PRINCIPAL INVESTIGATOR: Christine Alewine, MD

STUDY TITLE: A Phase I Study of Mesothelin-Targeted Immunotoxin LMB-100 in Combination with tofacitinib in Persons with Previously Treated Pancreatic Adenocarcinoma, Cholangiocarcinoma and other Mesothelin Expressing Solid Tumors

STUDY SITE: NIH Clinical Center

Cohort:	*Screening*
Consent Version:	*6/25/20*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Christine Alewine, M.D., Ph.D.
Phone: 240-760-6146
Email: Christine.alewine@nih.gov

KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes the 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 consider joining this study because you have a solid tumor that has either worsened after previous treatment or you are unable for some reason to receive standard treatment.

This consent form requests your permission for us to test if you are eligible for our study. Patients on the study will receive LMB-100 and tofacitinib. LMB-100 is an investigational drug, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat your cancer. LMB-100 has been given in other clinical trials, but its effect has not lasted for as long as we hoped. Tofacitinib is approved by the FDA for treating specific kinds of arthritis and bowel inflammation.

You may only participate in this study if your cancer is positive for mesothelin. With your consent, we will first obtain your tumor tissue to test for mesothelin. If your cancer is positive for mesothelin, before beginning the study, you will need to have tests and/or procedures to help your doctor verify whether you can participate. This is called screening. The exams, tests, and procedures you will have are part of the usual approach for your cancer. Most must be performed within 28 days before enrollment. These basic tests include blood tests, x-rays, and

physical exams, etc. Other tests are described further on in this consent form. It is important that you read these. These tests will not be performed if your tumor tissue tests negative for mesothelin.

You will not benefit from this screening evaluation.

You may choose not to be tested for eligibility or to have any other studies done.

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 this 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 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.

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 receive care 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 determine a safe dose of LMB-100 plus tofacitinib in patients with solid tumors that make a protein called mesothelin. Mesothelin is found on many different tumors, but on very few non-cancer cells.

We are asking you to screen for this research study because you have a solid tumor that might make mesothelin. You have either received or are unable to receive standard therapy. If you have received standard therapy, your disease has gotten worse after that treatment.

If your cancer cells do not make mesothelin, you will not be eligible for this study. Your blood, biopsy or other tissue may also be tested for other factors for research purposes. However, this consent does not permit any additional studies that would test for genes (i.e. tendency for diseases) that might be inherited from you by your children.

WHAT WILL HAPPEN DURING THE STUDY?

The following research test will be performed to determine whether you are eligible for this trial:

- Mesothelin testing. You must provide a sample tumor tissue for formal evaluation by the NCI Laboratory of Pathology. The tissue may be from a previous surgery or biopsy. If none is available, we will ask you to have a biopsy to provide a fresh sample. Your tumor tissue will be used to determine whether your tumor cells have mesothelin. If no tumor

tissue is available for this evaluation and new biopsy is not possible then you will not be eligible for the trial.

In addition, this sample of tumor tissue will be used for confirmation of diagnosis by the NCI Laboratory of Pathology.

If this research test shows that your tumor does not make mesothelin, then further screening tests will not be performed. Otherwise, screening will continue as described below with standard clinical tests that are normally used to assess your disease.

You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements. Some medications may interact adversely with the study drugs and it is important that your study doctor and prescribing physician be aware of any potential risks so that they can prescribe alternative medications as necessary. If you do not already do so, please carry a list of your medications at all times.

Laboratory results performed outside of the NIH may be accepted if they have been performed recently. Otherwise, you will need to come to NIH Clinical Center to have the following standard, clinical tests performed at the NIH to determine whether you are eligible for this trial, which include:

- Medical history and physical examination
- Routine blood and urine tests including pregnancy test in women who can have children. Pregnant women will not be allowed on study.
- Scans and x-rays
- Electrocardiogram (ECG)
- Echocardiogram
- Blood for tumor markers
- Test for tuberculosis infection
- Tests for viruses (hepatitis B and C)
- HIV testing: 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.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this screening and your cancer makes mesothelin, your involvement will last for as long as it takes us to know if you are eligible to participate on the treatment phase of the study. The length of time may range anywhere from 1-4 weeks. You will be required to come to NIH at least 1 time during screening. This visit may last anywhere from 1 to 3 days.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

As not all persons screened will be eligible for study therapy, up to 45 patients will be screened in this study in order to treat up to 32 subjects on the study.

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

The following study procedures may have risks and cause discomfort while you participate on this study:

Blood draws

The risk for taking blood samples involves the withdrawal of between a few teaspoons and a half-cup of blood and the potential for bruising or infection that occurs with any blood draw.

Each time a blood sample is needed, a needle will be put into a vein in your arm (or into your central venous catheter, if you have one). You may feel pain when the needle goes through the skin. Other side effects associated with drawing your blood for blood tests may include infection, bruising, redness, discomfort or bleeding at the site of the needle stick, and possible lightheadedness and fainting.

Electrocardiogram (ECG)

An electrocardiogram or ECG is a test that records the electrical activity of the heart. It is used to measure the rate and regularity of heartbeats as well as the size and position of the heart chambers, and the presence of any damage to the heart. For this test, you will be asked to lie down, and small patches that have an adhesive edge with a gel in the middle, called electrodes, will be placed on your arms, legs, and chest. The areas where the electrodes are placed will be cleaned and, if needed, some hair may be shaved or clipped to allow for better attachment of the electrodes. The adhesive from the patches may irritate your skin.

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 assist in healing.

Radiographic Tests

MRI, CT, X-ray, Nuclear Medicine and PET Scans are common standard imaging tests used in the diagnosis and monitoring of many diseases. Although these tests have been in use for many years, their potential long-term effects on the body are still being learned. The most common discomfort is the length of time a patient must lay still or flat while an X-ray or scan is being performed. Occasionally, a patient may become uncomfortable within the closed space of the scanners (claustrophobia), particularly during an MRI. If this occurs, cool air can be blown over you by a fan if desired or your doctor can order a medicine for you to help you relax during this scan. Keeping the room well lit can also reduce this claustrophobic feeling. If a contrast agent (the special dye) is given with the scan there is a small risk of having a reaction to the contrast. In the small group of patients who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was given, headache, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely, these symptoms may require

treatment. In very rare cases, people have had more severe allergic reactions that result in skin rashes, shortness of breath, wheezing, or lowering of the blood pressure. If you have had a reaction in the past, be sure to tell your doctor or nurse about it. The radiation dose you receive, if your scan includes the use of X-rays or radioactive chemicals, is within the safe limits defined by the NIH Radiation Safety Guidelines, and is considered essential for your medical care. In some cases, you may require medicines to make you sleep so you can be still during the procedure. The risks from this sedation or anesthesia are dependent on the types of medication used. These risks will be fully explained to you prior to the procedure and a separate informed consent will be obtained for anesthesia.

An IV line may need to be inserted for administration of the contrast agent or anesthetic. This can cause pain at the site where the IV is placed and carries a small risk of bruising or infection.

Patients with a cardiac pacemaker, neural pacemaker, some types of surgical clips, cochlear implants, foreign metal objects, permanent retainers, or any iron-containing material within the body should not undergo MRI, because of the effect of the strong magnet on these objects.

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 3 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 member 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 member 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 one CT-guided biopsy, and one CT scan. The amount of radiation exposure you will receive from these procedures is equal to approximately 1.9 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.” No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT-guided biopsy, CT scan and PET scan that you get in this study will expose you to the roughly the same amount of radiation as 6.3 years' worth of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

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 BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

However, if eligible for the study protocol the potential benefit to you might be that your lesions could go away or get smaller if the treatment is effective. The treatment could also decrease some of your symptoms, including pain, that are caused by your lesions.

Are there any potential benefits to others that might result from the study?

We do not know if you will receive personal medical benefit from allowing us to perform these tests. However, this testing may make you eligible for our trial.

If you become eligible for our treatment study and you choose to participate, you would need to give additional informed consent regarding the risks of the treatment.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

You may choose not to be tested for eligibility or to have any other studies done.

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 from the evaluations for this screening will be reported to you. You will be informed at that time if you are eligible for the main study at that time.

EARLY WITHDRAWAL FROM THE STUDY

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

- if he/she believes that it is in your best interest
- if you are ineligible for the study
- if you become pregnant

- if new information shows that another treatment would be better for you
- if the study is stopped for any reason

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

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. However, according to FDA guidelines, information collected on you up to that point may still be provided to our collaborators or designated representatives.

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 data for studies going on right now, as well as studies in the future.

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 also 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. If your individual research data is placed in one of these repositories, it will not contain information that can 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 that monitor the use of the research information.

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 and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, if the specimens and data has been shared already with other researchers, it might not be possible to withdraw.

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

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

_____ Yes _____ No

Initials Initials

My specimens and data 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 Data be Stored by the NIH?

If you are eligible for the study, your data will be stored at NIH indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your tissue 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 by removing 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 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 screening.

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. 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 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.
- 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.

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 website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website 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) and the Office for Human Research Protections, which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

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 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, Christine Alewine, Christine.alewine@nih.gov, at 240-760-6146. 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 to the oral short-form consent process only:

Witness:

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: _____.