INSTITUTE/CENTER:	National Cancer Institute
PRINCIPAL INVESTIGATOR:	Azam Ghafoor, M.D.
STUDY NUMBER:	19C0127
STUDY TITLE:	A Phase II Study of LMB-100 Followed by Pembrolizumab in the Treatment of Adults with Mesothelin-Expressing Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
Cohort:	Affected Patients
Consent Version:	12/3/2021

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 to in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to join this study because you have a kind of lung cancer (NSCLC) that has not responded to prior standard therapies, such as chemotherapy and immunotherapy.

The purpose of this study is to find out if LMB-100 followed by pembrolizumab can help your tumors to shrink.

LMB-100 is an immunotoxin (a kind of artificial protein) that targets the mesothelin protein found on different tumors, including NSCLC. It is found only in a very small number of normal tissues. After binding to the mesothelin on tumors, LMB-100 attack and kill cancer cells.

Pembrolizumab is a drug that helps your immune system to fight against your cancer.

LMB-100 is an investigational agent, meaning that it has not been approved by the US Food and Drug Administration. Pembrolizumab (Keytruda®), is approved in the USA and some other countries for many cancers including NSCLC. Pembrolizumab use in this study is

investigational as it has not been approved in the combination with LMB-100. However, the FDA has given us permission to use pembrolizumab and LMB-100 in this study.

There are other drugs/therapy that may be used to treat your disease, and these can be given by your regular cancer doctor if you are not in this study. For example: standard chemotherapy or other clinical trials are some possible treatments that you could receive. Because LMB-100 is being added to the standard therapy, the side effects from the study therapy will be slightly different than if you were to receive standard care alone. Please ask your study doctor for more details regarding alternative treatments and their side effects.

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

To take part in this study, you must provide a sample of your previously collected tumor tissue. If it is not available, we will ask you to provide a fresh tissue sample that we can use to confirm your diagnosis (for mesothelin expression) and to use later for research studies. You will be asked to provide medical history and confirmation that your tumor does not have certain gene changes. This has been explained later in the consent.

Once it is decided that you are eligible to take part in the study, the treatment is given as follows:

LMB-100 and pembrolizumab are given as intravenous (IV) infusions. An IV line (kind of small plastic tube) is placed in your arm. First, you will receive LMB-100 for up to 2 cycles (each cycle is 21 days in length). The drug is given over 30 minutes on days 1, 3 and 5 of each cycle. For each LMB-100 cycle, you will have to stay in the hospital (NIH Clinical Center) for 7 – 10 days. We will decide whether to give 1 or 2 cycles of LMB-100 based on how your tumors respond. If your tumors keep growing during the first cycle of LMB-100, we may decide to stop LMB-100 and start Pembrolizumab during cycle 2. If your tumors are responding or stay the same, we will give you a second cycle of LMB-100. After 1-2 cycles of LMB-100, we will give you Pembrolizumab. Pembrolizumab is given every 3 weeks for up to 2 years. We may stop giving you the drug sooner if your cancer worsens, or if you develop unacceptable side effects. Each pembrolizumab infusion lasts about 30-60 minutes and will usually be done without admitting you to the hospital. Pembrolizumab can be given as an outpatient.

You will have tests done (such as: physical exams, ECG, blood work and PET/CT imaging scans) to see how you are doing and to see how your disease is responding. We will also collect samples from you (such as: blood, and tissue) for research purposes.

Unless permanently sterile, male and female participants of this study must use effective birth control methods and try not to become pregnant while participating in this study and for at least 180 days after the last dose of study treatment. If you or your partner become pregnant, there may be unknown risks to the fetus or unborn child. After two years of treatment, you will be seen in the clinic after 30 and 90 days for follow-up. After your 90-day follow-up visit, you will be seen at the NIH Clinical Center every 6-12 weeks depending on whether or not your tumor has grown. If it has not grown, we will need to see you every 6 weeks to check on your health and the size of your tumor. If you are unable to return to the Clinical Center for any of these visits, we will contact you to check on your health and ask you to send certain lab results to us.

If your tumor starts to grow, we will still need to keep in touch, but you will no longer need to come to the Clinical Center. For the rest of your life, we will contact you by phone or email every 12 weeks to check on your health.

Whether or not your tumor has grown, we will continue to follow you for the rest of your life.

In some cases, if your tumor grows or returns, you might be eligible to have a second course of pembrolizumab, 17 additional cycles (another year of treatment). This will depend on how your tumor responded to the first course.

You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent. Any could lead to death. Examples of some of the side effects that you may have include:

- possible allergic reactions (symptoms that start during or within a few hours of the infusion, e.g., wheezing, tightness in the throat or chest, rash, and facial swelling)
- chest pain
- shortness of breath
- fast heartbeat
- bleeding and high fever
- reduced brain function (e.g., dizziness, blurred vision, confusion, paralysis or numbness)
- ongoing diarrhea
- skin rash that is spreading or causing your skin to peel

They have been described later in more detail in this consent form.

If you experience any severe or dangerous side effects, you should:

1. Seek professional medical help immediately.

2. Call your study doctor.

3. If necessary, go to the nearest emergency room.

Just as we do not know what side effects you might have, we cannot predict if you will benefit from taking part in this study. If you do not benefit, this study and the results from our research may 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 more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described 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 needed 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 to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

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 main purpose of this research study is to find out if giving LMB-100 followed by pembrolizumab can help your tumors shrink.

You are being asked to join this study because you have a kind of lung cancer (NSCLC) that has not responded to prior standard therapies such as chemotherapy and immunotherapy. Your cancer is also mesothelin positive.

LMB-100 is an investigational agent, which means that it has not been approved by the US Food and Drug Administration. Pembrolizumab (Keytruda®), is approved in the USA and some other countries for many cancers including NSCLC. It is considered investigational in this study because we are testing it in combination with LMB-100. The FDA has given us permission to use pembrolizumab and LMB-100 in this study.

As indicated above, we are testing it in this research study to see if pembrolizumab given after LMB-100 can help your mesothelin positive tumors to shrink.

WHAT WILL HAPPEN DURING THE STUDY?

You will be admitted to the hospital for approximately 7-10 days for the first two 21 day cycles to receive IV infusions of LMB-100 on days 1, 3 and 5. The infusions will usually be done through a vein in your arm or through a vascular access device if you already have one installed. Rarely, we might have to install a vascular access device if we cannot give the infusion through a vein in your limbs. Each infusion will last about 30 minutes, but it might take longer if your study doctor decides it is needed for your safety. You will be monitored before infusion, every 15 minutes during infusion, and then every 30 minutes after infusion for side effects for up to 2 hours. We will give you standard pre-medications that include an antihistamine (such a Benadryl), acetaminophen (Tylenol) and famotidine (Pepcid).

Unless any side effects during the first two cycles of LMB-100 persist longer than 4 weeks, you will be given pembrolizumab on day 1 of the 3rd cycle and each 21-day cycle for up to two years. However, if your tumor grows quickly on imaging after only one cycle of LMB-100 and you are experiencing symptoms from the tumor, you may be given pembrolizumab starting in cycle 2. Pembrolizumab treatments may end sooner if you have unacceptable side effects or if your disease worsens while you are taking pembrolizumab.

Please note that sometimes it might appear as though your disease has worsened according to our scans, but because of the nature of the immunotherapy, we cannot immediately be sure that your tumor has actually gotten worse. In such cases, we would like to continue your pembrolizumab infusions until we are able to positively confirm through additional scans that your tumors have grown. As this is not standard practice, we will ask you to sign a separate consent if we decide to continue pembrolizumab after the scan indicating that your disease has grown is obtained. Each pembrolizumab infusion will last for about 30 minutes. We do not expect that you will be hospitalized during this part of the study, though it is possible that a situation may come up that requires it.

Clinical Testing

While you are taking study medication, we will perform a number of tests and examinations for safety and to test the effect of the study therapy.

These include:

- medical history and physical examination
- routine blood tests that will be done 4 – 5 times per cycle during the first two cycles (LMB-100 alone) and on day 1 of each subsequent cycle (pembrolizumab alone)
- routine urine tests on day 1 of each cycle
- PET/CT imaging scans that will be performed approximately every 6 weeks. In a year approximately 9 such scans will be done. Out of 9 scans, five will be part of research testing and 4 part of clinical testing.
- electrocardiograms (ECGs) that will be done just before each (LMB-100 or pembrolizumab) infusion.

Additional research testing

In addition to the 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 done to look at the effects of therapy on your immune system and markers of tumor activity, including collecting and testing tumor cells.

We will also perform tests for research studies on blood to find out how your body handles LMB-100 (PKs), how your body reacts to LMB-100, the mechanism of how certain side effects occur, the types of immune cells and other molecular characteristics present in your tumor, whether or not certain substances that are targeted by the study drugs are present in your blood and if LMB-100 might cause kidney damage.

- PK studies will be performed during cycles 1 and 2. These samples will be drawn before and after your LMB-100 infusion as well as periodically for up to 6 hours after the start of the LMB-100 infusion on day 1 of these cycles. We will put a separate peripheral IV line in your arm to draw these samples.

- Research blood samples will be collected on day 1 of each cycle (just over 1 tablespoon)

- Optional tissue collection using biopsies collected before the first dose of LMB-100 (if you have not given a biopsy at screening), after you have completed LMB-100, and after you have completed 2 cycles of pembrolizumab. The biopsies to be performed are 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. All tissue will be reviewed by the NCI Laboratory of Pathology.

- In the event that you have fluid collecting around your lung (known as a pulmonary effusion), and it needs to be drained, we may collect up to 1 liter of fluid from around your lung to develop cell lines.

All of your samples collected for research purposes on this study (such as the tumor tissue and blood) may be used to look for specific changes in the DNA. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow.

For research studies, we will sequence your DNA in your tumor using a commercially available test and follow these DNA changes in the blood for research purposes only.

We may also use cancer cells derived from your body for other research studies such as growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), placing or growing cells in another animal, such as mice, and looking in detail at the parts of the DNA that produce specific proteins.

Because the testing is for research test and has not been cleared by the FDA, we will not give you the results of the genetic tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described later in this consent form in the section for "**Return of research results**."

When you are finished taking the treatment (Follow Up)

Approximately 30 days and 90 days after you have had your last dose of study drug, you will be asked to return to the NIH for a follow up visit to have the following tests:

- Medical history and physical exam
- Routine blood tests
- Scans if your disease has not worsened since the beginning of the study
- ECG

If after these visits, your disease remains stable or improves, you will continue to be scanned every 6 weeks for long term follow up until your disease worsens.

If your disease worsens after you have stopped taking pembrolizumab AND if pembrolizumab was stopped for a reason other than worsening disease or unacceptable side effects, you may be eligible

for a second course of pembrolizumab lasting for approximately one year. Clinical tests will be the same; however, research tests will not be performed during the second course.

If we do not need you to come to the NIH Clinical Center for scans, we will contact you or your physician by telephone or email about every 12 weeks to ask about any other cancer therapies you may have started and about your survival status.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement will last for the rest of your life. The treatment portion of the study will last 2 – 3 years depending on whether you have a second course of pembrolizumab. You will be seen at least monthly during this time. After that, we will continue to follow you with scans and phone calls every 6 – 12 weeks as described above.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Up to 23 people will be treated in this study at the NIH, however, a total 100 patients will be screened for the study.

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

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. 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

Occasional, Some May Be Serious

In 100 people receiving LMB-100, from 4 to 20 may have:

- Abnormally fast heartbeat, with regular or irregular rhythm
- 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
- 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
- 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.

There may also be pain and swelling at the infusion site.

Risks of Pembrolizumab

As noted above, pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work. This can result in side effects that may become serious or life-threatening, and in some cases may lead to death. These side effects can affect more than one of your normal organs and tissues at the same time. To prevent complications, we may need to treat you with steroids or immunosuppressant drugs.

Very Common, Some May Be Serious (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

Common, Some May Be Serious (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

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

- Joint pain
- Rash
- Fever
- Back pain

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

Uncommon, Some May Be Serious (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

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

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

Rare, Some May Be Serious (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

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

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches

- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain, leading to temporary dialysis
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to changes in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy
- A condition called myasthenia gravis, or a flare up of myasthenia gravis, that may make you feel weak and tired and might cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness
- Inflammation of the spinal cord that may cause pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including more frequent urination, urinary incontinence, difficulty urinating, and constipation

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling

- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures and even coma. This condition is called Hemophagocytic lymphohistiocytosis (HLH).

- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss

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

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

Risks from Research Procedures

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.

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, infection or of an allergic reaction to the anesthetic agent used to anesthetize the skin at the biopsy site. Once the sample has been obtained, a stitch may be used to close the wound and facilitate healing.

Central Line Insertion (If required for infusion)

- Contamination of the catheter which would result in a serious blood stream infection, requiring admission to the hospital and giving you antibiotics through the vein.

- Collapsed lung particularly if the central line is placed in the vein under your collarbone. Collapsed lung is treated with a chest tube when necessary.

- During the insertion of some types of central lines, the heart may be irritated by the process while the line travels through the blood vessels near the heart, causing an alteration in the heart's rhythm. This typically gets better once the line is in place but may require medication for some rare individuals.

- Air embolism, a condition where air enters the blood stream and begins to travel through the body. This condition, which is very serious, is also very rare and largely preventable.

What are the risks related to pregnancy?

If you are capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment and for 180 days 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 research team member identified at the top of this document as soon as possible.

You may not participate in this study if you are pregnant. If you are capable of becoming 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.

If you are a sexually active person with a partner capable of becoming 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 research team member identified at the top of this document 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.

CT 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. More serious reactions that would include difficulty breathing, increased heartrate and swelling of your throat or other body parts.

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 CT guided biopsies, CT scans and/or FDG PET scans. The amount of radiation exposure you will receive from these procedures is equal to approximately 23.9 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 guided biopsies, CT scans and FDG PET scans that you get in this study will expose you to the roughly the same amount of radiation as 79.7 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 2.4 out of 100 (2.4%) and of getting a fatal cancer is 1.2 out of 100 (1.2%).

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.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

MRI Risks

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. You may need to have an MRI completed if you are unable to have a CT scan to monitor your cancer. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. You will be in the scanner for about 45 minutes. You may be asked to lie still for up to 15 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time. It is very important that you do not move your body inside the scanner.

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. 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.

There are no known long-term risks of MRI scans.

Risks for gadolinium enhanced MRI scans:

Procedure

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for both research and medical purposes.

Risks

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" which 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 not normal or if you received gadolinium within the previous month.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA recently issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. The NIH IRB has approved the gadolinium schedule for this study.

Some types of gadolinium contrast drugs are less likely to remain than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain.

Please tell your research team if you have had any MRI scans in the past 12 months. 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.

Psychological or Social Risks Associated with Loss of Privacy

The following general points are indirectly related to your participation in the research study:

1. Unanticipated medical information: During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.
2. Release of genetic information:

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
- Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.
- Your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease.
- There also may be other privacy risks that we have not foreseen.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

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 to be in this study, we will discuss the other options that are available to you. Instead of being in this study, you could:

- Choose to be treated with standard therapies such as chemotherapy 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 such as pain, fatigue, low appetite, and other symptoms. This does not treat the cancer directly, but to improve your quality of life.

You should discuss with your doctor your other choices and their risks and benefits.

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

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

Since the analyses that we perform in our laboratory are for research test and has not been cleared by the FDA, we will not give you the results of the genetic tests done on your research samples in most cases. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

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 progresses during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if you become pregnant
- if the LMB-100 or pembrolizumab become unavailable
- 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 30 days and 90 days 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.

WILL YOUR SPECIMENS OR DATA BE SAVED FOR USE IN OTHER RESEARCH STUDIES?

As part of this study, we are obtaining specimens and data from you. We plan to use these specimens and data for studies going on right now, as well as studies in the future. These studies may provide additional information that will be helpful in understanding non-small cell lung cancer, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to 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. By agreeing to let us use your specimens and data, you give the NIH any rights you may have in the specimens and data.

We may share your specimens and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or industry sponsors of research.

We may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. The information in this database could include but is not limited to genetic information, ethnicity and sex. If your individual research data is placed in one of these repositories, it will not be labeled with your name or other information that could be used to easily identify you, and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

Your summary genomic data is being placed in an unrestricted database, so researchers will be able to access summary information about all the participants included in the study (including

you), or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

In addition to the use and sharing of your specimens and data described above, we will remove any information from your specimens and data that can identify you such as name, address, or medical record number, and then use the specimens and data for additional research studies at the NIH or other places. If we do this, we might not contact you to ask your permission or otherwise inform you.

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw the specimens and data.

Please place your initials in the blank next to Yes or No for each of the questions below:

My data and specimens may be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

My data and specimens may be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data will be stored at 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 someone may 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.

The NCI generally does not cover expenses during screening. If you are scheduled for and begin treatment, 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. Someone will work with you to provide 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 if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

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.

The National Institutes of Health and the research team for this study have developed LMB-100 being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of LMB-100.

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 National Cancer Institute (NCI) 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)

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens and data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

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 records 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 medical 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, Principal Investigator Azam Ghafoor, azam.ghafoor@nih.gov at 240-858-3289. 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**
2. **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: _____.