INSTITUTE: National Cancer Institute

STUDY NUMBER: 16-C-0145 PRINCIPAL INVESTIGATOR: Raffit Hassan, M.D.

STUDY TITLE: Phase II Trial with Safety Run-in of the Anti-Mesothelin Antibody Drug Conjugate Anetumab Ravtansine for Mesothelin Expressing Lung Adenocarcinoma

Continuing Review Approved by the IRB on 05/22/17

Amendment Approved by the IRB on 02/03/18 (D) Date posted to web: 02/08/18

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. 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 be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, 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). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

Anetumab ravtansine is an investigational drug, meaning that it has not been approved by the US Food and Drug Administration. It is a drug that kills cancer cells that carry mesothelin, a protein

found on the surface of tumor cells in many types of tumors, including a majority of lung cancers.

This study comprises two parts: the first part of the study, called the run-in portion of the study, is designed to find a safe dose with this experimental drug in your disease. This is done because the drug has been tested in other diseases but not in lung cancer. Six patients will be included in this part of the study. The second part of the study, called a phase 2 study, will further test the safety of the drug in lung cancer and determine if anetumab ravtansine can shrink tumors in mesothelin-positive lung cancer.

Why are you being asked to take part in this study?

You are being asked to participate in this study because you have lung cancer that has gotten worse on prior therapy.

How many people will take part in this study?

Since not all lung cancers are positive for mesothelin up to 55 participants will be tested for mesothelin, and ~ 26 of these will receive study therapy.

What will happen if you take part in this research study?

Before you begin the study

Before beginning the study, you will need to have tests and/or procedures to help your doctor decide whether you can take part. This is called screening. Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests that you will need to have if you take part in this study. If you have already had some of these examinations very recently, your doctor may decide not to repeat them.

The screening will be done in two parts.

Part 1 consists of the following:

- Medical history and physical examination
- You will provide us with sample of your tumor from a previous surgery or biopsy so that we may confirm your diagnosis and so that we may test for mesothelin. If a sample is not available, you will be required to have a biopsy, a procedure to remove a piece of tumor tissue from your body.

If the results of these tests show that you are not eligible for the study, we will remove you from the study. If the results show that you are eligible, you will continue to part 2 of screening. It is possible that several months may elapse between part 1 and part 2 while you complete your current treatment regimen.

Please be aware that the test that will be used in this study determine the mesothelin status of your tumor is experimental (Investigational Device) and is limited by United States law to experimental use. Experimental means that the test is not approved by the U. S. Food and Drug Administration (FDA) and is still being tested in research studies.

Part 2 consists of the following:

- Medical history and physical examination
- Tests for hepatitis
- 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.
- CT scan or MRI
- FDG-PET scan - an imaging technique during which a small amount of a radioactive substance is injected in your blood so that the scan can produce images of your tumor(s).
- Echocardiogram
- Electrocardiogram (ECG)
- Eye examination that includes:
    - tests of your vision
    - measurement of the pressure in your eye
    - test of tear production (dry eye test)
    - an examination of the various parts of your eye under a bright light (slit-lamp test)
- Routine blood and urine tests
- Pregnancy test in women who can have children (you will not be allowed to take part if you are pregnant)

If the results of these tests show that you are not eligible for the study, we will remove you from the study. If the results show that you are eligible, you will continue to the treatment portion of the study.

During the study

In the run-in portion of the study, which will include the first 6 subjects enrolled, the highest planned dose of anetumab ravtansine will be tested. If fewer than 2 persons have intolerable side effects, this dose will be chosen as the phase 2 dose. If 2 or more persons have intolerable side effects, the next lower dose will be chosen as the phase 2 dose.

In either part of the study, you will receive anetumab ravtansine through an IV (a tube inserted in a vein, usually in your arm) on day 1 of each 21-day cycle until you meet any of the conditions in the stopping therapy section on page 9.

While you are on study therapy, we will perform tests and exams for safety and to find out about the effect of the study drug. These may include a physical exam, routine urine tests, pregnancy tests (if you are woman who can have children) and eye tests as described in the screening section each time you receive the study drug. ECG testing will be performed on the first day of cycle 1 after you receive the study drug and on the first day of cycle 2, both before and after you receive the study drug. Routine blood tests will be done weekly during cycle 1 and on days 1 and 8 of the rest of the cycles. (Some of these may be done by your local laboratory). You will also have scans (FDG-PET scan and CT scan or MRI) every 6 weeks during the first 6 months, then every 9 weeks until the end of year 2, then every 12 weeks. An echocardiogram will be performed every 6 weeks during the first 6 months, then every 12 weeks.

In addition to the safety tests, we will also perform tests for research studies on your blood and tumor tissue.

- We will collect blood for research studies before you have begun study therapy, on day 1 of cycle 3 and at the end of therapy.
- We will collect optional biopsies before you have begun study therapy (if you have not had a biopsy at screening) and after you have completed two cycles of therapy. The biopsies are exclusively for research purposes and will not benefit you. It might help other people in the future. You will have the chance to decide whether you want to have these samples collected at the time of each biopsy.
- Leftover tissue from the sample from a previous surgery that you provided at screening will also be used

When you are finished taking the drugs

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

- Medical history and physical exam
- Routine blood tests
- Pregnancy test (if you are a woman who can have children)
- ECG
- Eye exam (as described in the screening section)

After the safety visit, we will also contact you or your physician about once every three months by telephone to ask about any other cancer therapies you may have started and about your survival status.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice two effective forms of birth control before starting study treatment, during study treatment, and for six months after you finish study treatment. Male participants should also refrain from donating sperm during this time period. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

Risks from anetumab ravtansine

As with any drug administered, side effects may occur with the study drug anetumab ravtansine. As of 13 July 2017, a total of 411 patients have already received the study drug in different dosages in different studies.

The following side effects have been reported from 323 patients who received anetumab ravtansine alone in all doses and all regimens without combination partners.

The most common side effects (10% or more study subjects have experienced these side effects):

- Fatigue
- Nausea
- Diarrhea
- Decreased appetite
- Eye disorder (e.g., dry eye, blurred vision, eye redness, eye irritation) Vomiting
- Abnormal liver tests Numbness, tingling and burning pain usually in hands, legs and feet

Between 1% and 10% of study subjects have experienced these side effects:

- Muscle pain, cramp, and muscle weakness

- Low platelet count (may lead to easy bleeding and bruising if severe)
- Decrease in the number of red blood cells which can cause tiredness or shortness of breath
- Low white blood cell count (may lead to infection)
- Reaction to drug infusion (could present as rash, hives, swelling, flushing, trouble breathing, faster heart beats)
- Joint pain
- Abnormal blood test of pancreas function
- Abnormal taste sensation (for example, metallic taste)
- Heart burn (gastroesophageal reflux)
- Chest pain not related to heart
- Decreased thyroid function (presenting as cold intolerance, modest weight gain and low body temperature)
- Night sweats
- Abnormal electrical activity of the heart (abnormal electrocardiogram/ECG)
- Increased levels of uric acid

Less than 1% patients experienced these side effects:

- Mouth sores
- Presence of protein in urine

Two cases reported side effects with a fatal outcome which were considered related to the study drug by the reporting investigator. One case reported liver failure in which the patient had extensive late stage pancreatic cancer with widespread liver metastasis. The other case was an infection of the blood (sepsis).

You may ask your study doctor for detailed information about the side effects caused by the study drug anetumab ravtansine. You will be notified of any new side effects that occur during the time you are in the treatment phase of this study that may affect your decision to continue in this research study.

Risks from tumor biopsies

A numbing agent will be given prior to any tumor biopsy in order to prevent painful sensations. However, it is possible that you will 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.

In some cases, we may use CT scans to help guide us during your biopsy. This introduces the added risk of research radiation. This research study may involve exposure to radiation from up to 2 CT guided tumor biopsies**.** This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.29 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

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.

Risks from research blood collection

There is the risk of slight pain, bruising or infection when your blood is drawn. Drawing blood may cause some people to faint.

Risks from eye examinations

You will have a strong light pointed in your eyes and this may cause mild and short-lived discomfort which is completely reversible and doesn't cause damage. The eye exam will require dilatation (widening) of your pupils (dark part in the front of the eye) by medicated eye drops. This dilatation of the pupils will prevent you from driving or operating machines for several hours after the eye exam, and will make your eyes sensitive to bright daylight and sunshine. Wearing sunglasses may be necessary for several hours after the eye exam. These effects of dilatation of the pupils are completely reversible after several hours.

In order to test your tear production, you may be asked to remove your contact lenses and you may receive a local anesthetic eye drop.

Potential Benefits of Participation

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of 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, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. 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 Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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 Cancer Institute Institutional Review Board
- Qualified representatives from Bayer HealthCare Pharmaceuticals, Inc., the pharmaceutical company who produces BAY 94-9343 (anetumab ravtansine).

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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Stopping Therapy

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

- if he/she believes that it is in your best interest
- if you need treatment that is not allowed on the study
- if you become pregnant

- if he/she decides to stop the study
- if your disease comes back during treatment and he/she does not think you are benefitting from the study therapy
- 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

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 Bayer HealthCare Pharmaceuticals, Inc. or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

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

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug developed by Bayer HealthCare Pharmaceuticals, Inc. through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. 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.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Raffit Hassan, M.D., Building 10, Room 4-5342, Telephone: 240-760-6232. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 22, 2017 THROUGH MAY 21, 2018.

Signature of Investigator | Date

Print Name

Signature of Witness | Date

Print Name