PRINCIPAL INVESTIGATOR: Raffit Hassan, M.D.

STUDY TITLE: Phase I Study of Intratumor Injection of anti-Mesothelin Immunotoxin LMB-100 with Ipilimumab in Malignant Mesothelioma

STUDY SITE: NIH Clinical Center

Cohort: Affected Participants

Consent Version: 04/24/2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have malignant mesothelioma that cannot be cured by surgery and which was unsuccessfully treated with the standard chemotherapy and immunotherapy for this disease.

The purpose of this study is to find a safe dose of LMB-100, an agent that targets the mesothelin on your tumor cells, in combination with ipilimumab, a drug that helps your immune system to fight against your cancer. LMB-100 will be injected directly into your tumor.

LMB-100 has not been approved by the US Food and Drug Administration (FDA) for the treatment of any disease. Ipilimumab is approved in combination with nivolumab for the treatment of multiple cancers, including pleural mesothelioma. Therefore, the use of the drugs in this study is investigational as a combination of LMB-100 and ipilimumab has not been approved. However, the FDA has given us permission to use LMB-100 in combination with ipilimumab in this study.

There are other drugs that may be used to treat your disease, and these can be prescribed/given by your regular cancer doctor, even if you are not in this study. The way in which treatment is given in this study and the side effects are different than if you were to receive standard care. Although the treatment is given directly in the tumor, we hope that killing of the tumor cells by

LMB-100 will stimulate your immune system to attack tumor cells not only at the sites of LMB-100 injection but also at other un-injected tumor sites. Administration of ipilimumab could stimulate the immune response generated by LMB-100 injection to make it more effective against the tumor. There could be side effects due to local injection of LMB-100 as well other sites in the body.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- You will be evaluated to find out if you are a suitable candidate for this study. This will involve having standard blood and urine tests, scans, tests of your heart and lung function and a confirmation of your diagnosis which would involve providing us a sample of your tumor. This can be an existing sample or if one is not available, we would collect one from you.
- LMB-100 will be injected into your tumor(s) on days one and four of one 21-day cycle. You will have to stay in the hospital for about 8 days each time you receive LMB-100. Your study doctor will decide what type of anesthesia you need for the procedure. At minimum, there will be a local anesthetic (like lidocaine) placed on the areas where the needles will be injected. To receive LMB-100, a needle will be inserted in one or multiple points in your tumor(s), using an ultrasound or CT scan to guide the needle.
- Ipilimumab will be given for up to three cycles. It will be given through a tube inserted in one of your veins on day 1 of cycles 2, 3 and 4.
- If your disease gets worse or you have side effects that are intolerable, the study drugs may be stopped sooner.
- You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and to assess your disease. We will also collect required samples from you (such as: blood and tumor tissue).
- You must use effective birth control methods and try not to become pregnant while participating in this study and for at least four months after the last dose of study treatment.
- You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death. Examples of some of the side effects that you may have include side effects of the study drugs such as kidney damage, leaky blood vessels, allergic reactions, itchiness, watery stools and inflammation of various organs. You will also be exposed to radiation from the CT guided injection procedure described above.
- After the study treatment has ended, we will see you in the clinic for a safety checkup 4-6 weeks after your last dose of study drug. After the safety-checkup, if your disease has not gotten worse while on study, we would like to see you every 6 weeks so we can perform scans. If your tumors do increase in size at any point, the follow up assessments will be done every 12 weeks and will consist of a phone or video call or email to find out how you are doing, whether you are having side effects and if you have started any new cancer treatment. This assessment will continue for the rest of your life.

We do not know if you may benefit from taking part in this study. If you do not benefit, this study and the results from our research will help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This is a research study. The purpose of this research study is to find a safe dose of LMB-100 injected into your tumors.

We are asking you to join this research study because you have malignant pleural or peritoneal mesothelioma that cannot be cured with surgery and which has not responded to the standard first line treatments given for mesothelioma.

LMB-100 has not been approved by the US Food and Drug Administration (FDA) for the treatment of any disease. Ipilimumab is approved in combination with nivolumab for the treatment of multiple cancers, including pleural mesothelioma. Therefore, the use of the drugs in this study is investigational as a combination of LMB-100 and ipilimumab has not been approved. However, the FDA has given us permission to use LMB-100 in combination with ipilimumab in this study for your mesothelioma. We are testing it in this research study to see if LMB-100 can be given safely in combination with ipilimumab when LMB-100 is directly injected into your tumors. We are also interested in finding out whether the combination might cause your tumors to shrink or allow you to live longer with or without tumors.

WHAT WILL HAPPEN DURING THE STUDY?

Before you begin the study

Before beginning the study, you will need to undergo tests and/or procedures to help your doctor verify whether you can participate. This is called screening. Most of the exams, tests, and

procedures you will have are part of the usual approach for your cancer. However, there are some extra procedures that you will need to have if you take part in this study. If you have already undergone some of these examinations very recently, your doctor may decide not to repeat them. Briefly, these tests, which may be performed under a separate protocol, include:

- Confirmation of diagnosis (You must provide a sample of tumor tissue for an evaluation by the NCI Laboratory of Pathology. The tissue may be from a previous surgery, biopsy or collection from a tumor effusion (fluid around the tumor). If none is available, we will ask you to have a biopsy or a collection of effusion material to provide a fresh sample). Please see page12, Tumor Biopsies and Effusions for a description of the procedure.
- Medical history and physical examination
- Routine blood (4 – 5 teaspoons) and urine tests including pregnancy test in women who can have children. Pregnant women will not be allowed on this study.
- CT scan or MRI, and PET scans – to allow us to see your tumor(s)
- Electrocardiogram (ECG) – which test the electrical activity of your heart
- Echocardiogram – which uses soundwaves (like an ultrasound) to test the functioning of your heart
- Hepatitis B and C testing (~2 teaspoons)
- HIV testing (~ 1 teaspoon)

  As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

Your Responsibilities

You will need to follow the study team's instructions and plan to attend all required study visits

Before you are given ipilimumab, tell your healthcare provider about all your health problems if you:

- have an active condition where your immune system attacks your body (autoimmune disease), such as ulcerative colitis, Crohn's disease, lupus, or sarcoidosis
- had an organ transplant, such as a kidney transplant
- have liver damage from diseases or drugs
- have any other medical conditions
- are pregnant or plan to become pregnant.
- are breastfeeding

Tell your study doctor about all the medicines you take, including all prescription and non-prescription medicines, steroids or other medicines that lower your immune response, vitamins, and herbal supplements. Please also let your study doctor know about any vaccinations you plan to receive.

There are some types of medications and vaccines that you will need to avoid while you are receiving study therapy.

Study Drugs

If you decide to take part in this study, once we know that you are eligible LMB-100 will be given directly into your tumors through needles on days 1 and 4 of one 21-day cycle as described in the key information section. You will have to stay in the hospital for about 8 days each time you receive LMB-100. LMB-100 will be injected into each lesion gradually. The time it takes will depend on the size of the tumor, but it will be no more than a few minutes. You will receive medications to help manage pain during these injections.

- This will include a shot at the site of collection (local anesthesia) which numbs the area.
- You may also undergo conscious sedation which is usually given during minor surgical procedures to relax participants and minimize discomfort. It can be given as a pill, a shot, an IV or even inhaled. You may have to wait up to an hour to start feel the effects depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. You will be monitored throughout the procedure for any changes to your breathing and blood pressure.
- You may receive general anesthesia which involves a combination of medications (inhaled and/or given through an IV drip) that puts you in a sleep-like state before surgery or other medical procedure. You will not feel pain as you will be completely unconscious. While you're under anesthesia, the anesthesiologist monitors your body's vital functions and manages your breathing through a tube inserted into your mouth and down your windpipe. The tube will also protect your lungs from blood and other fluids.

You will receive medication before each dose of LMB-100 to help prevent side effects. These medications include an antihistamine (such as Benadryl), a histamine 2 blocker (such as Pepcid) and acetaminophen (Tylenol). Participants who have a reaction after any dose of LMB-100 will also receive a steroid, such as dexamethasone before the remaining LMB-100 doses.

After each dose of LMB-100, your vital signs (blood pressure, pulse, temperature, oxygen levels) will be monitored for at least 5 hours.

Ipilimumab will be given for up to three cycles. It will be given through a tube inserted in one of your veins (IV) on day 1 of cycles 2, 3 and 4. After each dose of ipilimumab, we will monitor your vital signs for up to an hour.

We will continue to check vital signs while you remain in the hospital.

Assessments While Receiving the Study Drugs

During the study, you will have certain clinical procedures performed so that we can assess your health and find out if the study drugs are having an effect on your tumor.

These tests/procedures include the following:

(Some tests which may have already been done during the screening process may not need to be repeated on day 1 of cycle 1)

Performed once before you receive any study drugs

- Test of certain markers on your immune cells

Performed daily while hospitalized during cycle 1, then on day 1 of the next three cycles

- Medical history and physical exam including weight and vital signs (pulse, temperature, blood pressure, etc.)

Performed only on day 1 of each cycle

- Routine urine tests
- Assessment of how well you perform daily activities
- Pregnancy test if you are woman who can have children
- ECG (electrocardiogram)

Performed on days 1, 3, 5, 8 and 15 of the first cycle and on day 1 of the next three cycles

- Routine blood tests (up to 12 teaspoons at each collection, no more than 1.5 cups over 8 weeks)

Performed every 2 cycles (or every 6 weeks)

- CT scans or MRIs of your tumors
- FDG PET scans of your tumors

In addition to the above tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of research only. The samples are being collected to look at how your body processes the study drugs, how your immune system reacts to the study drugs and how the presence of certain markers such as mesothelin or affect your response to the study drugs. We will also collect samples to find out which genes are expressed both before and after treatment. Gene expression is the when the information stored in our DNA is converted into instructions for making proteins or other molecules. This process allows a cell to respond to its environment. We are interested to know if the study therapy changes the environment around the tumor.

The samples included for these studies include:

- Blood samples will be collected on day 1 of each cycle on days 4 and 7 of cycle 1 and after your last dose of study therapy. These will include serial collections of blood before and for up to four hours after your LMB-100 injection.
- Tissue samples collected with the tumor injection if feasible (days 1 and 4 of the first cycle, day 1 of the second cycle and after you have finished your last dose of ipilimumab). The tumor samples are collected exclusively for research purposes and will not benefit you. It might help other people in the future. You will be given the opportunity to decide whether you want to have these samples collected at the time of each biopsy/effusion collection. As your tumor collection during the first cycle will be done at the same time that we are injecting your tumor(s) with study drug, the drugs used to manage pain for those injections will be the same drugs used to manage pain during the biopsy. After cycle 1, we will only use local anesthesia or conscious sedation for pain management.

After You Have Finished Taking the Study Drugs

Safety follow up

We will need to see you for a safety visit 4- 6 weeks after you have taken your last dose of study therapy. At this visit, we will take a medical history and perform a physical exam. We will collect blood for routine blood tests and perform a pregnancy test if you are woman who can have children CT scans or MRIs, and FDG-PET scans to monitor your disease will be performed if your tumors have not grown up to this point. We may also collect the end of treatment research blood sample (about three quarters of teaspoon) if we were unable to collect one the end of therapy.

Long Term-Follow Up

We will continue to perform scans every 6 weeks until your disease gets worse. If you are unable to come to the NIH Clinical Center for these scans, you may have them done at a local center and send them to us. Your study team can instruct you on how. We may also contact you by phone, email or video chat (remotely) to speak with you directly and find out how you are doing. Once your tumors have started to grow, you will no longer be scanned. However, we will be in touch remotely every 12 weeks for the rest of your life, so we can find out how you are doing, what medications you are taking and if you are experiencing any side-effects.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for the rest of your life as described in the key information section and the section above.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have about 14 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the standard drugs available for treatment of your cancer at shrinking or stabilizing your tumor.

There is also a risk that you could have side effects from the study drugs and study procedures. These side effects may be worse and may be different than you would get with the usual approach for your cancer. Some of these side effects may become serious or life-threatening, and in some cases, may lead to death.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

Risks and Possible Undesirable Effects of LMB-100

LMB-100 has only been given to a limited number of subjects; therefore, we do not know all of the possible side effects. In addition, to this point, we have only given LMB-100 by IV route. However, below is a list of the most common and most serious side effects occurring on our earlier studies, some occurring at higher doses than will be used in this study.

Possible Side Effects of LMB-100

COMMON, SOME MAY BE SERIOUS In 100 people receiving LMB-100, more than 20 and up to 100 may have:
• Low levels of the blood protein albumin which may lead to swelling, muscle weakness or loss of appetite • Tiredness • Swelling localized to some part of the body, such as the arms and legs, face • Anemia, which may require a blood transfusion • Low blood pressure which may cause you to feel faint • Increase blood level of creatinine (a substance normally eliminated by the kidneys into urine) • Muscle pain • Increased blood levels of liver enzymes • Nausea • Shortness of breath • Decreased number of a type of white blood cell • Decreased blood level of sodium which can cause headaches, confusion, seizures, fatigue or coma • Weight gain • Fever • Abnormally fast heartbeat, with regular or irregular rhythm

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving LMB-100, from 4 to 20 may have:
• Decreased appetite • Infection, especially when white blood cell count is low • Bruising, bleeding due to decreased number of type of blood cell • Vomiting • Dizziness • Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles • Hair loss • Pain, including belly pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving LMB-100, from 4 to 20 may have:
• More protein leaking into the urine than usual, often a sign of kidney disease • Headache • Reactions during or following the infusion of the drug which may cause fever, chills, rash or low blood pressure • Abnormal laboratory results • Fluid around the heart that can lead to a life-threatening condition where the heart is unable to pump correctly due to external pressure. We would need to drain the fluid around the heart to relieve the pressure. • Numbness, tingling or pain in the arms and legs • Fluid around the lungs • Joint pain • Chest pain, not heart related • Kidney damage which may cause swelling and may require dialysis • Increased blood level of a heart muscle protein indicating damage to the heart muscle • Chills • Constipation • Increased blood level of enzyme from muscle • Dehydration • Diarrhea • Decreased oxygen supply to the tissue
RARE, AND SERIOUS In 100 people receiving LMB-100, fewer than 4 may have:
• A condition in which there is muscle breakdown or injury that may lead to kidney damage that may have been caused by LMB-100. People experiencing this condition may notice muscle pain or dark red urine and may have abnormal results in laboratory tests for muscle. • Inflammation in membranes around your heart or lungs causing chest pain, shortness of breath, low blood pressure, and heart failure. • Inflammation of the heart muscle

As with other drugs similar to LMB-100, there is a chance that the drug could cause the body to produce an unwanted response called 'Anti-drug antibodies' (ADAs). These might not cause problems however there is a chance they could lead to a severe anti-drug response in the body. ADA levels will be measured during the study to monitor any changes as part of the research on this study.

Risk of Giving LMB-100 Directly into the Tumor

In addition to the risks of radiation from the use of CT scans to guide our injections addressed above, risks of this procedure include pain and fever lasting 1-4 days. If the pain is severe, we will need to give you pain medications intravenously. Although rare, there is also a possibility, that while injecting the drug into the tumor we could injure the normal lung leading to air around the lungs or injure the bowels. There may also be reddening around the injection site. Anesthesia will be provided as needed.

You may feel pain at the injection sites(s)

Risks of Ipilimumab

Common side-effects (occurring 5 or more of every 10 patients receiving ipilimumab):

- Fatigue
- Diarrhea
- Itching
- Rash
- Stomach pains

Less common but potentially life-threatening side-effects:

As noted above, ipilimumab works by helping your immune system to fight your cancer. However, ipilimumab can also lead to autoimmune disease where your immune system attacks normal organs and tissues in your body and can affect the way they work This can cause:

- Inflammation of the intestines (colitis) that can cause tears or holes (perforation) in the intestines. Signs and symptoms of colitis may include:
    - diarrhea (loose stools) or more bowel movements than usual
    - blood in your stools or dark, tarry, sticky stools
    - stomach pain (abdominal pain) or tenderness
- Inflammation of the liver (hepatitis) that can lead to liver failure. Signs and symptoms of hepatitis may include:
    - yellowing of your skin or the whites of your eyes
    - dark urine (tea colored)
    - nausea or vomiting
    - pain on the right side of your stomach
    - bleeding or bruise more easily than normal
- Inflammation of the skin that can lead to severe skin reaction (toxic epidermal necrolysis). Signs and symptoms of severe skin reactions may include:
    - skin rash with or without itching
    - sores in your mouth
    - your skin blisters and/or peels

- Inflammation of the nerves that can lead to paralysis. Symptoms of nerve problems may include:
    - unusual weakness of legs, arms, or face
    - numbness or tingling in hands or feet
- Inflammation of hormone glands (especially the pituitary, adrenal, and thyroid glands) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include:
    - persistent or unusual headaches
    - unusual sluggishness, feeling cold all the time, or weight gain
    - changes in mood or behavior such as decreased sex drive, irritability, or forgetfulness
    - dizziness or fainting
- Inflammation of the eyes. Symptoms may include:
    - blurry vision, double vision, or other vision problems
    - eye pain or redness
- Inflammation in other organs (e.g., lungs, pancreas, kidneys, heart)

Other less common side-effects include:

- Infusion reaction, including dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.

What Are the Risks Related to Pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for four months after you finish study treatment (the restricted period). If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact the study team as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

What Are the Risks of Radiation from Being in the Study?

During your participation in this research study, you will be exposed to radiation from nine CT scans, five CT guided tumor injections and biopsies and nine FDG-PET scans each year. The

amount of radiation you will receive from these procedures is equal to approximately19.3 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation". This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans (including those for the biopsies) and FDG PET scans that you get in this study will expose you to roughly the same amount of radiation as 64.3 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.9 out of 100 (1.9%) and of getting a fatal cancer is 1.0 out of 100 (1.0%).

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

What Are the Risks from the Study Procedures?

Many of the interventions you will undergo during the study are not associated with any significant risk or discomforts aside from possible breaches of confidentiality. These include urine collection, echocardiograms, ECGs, physical examination and collection of your medical information.

However, the following study procedures and treatments may have risks and cause discomfort while you participate on this study:

Blood draws

There is the risk of slight pain, bruising or infection when your blood is drawn. Drawing blood may cause some people to faint. Including both routine and research blood collections, no more than 5 tablespoons of blood will be collected at single timepoint and up to a little over 1.5 cups may be collected over a given 8-week period.

Tumor Biopsies and Effusions

Tumor biopsies and tumor effusions: local anesthesia of the skin will be given prior to any tumor biopsy or effusion collection, in order to prevent painful sensations. However, you may still experience pain or discomfort at the biopsy site. Irritation, redness, swelling and/or bleeding may also occur. There is a risk of abnormal healing, fever or infection. Once the sample has been obtained, a stitch may be used to close the wound and facilitate healing.

Anesthesia

Local anesthesia

You may experience an allergic reaction that can include itching and hives.

Conscious Sedation

Potential side effects of conscious sedation include headache, nausea, slow reflexes, low blood pressure, loss of memory of what happened during the procedure and drowsiness. These side effects usually go away quickly.

General Anesthesia

Potential side effects of general anesthesia include temporary confusion and memory loss, dizziness, difficulty passing urine, muscle aches, itching, bruising or soreness from the IV drip, nausea, and vomiting, shivering and feeling cold, and sore throat due to the breathing.

CT Scans and PET scans

In addition to the radiation risks from the scans discussed above, you may experience an allergic reaction to the dye we inject into your veins to help us view the scan better. You might experience hives, itching, headache and water retention. More serious reactions that would include difficulty breathing, increased heartrate and swelling of your throat or other body parts.

MRIs

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. You will be screened before each MRI scan to determine if you might have metal in your body. If you have a question about metal in your body, you should inform the staff.

If you have a fear confined spaces or have back problems, you might experience anxiety or discomfort during the MRI.

The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

During part of the MRI, you may receive gadolinium, a contrast agent, through an intravenous (iv) catheter.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with

gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The long-term effects of gadolinium retention are unknown. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefit to you might be shrinking of your tumor or decrease in your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study.

Are There Any Potential Benefits to Others That Might Result from the Study?

In the future, other people might benefit from this study because what we learn in this study may eventually be used to treat others with your disease.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with surgery, radiation or with drugs already approved by the FDA for your disease
- choose to take part in a different study if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

DISCUSSION OF FINDINGS

New Information About the Study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of Research Results

The results of the standard tests performed as part of the research are available to you as part of your medical record. We do not plan to return the results of your research only tests to you.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease gets worse during treatment (after confirmed by a second scan)
- if you have side effects from the treatment that your doctor thinks are too severe
- if you require medication that is not permitted on this study
- if new information shows that another treatment would be better for you
- if you become pregnant
- if you do not follow the study rules
- if the study is stopped for any reason

In this case, you will be informed of the reason therapy is being stopped.

After therapy is stopped, we would like to see you for a safety visit 4 – 6 weeks after your last dose.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand mesothelioma, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my identifiable specimens and data to be stored and used by the study team for future studies as described above.

_____ Yes _____ No

Initial Initial

Will your specimens or data be shared with other researchers for use in other studies?

We may share coded specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

I give permission for my de-identified specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In some cases, it may help other researchers to know that the specimens or data were collected from you (i.e., they will have your identifiers). If we share your identity with other researchers, their study will be reviewed and approved by an Institutional Review Board who will make sure that the study team is protecting your confidentiality.

I give permission for my **identifiable** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that

research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or that no one will gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will You Receive Compensation for Participation in the Study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will You Receive Reimbursement or Direct Payment by NIH As Part of Your Participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will Taking Part in This Research Study Cost You Anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

Will Your Medical Information Be Kept Private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, Center for Cancer Research, NCI, or their agents

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Raffit Hassan, M.D., Raffit.Hassan@nih.gov, 240-760-6232. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
   An oral presentation of the full consent has been used to enroll a blind or illiterate subject

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.