INSTITUTE: National Cancer Institute

STUDY NUMBER: 00-C-0133 PRINCIPAL INVESTIGATOR: Christopher Melani, M.D.

STUDY TITLE: Pilot Study of Idiotype Vaccine and EPOCH-Rituximab Chemotherapy in Untreated Mantle Cell Lymphoma

Continuing Review Approved by the IRB on 08/06/18
Amendment Approved by the IRB on 07/25/18 (M) Date Posted to Web:08/16/18

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?

Mantle cell is a form of cancer of the white blood cells called lymphocytes. In mantle cell, the abnormal lymphocytes multiply and accumulate in lymph nodes and elsewhere. Standard treatment with chemotherapy can often control the mantle cell for a period but in most patients,

the disease does not go entirely away or comes back. In this study, we are testing a vaccine to determine if it can stimulate your own immune system to fight the cancer. Experiments in the laboratory have shown that vaccines of this type work better if there is very little lymphoma present when the vaccine is given. For this reason, we will first treat all patients with EPOCH chemotherapy and rituximab (called EPOCH-R). EPOCH (each letter stands for one of the drugs used in the combination) uses standard chemotherapy drugs and has been shown to have a high degree of effectiveness in lymphomas. Recent evidence indicates that the effects of chemotherapy may be improved by the use of a new drug called Rituximab. Although rituximab is not an experimental drug, its use in this study is considered to be experimental because it is unproven if it will increase the effectiveness of EPOCH therapy. Rituximab is a special kind of drug called an antibody, which binds to a specific molecule (called CD20) present on mantle cell lymphomas. It is important to note that although the drugs in EPOCH-R are standard, we do not know how effective this combination will be in patients with mantle cell lymphoma.

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

You have been invited to participate in this study because you have mantle cell lymphoma. This is a clinical research study to test a new investigational approach using EPOCH-R chemotherapy and a vaccine directed against your lymphoma cells.

Description of Research Study

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

Study Design

The study is divided into 3 parts. In the first part, you will undergo a series of tests to determine if you are eligible for the study and to determine the extent (called stage) of your lymphoma. If you are found not to be eligible for the study, you will be referred back to your home physician. If you are eligible, we will ask you to undergo a procedure to obtain lymphoma cells for the vaccine and research tests. A piece of lymphoma tissue to make the vaccine will be removed from places that are safe to biopsy. Alternatively, it may be possible to obtain lymphoma cells from your blood by a procedure called apheresis or bone marrow. These studies and procedures may take up to 4 weeks. In the second part, you will receive a series of treatments with EPOCH-R. It usually takes 18 weeks to complete this part of the study. In the third part, you will receive 4 injections of vaccine administered 4 weeks apart, and a 5th injection 8 weeks after the 4th injection. The vaccine treatments will begin around 3 months after you complete EPOCH-R, but in some cases it may be longer, depending on when the vaccine is ready. After the vaccine treatments are completed, you will be followed in our clinic, every few months at first, and then less frequently if the lymphoma does not return. In some circumstances, it is possible you may not receive all or part of the vaccine treatments. In approximately 10% of patients, it is not possible to make a vaccine, or rarely, a patient may have a severe reaction to a vaccine which would make it dangerous to continue. In addition, if a patient's lymphoma begins to grow before the vaccine treatments are completed and they need chemotherapy or radiation that are not part

of this study, the vaccine will not be given. We estimate that around one third of patients will not be able to complete the vaccine treatments for these reasons.

EPOCH-R treatment

Each chemotherapy treatment period is called a cycle. The cycle is repeated every three weeks and the chemotherapy drugs are administered only during the first five days of every cycle. EPOCH-R consists of prednisone by mouth on days 1 to 5, and etoposide, doxorubicin, and vincristine as an infusion over days 1 to 5 (total of 96 hours), and cyclophosphamide on day 5 by vein. You will receive the infused drugs as an outpatient through a lightweight, portable infusion pump, about the size of a portable tape recorder. The pumps deliver the therapy through an intravenous catheter which is placed in your vein beforehand. You will be taught about the use and care of the pump and what to do if it stops working. The rituximab will be given by vein over several hours on day 1, immediately before the chemotherapy infusion begins, and the cyclophosphamide will be given by intravenous injection over about 15 minutes on day 5, immediately after the chemotherapy infusion is completed. Each cycle lasts 3 weeks: 5 days of chemotherapy followed by 16 days of no chemotherapy. You will receive 6 cycles of EPOCH-R. If your lymphoma grows, however, EPOCH-R will be discontinued. Between cycles of treatment, we give another drug, G-CSF, to help your normal bone marrow cells recover from the chemotherapy and produce normal white cells. You will be taught how to inject the G-CSF under your skin (like an insulin shot) each day beginning on day 6 of each cycle and continuing until recovery of the white blood cell count or until day 19 of each cycle. If your white blood cell count is still very low on the day treatment is due to begin again, the chemotherapy may be delayed and the G-CSF restarted until recovery of the white count. Because several of the chemotherapy drugs can lower your resistance to infection, you will receive an antibiotic called Bactrim for three days each week while you are on chemotherapy. If you are allergic to this antibiotic, you will receive the drug, pentamidine, by inhalation once monthly.

Vaccine treatment

At least 3 months is necessary to produce the experimental customized vaccine from your lymphoma cells. It is not always possible to successfully make a vaccine for every patient, so we cannot promise that you will receive a vaccine or that you will have any benefit from the vaccine if you do receive it. The vaccine treatment is given in the clinic and you will be carefully observed. To help the immune system respond to the vaccine, you will also receive daily injections of GM-CSF under the skin, beginning on the day of vaccination and for the three following days. This drug is a naturally occurring protein in our own bodies which has been made into a drug. The vaccine treatments (maximum of 5) will only be given if there are no serious side effects during previous vaccine treatments. It is important that you not take steroid medications or drugs such as aspirin or ibuprofen during the period you are receiving the vaccine without consulting your NIH physicians, unless it is an emergency.

Research tests

Research studies will be performed on your blood, bone marrow, tumor tissue or other fluids to look at different genes and proteins that may be involved in the development of your lymphoma or the reaction of the immune system. We will not examine mutations of normal genes from your tissue without obtaining additional permission from you. It may be important to obtain repeat biopsies of tumor tissue after you have enrolled on the study. Repeat biopsies requiring major surgery (e.g., in the chest or the abdomen) will not be performed for research purposes alone but only if absolutely necessary for your medical care. You may decide not to have a biopsy for research purposes and this will not affect your eligibility for this study. Blood samples of approximately 1 teaspoon in size may be drawn up to 5 times on each cycle of EPOCH-R to measure concentrations of chemotherapy drugs. Up to 5 tablespoons of blood may also be drawn during each vaccination to measure the effects of the vaccine. Additionally, a procedure called apheresis will be performed immediately before beginning EPOCH-R chemotherapy and again just before beginning the vaccine treatment to obtain cells for the study of your immune function and possibly for collection of tumor cells for the vaccine. This procedure takes approximately 60 to 90 minutes and is performed in the NIH Department of Transfusion Medicine. In this procedure, your blood will be filtered through a machine to remove the white cells, and your normal blood cells and platelets will be returned to you. The progress of your response will be followed by CT scans of your body and blood tests.

What tests will be done on my samples?

Your blood and tissue that is collected will be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass 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, forming the cancer genome or DNA. In order to determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. When we are examining these pieces of 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.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. 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 (at our expense) to have genetic education and counseling to explain the results. If you do not want to come to NIH, we will help you find a local genetic healthcare provider who can explain it to you (at your expense).

You should not assume that if you are not contacted, that you do not have any gene variants that might be related to a disease.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to key research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we will keep the samples for future research.

What happens after treatment is completed

This depends on how you have responded to the therapy. If all evidence of disease has disappeared, we will schedule periodic visits to the Clinical Center for follow-up examination

and tests. If the disease does not disappear entirely or if it should recur after having disappeared for a period of time, then you may need further therapy. At that time you will be given the opportunity of participating in additional research protocols that may be appropriate for you. If no such protocols are available, you will be returned to the care of your local physician. It is important to stress that participation in this protocol does not constitute a promise of long-term medical care here at the Clinical Center. It is conceivable that participation in this study may make you ineligible to participate in certain other research protocols because the requirements for entry onto these protocols may not allow patients who have already been treated with certain drugs or who have had certain side effects from previous treatment. You may decide now not to receive treatment on this protocol, or you may choose at any point in time to stop the treatment and withdraw from the protocol; in either case you will be returned to the care of your referring physician.

Risks or Discomforts of Participation

In order to determine whether this study is suitable for you, a number of tests will have to be done. This period of evaluation may take up to two weeks and is usually done on an outpatient basis. Some or all of these tests will be repeated during and after the chemotherapy and vaccine at different times. Depending on the tests you had before coming here, these may include blood and urine tests, studies of lung function, CAT or MRI scans, colonoscopy with biopsies, radioisotope scans, and biopsies of tumor tissue, bone marrow, liver, or other sites. Biopsies will, when possible, be done under local anesthesia. The risks associated with bone marrow biopsies include pain, bleeding, and local infection. Risks of biopsies include pain, bleeding, infection, and the risks to the particular area undergoing surgery. General anesthesia itself is generally very safe but has a very small risk of major complications such as heart attack or stroke. The surgical and anesthetic risks will be explained to you in more detail at the time of surgery, if this is needed. Risks of colonoscopy with biopsies include discomfort and bleeding from the rectum; rarely the colon may be punctured and if this occurs, it is serious and may require surgery. A separate consent describing all of the complications and side effects of colonoscopy with biopsies will be obtained from you.

In order to receive this therapy, you will need to have an intravenous catheter placed. This catheter is usually placed in the arm, chest or neck area into a major vein inside your chest. We usually remove the catheter after each cycle but on occasion it can be left in for several cycles. The catheter is necessary for infusion of chemotherapy and for the drawing of blood. It is usually inserted under local anesthesia. The risks associated with the procedure include pain, bleeding, infection, and puncture of the underlying lung. Lung puncture can result in lung collapse, which might require that a chest tube be placed into the chest cavity (usually for a day or two) to help the lung reinflate. The long-term risks of the catheter include infection and clotting of the vein in which the catheter sits. If these occur, it may be necessary to remove the catheter. These risks will be explained to you in more detail at the time of the insertion. The apheresis requires the insertion of an intravenous line in to the arm or chest and peripheral blood

will be removed and passed through an apheresis machine; this machine allows us to collect immune cells for research, and to return your own red blood cells and platelets back in your intravenous line. In some patients, we may also collect tumor cells by apheresis to produce the vaccine. Serious reactions associated with apheresis are rare and generally mild. They include pain and bruising at the insertion site of the intravenous line, and a temporary decrease in the platelet count and/or hemoglobin levels. Fainting episodes related to needle insertion can occur, and skin tingling caused by low calcium levels can rarely occur. During the leukopheresis, at least two apheresis nurses will be present, and a blood bank physician will be available in the clinic area where the procedure is performed. For this study, the procedure will typically take about 60 to 90 minutes. Side effects that have been observed with the drugs in this program when they are used individually include the following:

- Doxorubicin may cause sore mouth, loss of hair, a fall in blood counts with increased risk of serious infection or internal bleeding, tissue damage if the drug contacts the skin, heart damage and, rarely, death due to heart failure. However, the infusion method used in this study has been shown to reduce the risk of heart damage.
- Cyclophosphamide may cause a fall in blood counts with increased risk of serious infection or bleeding, loss of hair, damage to the lining of the urinary bladder with painful and bloody urination, loss of function of the ovaries or testes, and nausea and vomiting. Bladder irritation can be minimized by drinking at least two quarts of fluid each day.
- Vincristine often causes numbness of the hands and feet after several cycles. Rarely, patients may develop pain and/or weakness of the foot muscles. Patients also may have constipation and medications will be given to reduce this. In most instances, these symptoms resolve when the drug is stopped, but resolution of the numbness in the hands and feet may sometimes take months or even years. The drug can also cause tissue damage if it contacts the skin.
- Etoposide may cause nausea and vomiting, diarrhea, loss of hair, lowering of blood pressure during administration, mouth ulcers, and lowering of blood counts.
- Rituximab commonly causes fever, chills, nausea, headache, swelling, itchiness and rash. Low white blood counts may occur but are less common. Occasionally patients have developed low blood pressure, wheezing and rashes during administration of rituximab. Less common toxicities are abdominal pain, vomiting, low platelets and red cells, muscle and joint pains, dizziness and runny nose. Rarely, patients may die from the effects of rituximab due to an allergic reaction or lung problems.
- Prednisone may cause ulceration in the stomach or bowel, increased blood pressure, high blood sugar (diabetes), increased risk of infection, a round appearance of your face, weight gain, change in mood, thinning of your bones with increase in the risk of fracture. It can also cause or worsen acne.

- G-CSF can occasionally cause bone pain by stimulating normal bone marrow. This stops when drug administration stops. It has also been reported sometimes to cause skin rash, skin reddening around the injection site, muscle cramps, decreased platelets (not clinically significant), pain or numbness and tingling around the chin, worsening of certain pre-existing inflammatory conditions (such as psoriasis, eczema, or vasculitis), fever, body aches, and alterations in certain laboratory tests. With prolonged administration G-CSF has been associated with hair thinning and enlargement of the spleen.
- Vaccine treatment may produce some discomfort, such as redness, swelling and tenderness at the injection site. Fever, chills, rash and flu-like symptoms may also occur. All of these are usually temporary. Although very unlikely, it is possible that you could have a severe allergic reaction with shortness of breath and low blood pressure.
- GM-CSF may cause fever, chills, sweating, muscle aches, tiredness, headache, dizziness, shortness of breath, fluid collection in the lining of the lung, lack of appetite, indigestion, nausea, vomiting, diarrhea, tenderness at the site of injection, hives, rash itching, allergic reactions, bone pain, clotting of blood vessels, low blood pressure, leg swelling, elevated white blood count, elevated platelet count, low platelet count, and abnormal blood tests of the liver.
- Trimethoprim/sulfamethoxazole can cause a skin rash that goes away when the drug is stopped. Inhaled pentamidine can cause coughing, wheezing, and burning pain in the throat. All of these symptoms usually go away shortly after the inhalation treatment is finished.

It is important to emphasize that when you have a decreased white blood cell count from the EPOCH-R treatment, you are at risk of infection. Such infections can be very serious and can even cause death if not quickly and properly treated. Therefore, if you have a temperature greater than 38.3o C (101o F), you must call your doctor immediately. Chemotherapy may also cause your platelets to fall; since platelets are the blood elements that permit blood to clot, this may place you at increased risk of serious bleeding. It may be necessary to give you transfusions of platelets if your platelet counts reach very low levels. There is a small chance that damage to the normal bone marrow may eventually result in bone marrow failure, leading to a serious shortage of one or more kinds of cells in the blood, or to leukemia. Because this is a relatively new combination of drugs, it is always possible that unanticipated side effects may occur, including death.

Many of the drugs used in this treatment program are toxic to the cells in the ovary and testicle and may produce sterility. Recovery of normal fertility is not well studied although we know that some patients treated with this combination have remained fertile after the therapy has been completed. For this reason, men who are about to receive this treatment should, if they wish to have children in the future, consider sperm banking before start of the treatment. These drugs may also be very toxic to an unborn child. Therefore, adequate birth control measures (such as

the contraceptive pill, condoms, diaphragm with contraceptive foam or ointment, contraceptive sponge, etc.) should be used by participants or their sexual partners while receiving treatment on this study. Women of childbearing age will have a pregnancy test, which must be negative at the time of study entry. This test requires that blood be drawn from a vein one or two days prior to the study. The results of the pregnancy test will be made available to you prior to the initiation of the study. Your physicians will watch you closely for side effects and will stop treatment if any side effects become a serious threat to your life or well-being. Your physicians will also stop the treatments if it becomes clear that the treatment is not successfully controlling your disease.

Rarely, patients may develop a dangerous side effect from blood transfusions called graft versus host disease (GVH). This disease is caused by white cells from the blood transfusion that can attack your normal tissues and cause death. GVH is preventable by radiating the blood before you receive it. It is important to emphasize that you will not receive any radiation from the blood and the radiation procedure done on the donated blood will not harm you. If you require a blood transfusion at the NIH during this study, you will receive blood that has been radiated. However, if your local physician gives you a blood transfusion, it is important that you make sure the blood has been radiated.

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.
   - While the controlled-access databases developed for this project will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of

the computer systems used to store the codes linking your genetic and medical information to you.

- Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, 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.

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Most patients will have tumor shrinkage with chemotherapy. However, we do not know if the vaccine will be of benefit to you and do not know if you will be cured of your lymphoma. It is also possible that you may not respond to any of this treatment.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

It should be emphasized that we do not know at this point whether the EPOCH-R and vaccination we propose to give you is superior, inferior, or equivalent to standard combination chemotherapy for your disease. Alternative procedures that could be used to treat your disease include:

- Other combination drug regimens and other schedules of the same drugs used in this study. For example, a chemotherapy called CHOP given in the conventional manner

would be suitable standard therapy for your condition. You could also receive EPOCH-R as standard treatment.

- Treatment with single drugs. This is known to produce brief responses of a few months' duration in many patients but to have little beneficial effect in long-term control of the disease.
- Radiation (X-ray) treatments. This can stop tumor growth in particular locations, such as bone, abdomen, and other sites but is not successful in controlling the disease overall unless the disease is very localized at the start of therapy.
- Surgery. As with radiation, surgery can be successful in removing tumor from particular locations but cannot be used successfully to remove all lymphoma cells from the body, since the disease is almost always present in multiple locations. Also, surgery cannot be used against tumor in some of the organs most commonly involved by lymphoma, such as the liver or the lungs.
- Waiting, without active therapy. Although a period of watchful waiting is appropriate treatment for some kinds of tumors, in lymphomas similar to yours the disease will often grow and spread rapidly if no treatment is administered.

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
- Some of the specimens and/or data obtained may be sent to researchers outside of the National Cancer Institute to perform additional research studies designed to help us better understand lymphoma.
- Biovest International, Inc. will have limited access to the clinical data and results in NIH's possession and control as needed to support the registration of the Id-KLH Vaccine by the FDA in this disease.

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.

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.

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, 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 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, Christopher Melani, M.D., Building 10, Room 4N115, Telephone: 301-814-7117. 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 AUGUST 06, 2018 THROUGH AUGUST 05, 2019.

Signature of Investigator | Date | Signature of Witness | Date

Print Name | Print Name