PRINCIPAL INVESTIGATOR: Wyndham H. Wilson, M.D., Ph.D.

STUDY TITLE: Randomized Phase II Study of Dose-Adjusted EPOCH-Rituximab-Bortezomib Induction Followed by Bortezomib Maintenance versus Observation in Untreated Mantle Cell Lymphoma with Microarray Profiling and Proteomics

STUDY SITE: NIH Clinal Center

Cohort: Standard

Consent Version: 11/08/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the 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 in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This is a clinical research study to test a new investigational approach using VELCADE® (Bortezomib) For Injection with EPOCH-R chemotherapy to treat your mantle cell lymphoma.

VELCADE® (bortezomib) for Injection is a drug under development by Millennium Pharmaceuticals, Inc. VELCADE has received FDA approval for the treatment of multiple myeloma patients who have received at least one prior therapy and have demonstrated disease progression on the last therapy. Additionally, in October 2014, VELCADE received FDA approval for the treatment of Mantle Cell Lymphoma. VELCADE is still currently under investigation for other indications. VELCADE is the type of drug known as a "proteasome inhibitor." It has been studied in about 9000 patients with various types of cancer. VELCADE enters cells and affects the way they divide. VELCADE interferes with a substance found inside cells in your body. Mantle cell lymphoma is a form of cancer of the white blood cells called lymphocytes. In mantle cell lymphoma, the abnormal lymphocytes multiply and accumulate in lymph nodes and elsewhere. Standard treatment with chemotherapy can often control the mantle cell lymphoma for a period of time but in most patients, the disease does not go entirely away or comes back. In this study, we are testing VELCADE® in combination with EPOCH-R chemotherapy.

We hope that this is also the case in newly diagnosed mantle cell lymphoma and that the addition of this drug to EPOCH-R will lead to better cure rates. 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. In fact, we recently carried out a study using EPOCH-Rituximab in newly diagnosed mantle cell lymphoma and found that 92% of the patients had a complete remission after this combination. We hope that by adding VELCADE, the results will be as good if not better. Once chemotherapy is finished, we will assign patients by chance to receive VELCADE or not. For patients who are not assigned to receive this, they will be offered VELCADE, if their disease returns. Our hope is that this so called 'maintenance therapy' will improve the overall cure rate and increase the amount of time before the disease returns.

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.

Description of Research Study

The study is divided into 3 parts. Before being enrolled in the study, 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 lymph node biopsy before you start any treatment. In the first part of the study, you will receive VELCADE by itself. We will repeat the biopsy after you have received the second dose of the drug. Both of these biopsies are optional; we will ask you later if you agree to have the biopsies. In the second part of the study, you will receive a series of treatments with EPOCH-R-Bortezomib. It usually takes 18 weeks to complete this part of the study. In the third part, you will be assigned by chance to receive or not to receive VELCADE. If you are assigned to receive it, you will receive 4 doses of VELCADE every 8 weeks approximately. You will continue receiving VELCADE for up to 18 months. If before the end of 18 months, your disease returns, then the VELCADE will stop. If you have been assigned not to receive the VELCADE, you will be offered VELCADE if the disease returns.

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

Part A: VELCADE alone

You will first receive VELCADE alone. You will receive 1 cycle in total – that will be 4 doses of the drug given over 2 weeks. The VELCADE will be given by injection into the vein. This is given in approximately 30 seconds. Then 3 to 4 weeks from starting Part A, you will begin treatment with EPOCH-R and VELCADE. If your mantle cell lymphoma is too advanced, your doctor may decide to skip this part and have you start treatment in Part B.

Part B: EPOCH-R-B 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-B 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 VELCADE will be given by vein over 30 seconds before the rituximab on day 1 and again on day 4. 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-B. If your lymphoma grows, however, EPOCH-R-B will be discontinued. After each EPOCH-R-B 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 for 10 days. 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 a different drug that has the same function.

Part C: VELCADE alone

After you have completed the EPOCH-R-B therapy, you will be assigned by chance to receive or not to receive VELCADE alone. If you are assigned by chance to not receive it and your disease relapses, you will be offered it at this time. If you are assigned to receive VELCADE after EPOCH-R-B, the VELCADE will be given every 56 days, as 4 doses over 11 days. There will then be a break of 45 days before the next cycle. If you are not assigned to receive VELCADE but your disease relapses, you will be offered VELCADE as 4 doses over 11 days with a break of 17 days before the next cycle. The time over which you receive the 4 doses and the break before the next 2 doses is called a cycle. You will continue to

receive cycles like this for a period of up to 18 months or until your disease comes back or progresses. The VELCADE will be given by vein over 30 seconds.

Research Tests, Biopsies and Imaging

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. Your blood will be tested for your HLA type. This test is to identify surface groups of proteins which are unique to each person. We plan to do a tissue biopsy before you start treatment and a further biopsy a day after treatment has begun. Both of these biopsies are optional; we will ask you later if you agree to have the biopsies. 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. The progress of your response will be followed by CT scans of your body and blood tests.

As part of your clinical evaluation and follow up we will use CT scans and Positron Emission Tomography (PET) scan to determine the extent of your disease and response to treatment. In addition, we will do one CT scan and up to two PET scans for research purposes to look for any early effect of the VELCADE you will receive. Some patients may also undergo up to two biopsies under CT guidance for research purposes. This radiation is for research purposes only and is not necessary for your medical care. Positron emission tomography (PET) uses a radioactive sugar molecule called fluorodeoxyglucose, or FDG for short. This sugar is similar to glucose, an ordinary form of sugar that the body uses for fuel. The FDG is labeled with a type of radioactive element, an isotope, called Fluorine-18 (F-18) that emits particles called positrons that can be detected by a special camera and viewed on a computer screen. The FDG used for the research PET scans is an FDA approved agent.

You will not be eligible for the PET scan if:

- You weigh more than 350 lbs. Weight in excess of 350 pounds will exceed the weight limit for the scanner table.
- You need conscious sedation in order to perform the research PET scan
- Technical problems with the scanner would significantly delay your treatment

In addition, if you are a woman of childbearing potential, you must have a negative pregnancy test.

The FDG-PET scan will be done in the Nuclear Medicine or PET Department of the NIH Clinical Center. Prior to the test you will not be allowed to eat (including mints, sugar containing medicine or gum) or drink anything but water for 6 h. If possible you should drink 2 to 3 glasses of water before the test. The FDG will be injected into the vein after which you will rest quietly in a room for 1 hr after which the PET scan will be performed. Just before the initial scan, you will be asked to empty the bladder.

The PET camera is shaped like a doughnut and looks like a CT scanner. You will be asked to lie very still on a table within the machine and flat on the back with the arms over the head or to the side. Your head will lie on a soft cradle. For about 11/2 hour the picture-taking process will take place depending on your height. As part of the PET scan we will do a “transmission scan” with

the same scanner or using a CT to determine your body thickness and to align any abnormalities seen on the FDG scan with anatomical findings on CT. A PET technologist will be present at all times and a physician will be available throughout the procedure. If for any reason you feel that cannot continue, the scanning can be stopped and you can be removed from the scanner immediately. However, the information from the scan may be lost at that time. After the scan is finished, you will be asked to empty the bladder again every 1 1/2 hours for 6 hours to eliminate the radioactive sugar. One blood sample may be drawn during the PET scan to determine the blood sugar levels.

The most amount of blood to be drawn during any study visit/cycle is expected to be about 8.6 tablespoons.

Additional Research Testing

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, and to understand more about lymphoma. 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 the opportunity to come to NIH to have genetic education and counseling to explain this result. If you do not want to

come to NIH, a referral to a local genetic healthcare provider will be provided and the consultation will be at your expense.

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.

When you are finished taking the drugs (treatment)

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. Some or all of these tests will be repeated during and after the chemotherapy at different times. Depending on the tests you had before coming here, these may include blood and urine tests, studies of lung function, CT or MRI scans, colonoscopy with biopsies, radioisotope scans, and biopsies of tumor tissue, bone marrow, liver, or other sites.

You should talk to your doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the treatment are identified below.

Study Treatment Risks

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious or long-lasting or may never go away. There is also the risk of death from either the treatment or your/your child's disease.

Side effects of Velcade alone

VELCADE should not be taken if you are overly sensitive to bortezomib (VELCADE), boron or mannitol. You face some risks or discomforts when you are treated with the study drug, VELCADE. You are at risk of experiencing all, some, or none of these symptoms and they may vary in severity. The severity may be mild, moderate or severe, up to and including death. Any symptoms or conditions that you have before you start study drug may worsen. Also, there is always a chance that a rare or previously unknown risk may occur. If any of these symptoms occur, you must tell your doctor who may give you other drugs to ease any discomfort you experience. Your doctor may decrease or withhold the dose of VELCADE. Other drugs and supplements may affect the way VELCADE works. Tell your doctor about all drugs and supplements you are taking while participating in this study. In addition, if a severe reaction to the study drug occurs, your doctor may permanently stop the study treatment.

Most Common VELCADE Risks:

The most common risks are those that have occurred in greater than or equal to 30% of patients who have received VELCADE:

- weakness, fatigue, and general discomfort
- gastrointestinal effects such as constipation, diarrhea, nausea and vomiting
- fever very commonly with shaking chills
- painful sensations or numbness and tingling in hands and feet which may not get better after stopping VELCADE. Uncommonly, the nerves that control things like your heart rate, gut movement and urinary bladder may be affected.
- lowered platelets that may increase the chance of bleeding
- lowered red cells or anemia which may make you feel tired

Very Common VELCADE Risks:

The very common risks are those that have occurred in 10-29% of patients who have received VELCADE:

- decrease in white blood cells called neutrophils or lymphocytes that may increase your risk of infection and is uncommonly associated with fever.
- You may have lowered white blood cells or have lowered red blood cells at the same time
- loss of appetite, which may result in dehydration and/or weight loss
- abdominal pain
- symptoms of flu and other upper respiratory tract infections, such as chills, sore throat, and runny nose
- aches and pains in muscles and joints; and back pain
- skin rash
- cough, feeling short of breath, lung infections including pneumonia and commonly bronchitis
- headache
- dizziness
- Herpes virus such as shingles (herpes zoster) that can sometimes cause local pain that does not go away for a while and herpes simplex virus. Shingles can sometimes spread over large parts of the body. Both may also affect the eyes or brain, but this is uncommon.
- problems sleeping and feeling anxious

Common VELCADE Risks:

Common risks are those that have occurred in 1-9% of patients who have received VELCADE:

- changes in heart rate and heart beat that can cause you to possibly feel light-headed, dizzy, faint, short of breath, and/or have chest pain. This may also cause you to feel confused. An uncommon risk is a possible life threatening abnormal heart beat.
- new or worsening heart failure (which may appear as shortness of breath, swelling in the legs, and/or chest pain) or decreased heart function that can uncommonly be severe. If you have heart failure or other diseases that put you at risk of getting heart failure, you should tell your doctor.
- lowered blood pressure that can commonly cause you to feel dizzy or faint when you stand up. You should not drive or operate any dangerous tool or machines if you have these symptoms.
- accumulation of fluid in and around the lungs
- decreased level of oxygen in the blood
- infection and/or inflammation of the eyes or eyelids
- painful sores of the mouth and/or throat, which may make swallowing difficult
- heartburn, acid reflux and stomach bloating
- severe bleeding, including bleeding in the stomach and intestines (gut) that may be linked with low platelet counts, and blood clotting changes. Uncommonly, this bleeding may cause bloody diarrhea and/or bloody vomit.
- skin rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with skin peeling and mouth sores.

- swelling in the arms and legs, and weight gain
- nosebleeds
- deterioration in kidney function
- infections of the bladder, sinuses, throat, stomach and intestines, and skin and the area of skin where your catheter is placed
- nerve pain after herpes infection
- severe muscle weakness and paralysis (not being able to move your arms and legs)
- changes in blood sugar have been reported in a few diabetic patients receiving medicine for diabetes. If you are taking medicines for diabetes you may need close monitoring of your blood sugar levels.
- blood in the urine
- confusion
- abnormal liver tests. Uncommon risks are hepatitis, and liver failure in patients who got many other drugs and had other serious medical problems.
- reduction in white blood cell count
- lowered amount of potassium and sodium in your blood and increase in the amount of calcium in your blood.
- muscular weakness
- blurred vision
- changes in the way things taste

Uncommon VELCADE Risks:

Uncommon risks are those that have occurred in less than 1% of patients who have received VELCADE:

- pain, redness, swelling and infection in the area of the skin where VELCADE is injected into the vein.
- pain in the mouth and throat when swallowing
- decrease in or loss of hearing
- intestinal obstruction (blockage of the gut) that may get better on its own and not need surgery inflammation of the intestines, pancreas or stomach
- fungal infections in the mucous membranes such as the mouth and throat, and uncommonly in the skin and nails
- life-threatening infections in the blood (sepsis)
- coughing up blood
- bleeding in the brain and subdural hematoma, which is bleeding between the skull and your brain
- inflammation of the layers surrounding your heart or collection of fluid around the heart may cause chest pain or breathing problems and can be life-threatening or lead to death. If you have new or worsening chest pain or breathing problems you should tell your doctor.
- rapid death of cancer cells that may let toxins into the blood and injure organs, such as the kidneys
- allergic reactions that may include skin swelling and/or swelling of the face or throat and

could be severe or life threatening
- inflammation and fluid build up in the lungs, or pus build up between the layers surrounding the lungs that may cause bleeding problems, and can be life-threatening or lead to death. Increased blood pressure in the lungs, called pulmonary hypertension, has also been reported. This can also cause breathing problems, and can be life-threatening. If you have new or worsening breathing problems you should tell your doctor.
- changes in the brain that may cause convulsions and confusion
- A syndrome called "posterior reversible leukoencephalopathy syndrome" that affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures, but is usually reversible.
- loss of some to all vision affecting one or both eyes, which may be caused by damage to the nerve in the eye. Loss of vision may or may not be reversible.
- Progressive multifocal leukoencephalopathy (PML); PML is a rare, serious infection of the brain that is caused by a virus already in your body at the time of treatment onset. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. Tell your study doctor immediately if you have any of the following symptoms or if anyone close to you notices these symptoms: confusion or problems thinking, loss of balance or problems walking, difficulty speaking, decreased strength or weakness on one side of your body, blurred vision or loss of vision.

Side Effects of EPOCH-R-B

Likely:

- Lowered white blood cell count that may lead to infection
- Lowered platelets which may lead to an increase in bruising or bleeding
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath
- Should low counts occur, they can be treated with blood products (transfusions), antibiotics, and there may be a reduction in the amount of drug given to you
- Constipation
- Fatigue or tiredness
- Painful tingling and numbness of fingers and/or toes
- Hair loss
- Fever and/or chills
- Time away from work
- Urine colored red for a day or two after the doxorubicin infusion
- Fingernail and toenail changes
- Tearing or dry eyes
- Runny nose
- Bony pain

Less Likely:

- Nausea and/or vomiting
- Loss of appetite, change in taste and weight loss
- Temporary shortness of breath or dizziness while receiving rituximab

- Headaches
- Muscle aches and muscle weakness
- Hoarseness or pain in the jaw
- Elevated blood sugar levels
- Elevated or decreased blood pressure
- Confusion
- Mouth & throat sores. Temporary irritation to the mouth may lead to mouth ulcers (similar to canker sores). Medications to numb the mouth may ease the mouth discomfort.
- Stomach ulcers
- Skin rashes and/or dry skin
- Loss of control of muscles or reflexes
- Abnormalities in blood results such as elevated liver enzymes, low blood protein and low blood calcium
- Mood changes such as agitation or depression
- Trouble sleeping

Rare, But Serious:

- Severe constipation may result in abdominal pain and cramping
- Bladder irritation with painful and bloody urine
- Damage to the heart muscle
- Skin rash that may be serious and life-threatening
- Allergic reaction that may be severe or life-threatening. Symptoms may include difficulty breathing, low blood pressure, fast heart rate, and sweating.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Patients who may have had prior exposure to the hepatitis B and C virus may be at an increased risk of recurrence of the virus that may lead to severe liver damage that can be life-threatening. You doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection, and you will be treated, if appropriate, by your doctor.

Other Study Risks

Blood samples: The possible side effects of drawing blood include pain, bleeding, and bruising at the site of the draw. Sometimes you may have dizziness, light-headedness, or fainting. Rarely there is infection with redness and irritation of the vein.

Biopsies, including colonoscopy: 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.

If the doctor feels as though you need a colonoscopy, 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.

Intravenous catheter risks: In order to receive EPOCH-R-B 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.

Infection and bone marrow risks: It is important to emphasize that when you have a decreased white blood cell count from the VELCADE alone or the EPOCH-R-B combination 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.

Reproductive risks: 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. In addition, you must not be breastfeeding a baby during this 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.

If you or your partner becomes pregnant while in this study you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. Because of possible risks to your unborn baby, the study drug will be stopped permanently.

Risks of blood transfusions: 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.

Radiation risks: During the treatment portion of the study, scans were performed more frequently to see how the cancer was responding to therapy. Here we describe the risk of radiation exposure in follow-up only as scans are done less often and this is the portion of the study in which you are currently taking part.

During your participation in this research study, you will be exposed to radiation from to up to one (1) CT scans of the chest, abdomen, and pelvis and two (2) [18F]-FDG PET scans as well undergo up to two (2) CT guided. The amount of radiation exposure you will receive from these procedures is equal to approximately 3.9 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 PET scan, CT scan and CT guided biopsies that you get in this study will expose you to the roughly the same amount of radiation as 13 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.

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives.

Protections against misuse of genetic information

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

POTENTIAL BENEFITS OF PARTICIPATION

Most patients will have tumor shrinkage with chemotherapy. However, we do not know if the addition of VELCADE will add to this benefit and do not know if you will be cured of your lymphoma. We do not know if you will receive personal, medical benefit from taking part in this study. 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

It should be emphasized that we do not know at this point whether VELCADE combined with EPOCH-R with or without maintenance VELCADE is superior, inferior, or equivalent to standard combination chemotherapy for your disease. Alternative procedures that could be used to treat your disease include:

1. 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 CHOP-R or EPOCH-R as standard treatment.
2. 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.
3. 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.
4. 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.
5. Watching and waiting may be an option for select patients without symptoms.

EARLY TERMINATION

You will be discontinued from this study for any of the following reasons:

- You may be withdrawn from the study if you do not comply with the study requirements.
- Your doctors do not feel it is in your medical best interests to be continued on this study.
- You have had unacceptable toxicity which does not permit safe continuation on the study
- You require another treatment.

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 Millennium 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 cannot be recalled and destroyed.

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.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and

ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

This study does not offer reimbursement for parents and participants, or payment of, hotel, travel, or meals.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

If 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.

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.

Millennium Pharmaceuticals, Inc. is providing VELCADE for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from (Millennium Pharmaceuticals, Inc.,), the pharmaceutical company who produces (VELCADE).
- 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.

Millennium Pharmaceuticals, Inc is collaborating with us on this study. Thus, Millennium and its designees will have access to your research records and data which may include:

results from procedures conducted to find out if you are eligible for the study;

- information that is created or collected from you during the study, such as the results of any tests or procedures performed during the study;
- information about your medical history and treatment included in your medical records.

The above information and materials may identify you by name, address, telephone number, social security number, health plan number, study number, date of birth, dates relating to various medical procedures, or other identifying information. You cannot participate in this study if you do not sign this form, authorizing the uses and disclosures of your information described below.

You will be informed of any new findings related to the development or safety of VELCADE that may affect your willingness to continue to take part in this study.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect

reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Wyndham H. Wilson, wilsonw@mail.nih.gov, 240-760-6092. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.