone Side Effects

It is not known how often the side effects of prednisone may occur:

• enlarged heart • heart failure • high blood pressure • swelling (such as of the face) • headache • increased pressure between the skull and brain (possible headaches, vision changes, and/or mental status changes) • weakness • difficulty sleeping • mood swings • euphoria (unusual feelings of happiness or well-being) • personality changes • depression • seizure • fatigue/lack of energy • fatigue and anxiety • dizziness • bruising • nervousness • tiny dots on the skin • skin tests (such as for TB) may not be accurate • redness (face) • hair growth • thin fragile skin • hives • sweating	• Cushing's syndrome (possible weakness, diabetes, and/or bone weakness) • stunted growth • decreased ability to process carbohydrates • high blood sugar (possible diabetes) • diabetes • abnormal blood acid/base balance (possible organ damage) • body-wide loss of proteins (possible weakness and/or swelling) • low blood levels of potassium (possible muscle cramps) • high levels of salt in the body (possible swelling) • abnormal blood acid/base balance (possible organ damage) • abdominal swelling • inflammation of the pancreas (possible abdominal pain) • weight gain • increased appetite • indigestion • nausea • stomach ulcer	• esophagus sore • abnormal liver or bone tests (possible liver damage) • changes to the menstrual cycle • joint pain • pain or loss of function of the hips and/or shoulders due to bone death • muscle weakness • loss of bone strength (possible broken bones) • broken bone(s) • decreased muscle mass • decreased muscle mass • muscle damage causing weakness • tendon tear • increased pressure in the eye (possible vision loss, pain, and/or blurry vision) • cataracts (clouding of the lens of the eye) • eye irritation • swelling (eyelid) • nosebleed

• wound healing problems		

Rarely (in fewer than 3% of patients)

• blood clots in a vein (possible pain, swelling, and/or redness)

Prednisone may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.

Prednisone may cause you to develop another type of cancer (such as Kaposi's sarcoma).

Using the study drugs together with radiation therapy may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

EKGs may cause discomfort while lying on the exam table, and the tape on the EKG pads may cause skin irritation.

During the **MRI**, you may feel mild vibrations throughout your body. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. Some people, especially those who tend to feel uncomfortable in small or closed spaces, may feel “closed in” and become anxious while in the scanner. The scanner has an intercom, which will allow you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish. The MRI will require a catheter to be inserted into one of your veins in order to inject the MRI contrast agent. This may cause skin irritation, bleeding, and/or infection. You may have an allergic reaction to the contrast agent.

The magnetic field used in MRI scanning may harm you if you have certain types of metal in your body (as might be found in pacemakers, neurostimulators, or certain clips). It may cause problems with devices, such as pacemakers. If you have metal in your body or devices such as a pacemaker, you should discuss this with the study doctor.

PET/CT and CT scans send x-rays through the body at many different angles. You will be exposed to a small dose of radiation. All radiation adds up over a lifetime and may increase the risk of new cancer forming. Some people may feel "closed in" while lying in the scanner. However, the scanner is open at both ends, and an intercom allows you to talk with doctors and staff. If you feel ill or anxious during scanning, doctors and/or radiology technicians will give comfort, or the scanning will be stopped. Solution may also be given by vein to make the x-ray pictures more accurate. This may cause an uncomfortable feeling of warmth, nausea, and/or severe allergic reactions. The solution injection may also cause pain, bleeding, bruising, hives, and/or itching.

Although every effort will be made to keep **study data** safe, there is a chance that your personal health information could be lost or stolen, which may result in a **loss of confidentiality**. All study data will be stored in password-protected computers and/or locked file cabinets during the study and will continue to be stored securely after the study. Only authorized people who are working on this study will have access to study data.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study and for 6 months after your last dose of pembrolizumab if you are sexually active.

Birth Control Specifications: If you can become pregnant or father a child, you must use an effective birth control method. The study doctor will discuss this with you. Effective methods include:

- Birth control pills
- Intrauterine device (IUD)
- Double barrier method (a condom or diaphragm used in combination with spermicide)

Males: Do not donate sperm during this study. Tell the doctor right away if your partner becomes pregnant or suspects pregnancy. If your partner/spouse becomes pregnant while you are on this study, the supporting company (Nanobiotix) would like to collect information about the pregnancy. The study sponsor's contact information will be made available so that, if you and your partner wish to, you can share information about the outcome of the pregnancy with the sponsor. If you and/or your partner choose not to share this information, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away. The supporting company (Nanobiotix) will ask for information about the pregnancy.

Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, you will have a tumor biopsy at the End of Study visit or at any time the disease gets worse, whichever happens first, for immune system testing. The leftover tissue, if any, will be stored in a research bank at MD Anderson for use in future research related to cancer and/or other diseases.

Optional Procedure #2: If you agree, blood (about 4 tablespoons) will be drawn at the 6-, 12-, and 24-month follow-up visits and at any time the disease gets worse for biomarker testing. Leftover blood will be stored in a research bank at MD Anderson for use in future research related to cancer and/or other diseases.

Before your samples/data can be used for research, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson. The IRB is a committee of doctors, researchers, and community members. The IRB is responsible for protecting study participants and making sure all research is safe and ethical.

Your samples will be given a code number. No identifying information will be directly linked to your samples. Only the researcher in charge of the bank will have access to the code numbers and be able to link the samples to you. This is to allow medical data related to the samples to be updated as needed.

Some samples from this study may be sent outside of MD Anderson. Before your samples are sent to another location, your name and any personal identifying information will be coded to protect your privacy. Samples will be de-identified. Some samples may contain information that includes some items of protected health information, such as dates of treatment, which are needed to understand what is learned from the samples.

There are no benefits to you for taking part in the optional procedures. Future patients may benefit from what is learned. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedures.

Optional Procedure Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

MD Anderson and others can learn about cancer and other diseases from your **banked samples**. In the future, people who may do research with these samples may need to know more information about your health. This information may be collected from your medical record. MD Anderson will make reasonable efforts to preserve your privacy, but cannot guarantee complete privacy.

If you withdraw your consent to the storage of leftover samples in the tissue bank, then they will no longer be collected for storage. Any of your samples that remain in the tissue bank will no longer be used for research and will be destroyed.

However, if any of your de-identified samples were already released for research purposes before you withdrew consent, MD Anderson will not be able to destroy them.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

Circle your choice of "yes" or "no" for each of the following optional procedures:

Optional Procedure #1: Do you agree to have a tumor biopsy at the End of Study visit or at any time the disease gets worse for immune system testing and to store for future research?

YES **NO**

Optional Procedure #1: Do you agree to have blood drawn at the above timepoints for biomarker testing and to store for future research?

YES **NO**

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

The sponsor may pay for the treatment you received because you were hurt or sick during the study. MD Anderson does not know at this time what you may be reimbursed for. A financial counselor will be made available to you after the injury or illness is reported. If the sponsor pays any of your medical expenses, they may need to be given your name, date of birth, and Medicare ID or social security number.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Jay Reddy at 832-829-8977) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, Nanobiotix, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your

willingness to continue taking part in the study, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: Nanobiotix.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Data

Your personal information is being collected as part of this study. These data may be used by researchers at MD Anderson and Nanobiotix and/or shared with other researchers and/or institutions for use in future research.

Samples

Samples (such as blood and/or tissue) are being collected from you as part of this study. Researchers at MD Anderson may use any leftover samples that are stored at MD Anderson in future research. Leftover samples stored by Nanobiotix may be used in future research.

Before being used or shared for future research, every effort will be made to remove your identifying information from any data and/or research samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

If you do not want your samples or data to be used for future research, tell the study doctor. You may withdraw your samples at any time by telling your study team. If you decide to withdraw your samples, they will be returned to the lab they came from or destroyed. However, the data and test results already collected from your samples will be kept and may be used.

In some cases, all of your identifying information may not be removed before your data or research samples are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or research samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research
Research samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson
   - Nanobiotix, who is a supporter of this study and is the manufacturer of NBTXR3, and/or any future sponsors/supporters/licensees of the study technology
   - Johnson & Johnson
   - People, including third parties, who work with MD Anderson or Nanobiotix.
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form

   Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's

contracts require sponsors/supporters to protect this information and limit how they may use it.

The results of this research may be published. However, your name and other identifying information will be kept confidential. Your information will be protected from disclosure to others to the extent required by law. We cannot promise complete privacy.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. 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.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under this protocol.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS) and patients who are illiterate.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT