

To: CTEP Protocol and Information Office
From: Aaron Mansfield, M.D.
Date: October 25, 2021
Re: Amendment #16 (PVD 25Oct2021) for P10107: “Phase 1 Safety Run-In and Phase 2 Randomized Clinical Trial of Anetumab Ravtansine and MK-3475 (Pembrolizumab) Compared to MK-3475 (Pembrolizumab) Alone for Mesothelin-Positive Malignant Pleural Mesothelioma”

**SUMMARY OF CHANGES:
Model Prescreening Informed Consent (PVD 10/25/2021)**

#	Section	Comments
1.	General	Version date has been updated to match that of revised protocol

Research Study Informed Consent Document

Study Title for Study Participants: Screening for eligibility in a research study based on a protein test (i.e. test for mesothelin-positive malignant pleural mesothelioma)

Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>: 10107 / MC1721: Phase 1 Safety Run-In and Phase 2 Randomized Clinical Trial of Anetumab Ravtansine and Pembrolizumab (MK-3475) Compared to Pembrolizumab Alone for Mesothelin-Positive Malignant Pleural Mesothelioma (**Pre-screening**)

Overview and Key Information

What am I being asked to do?

We are asking you to submit tumor tissue for testing as part of a research study in order to see if you are eligible to participate based on a test that shows you have a mesothelin-positive malignant pleural mesothelioma, meaning your tumor cells make the mesothelin protein. The tumor tissue may be stored from a previous surgery or biopsy. If you do not have stored tumor tissue, we are asking you to undergo a biopsy to obtain tissue for testing.

The study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to submit tissue for this pre-screening procedure because you have malignant pleural mesothelioma for which you are currently receiving treatment with chemotherapy or which has grown or returned after initial treatment with chemotherapies.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This pre-screening procedure is being done to answer the following question:

Does your tumor tissue show a protein called mesothelin to a certain degree?

This tissue test is required because the research study requires that participants' cancer cells make mesothelin to a moderate or high degree. The reason behind this is that one of the study drugs used in the research study is designed to find the mesothelin protein in the body.

What is the usual approach to my mesothelioma?

The pre-screening test on your tumor tissue is only being done to see if you are eligible to take part in the research study. This test is not yet approved by the U.S. Food and Drug Administration (FDA). People who have mesothelioma do not usually submit tumor tissue to test for expression of the mesothelin protein.

There is no widely agreed upon treatment for people with mesothelioma in your situation; however, people who are not in a study may be treated with chemotherapy, immunotherapy, surgery or radiation therapy. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing.

What are my choices if I decide not to take part in this study?

You may choose not to submit tissue for the pre-screening test to see if you may be eligible for the treatment phase of the research study. If you decide not to submit tissue for pre-screening, you will not be able to take part in the treatment phase of the research study, even if you are otherwise eligible. However:

- 1) You may choose to have the usual approach described above.
- 2) You may choose to take part in a different research study, if one is available.
- 3) You may choose not to be treated for cancer.
- 4) You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part, a sample of your stored tumor tissue will be obtained and submitted for the pre-screening tissue test to see to what degree it expresses the mesothelin protein. If you do not have stored tumor tissue, you will undergo a biopsy to obtain a tissue sample for testing. It is expected to take about 5 days for the lab to share the test results after it receives your tissue. Your study doctor will receive the results and will share them with you. If your tissue does not express the mesothelin protein at a high enough level, you will not be able to take part in the research study. If your tissue does express the mesothelin protein at the required level, you will be invited to take part in other screening tests and procedures to see if you are eligible to take part in the research study.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the “What risks can I expect from taking part in this study?” section.

The following risks, associated with the possible research biopsy, are the most common: a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site.

Benefits

If it is found that your tumor tissue expresses mesothelin at a moderate or high level and you meet the other study eligibility criteria, you will be eligible to participate in the treatment phase of the research study. It is not possible to know at this time if the pre-screening tissue test is better than the usual approach which is not screening your tissue because it is not known if your cancer will respond better to treatment if you have a positive test result. It is not possible to know at this time if the study drug(s)/study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. Then, your study doctor will notify the lab and your tissue will not be tested if it has not already. If your tissue has been tested, your study doctor will receive a copy of the results. Results of the tissue test will not be placed in your medical record. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

1. Your health changes and the study is no longer in your best interest.
2. New information becomes available and the study is no longer in your best interest.
3. You do not follow the study rules.
4. The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor National Cancer Institute (NCI). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of the pre-screening test on your tumor tissue is to find out if mesothelin is overexpressed by your cancer cells, meaning they make too many copies of the mesothelin protein. The mesothelin protein is present on the surface of a small number of normal cells; however it is expressed from low to high levels on the surface of many cancer cells. For this reason, mesothelin could be a useful target for anti-cancer drugs.

Anetumab ravtansine, one of the drugs used in the research study, belongs to a group of anti-cancer drugs called antibody-drug conjugates (ADC). It is made up of the cytotoxic (chemotherapy) drug DM4 combined with a human monoclonal antibody (a large synthetic protein similar to a body's own). The antibody in anetumab ravtansine is designed to attach itself to the protein mesothelin, thereby delivering the chemotherapy it contains to cells which express that protein.

The purpose of the main study is to compare the effects, good and/or bad, of using anetumab ravtansine given in combination with pembrolizumab to using pembrolizumab alone in patients whose cancer expresses moderate or high levels of the mesothelin protein.

What are the study groups?

All potential study participants will submit a tumor tissue sample for testing to see if they may be eligible for the treatment phase of the research study. It is expected that 50-60% of patients will have sufficient expression of the mesothelin protein to be eligible for the study. Approximately 110 people are expected to take part in the treatment phase of the study so it is expected that 184-220 patients will provide tumor tissue.

What exams, tests, and procedures are involved in this study?

Submission of a tumor tissue sample for mesothelin expression testing is required to determine whether or not determine whether or not you may be eligible to participate in the treatment phase of the research study. You and your study doctor will get the results of this testing.

Your study doctor will need to use some of the tumor tissue left over from a previous biopsy or surgery. If there is not enough tissue left over, your study doctor will need to do another biopsy to get this tissue. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

The analysis of tissue sample can be performed while you are still receiving other ongoing treatment for your cancer or immediately before undergoing other screening tests to see if you

are eligible for the study. In any case, sufficient level of mesothelin expression on the cancer tissue must be confirmed before your doctor can determine whether you are suitable for the treatment phase of the study.

The archival or fresh tumor tissue sample will be prepared and sent to an external laboratory for testing. The tests used to detect mesothelin expression are not yet approved by FDA or other regulatory authorities and its role as a determiner of response to treatment has not yet been established. In light of the investigational nature of the tests, there is a small chance that a false positive result (the test shows high mesothelin expression when it is not there) or a false negative result (the test shows low mesothelin expression when it is high) may occur. However, the lab performing the testing has obtained the appropriate authorization to perform this test on human samples and regulatory approvals to perform the test in the context of this study.

If the results show that mesothelin is expressed at a high enough level on the cancer cells in your tumor sample, then your doctor will discuss the detailed study specific information with you and invite you to participate in the remainder of screening procedures for the study provided the study.

If the results show that mesothelin is expressed on the cancer cells in your tumor sample and you are still receiving another treatment, you should not stop your current treatment at the time you learn the mesothelin result, unless your scans show that you are no longer receiving any benefit from this current therapy and this decision is made independently of any decision to enter this trial. The positive result will continue to be valid in the future, in case you and your doctor want to consider participation in the main study at the later date. The participation in the main study is still voluntary and you may refuse to enter the screening for full study.

What risks can I expect from taking part in this study?

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Imaging Risks

For those undergoing a fresh tumor biopsy, you will be exposed to radiation from the CT-guided biopsy. The amount of radiation has a low risk of harmful effects.

Other Risks

Because the study requires additional tests, including the biopsy, you may lose time at work or home and spend more time in the hospital or doctor's office than usual.

As part of this study, we are also testing one of your tissue samples for a certain protein. The test is designed to find out if your tumor has the changes that are needed for this study.

Because the test itself is still being studied, there is a risk that the test results may be wrong. If the test results are wrong, you may be included in this study even though it may not offer the best treatment option for you. Or, you may not be included in this study even though it may offer a good treatment option for you.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
 - all medications and supplements you are taking
 - any side effects
 - any doctors' visits or hospital stays outside of this study
 - if you have been or are currently in another research study.

What are the costs of taking part in this study?

You or your insurance provider will not have to pay for the cost of obtaining your stored tissue or the potential research biopsy or for the testing on your tissue to see if you are eligible to take part in the research study.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case.

However, some of your medical information may be given out if required by law. If this should

happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI web site at <http://cancer.gov/> for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in this research.

Participant's signature: _____

Date of signature: _____

Signature of person(s) conducting the informed consent discussion:

Date of signature: _____