PRINCIPAL INVESTIGATOR: Mark Roschewski, M.D.

STUDY TITLE: Phase II Study of Dose- Adjusted EPOCH+/-Rituximab in Adults with Untreated Burkitt Lymphoma, c-MYC+ Diffuse Large B-Cell Lymphoma and Plasmablastic Lymphoma

STUDY SITE: NIH CC

Cohort: *Affected Patient*

Consent Version: 09/20/2019

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.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

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

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?

You are being asked to take part in this study because you have an aggressive B-cell lymphoma. The purpose of this study is to compare the good and/or bad effects of an experimental approach

to treating your disease and to analyze your tumor using new scientific laboratory studies. Many of the standard treatments for Burkitt lymphoma can cause severe side effects that may require long stays in the hospital. Our experience using this treatment, Dose-Adjusted EPOCH +/- Rituximab (DA-EPOCH-R) has been that it has not been associated with the same severity of side effects or long durations in the hospital. In addition, studies so far using DA-EPOCH-R in patients with your disease appear to be promising. We hope to confirm these very good results in this study.

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. It is likely that you will be asked to undergo another biopsy of your tumor to obtain fresh tissue to help us gain a better understanding of this disease. If you are found not to be eligible for the study, you will be referred back to your home physician. If you are eligible and agree to participate, you will receive DA-EPOCH-R chemotherapy, an experimental treatment for lymphomas developed over the last 14 years. If you have plasmablastic lymphoma, you will receive DA-EPOCH without the rituximab. In addition, your tumor will be analyzed using new scientific laboratory studies to better understand how to develop even more effective treatments.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A total of 194 people will be enrolled in this study.

DESCRIPTION OF RESEARCH STUDY

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

Based on the disease that you have and the tests that are performed before you start treatment, your doctor will determine if you have “high risk” or “low risk” disease.

High risk disease

If you have “high risk” disease the chemotherapy regimen known as DA-EPOCH-R will be given by intravenous (IV) infusion through a “central line,” an IV catheter (or tube) placed in the large vein in your arm or in your chest. Participants will receive DA-EPOCH-R chemotherapy which consists of the following drugs: etoposide (E), prednisone (P), vincristine (O), cyclophosphamide (C), doxorubicin (H), and rituximab (R). If you have plasmablastic lymphoma, you will not receive the rituximab. The drug rituximab will be given by IV infusion on the first day of treatment over several hours. When the rituximab IV infusion is complete, the drugs doxorubicin, etoposide, and vincristine will each be given by continuous IV infusion over the next 4 days (that is, continuously for a total of 96 hours). Cyclophosphamide will be given by IV infusion on Day 5 after you have received the previous chemotherapy drugs. Prednisone will be given by mouth (orally) on each day for 5 days. You will receive the drug filgrastim by subcutaneous (under the skin) injection starting on Day 6 to increase white blood cell counts. Filgrastim will be continued until your white blood counts have reached acceptable levels. The dose of doxorubicin, etoposide, and/or cyclophosphamide may be “adjusted” up or down each cycle depending on your white blood cell count (WBC) and/or platelet count. At the beginning of each cycle, your doctors will evaluate how low your WBC and platelets went during the previous cycle and decide if your doses of doxorubicin, etoposide, and/or cyclophosphamide need to be adjusted. The DA-EPOCH-R therapy will be repeated every twenty-one (21) days, which is known as a “cycle” of therapy. Most

people will receive a total of 6 cycles (18 weeks) of treatment. It is possible you will receive a total of 8 cycles (24 weeks) of treatment if the study doctor believes it is in your best interest. A PET scan will be performed after you have finished cycle 2. If the PET scan shows residual disease, you will have another PET scan repeated after you have completed cycle 6 or 8.

You will be given a drug commonly known as Bactrim to be taken by mouth (orally) three times a week (for example, on a Monday-Wednesday-Friday schedule) to guard against possible infections. You will also receive a drug each day to be taken by mouth (orally) to guard against stomach ulcers. In addition, you will receive Colace, or equivalent, by mouth twice daily to prevent constipation. If constipation becomes severe, you may also receive the laxative known as lactulose.

You may receive other drugs as needed to prevent or treat problems during your treatment. If this becomes necessary, your study doctor will explain the drug, its actions and side effects.

If you have high risk disease, you are at high risk of your lymphoma spreading into your central nervous system (CNS). To reduce the risk of the lymphoma spreading to your CNS, you will also receive eight doses of a drug known as methotrexate injected into the spinal fluid. You will receive this treatment on Days 1 and 5 of cycles 3-6 of therapy.

Your lymphoma may have already spread to the CNS, which includes the brain and spinal cord. If so, it will be necessary to treat the CNS with chemotherapy which usually includes the instillation of chemotherapy drugs (methotrexate and/or cytarabine) directly into the fluid (the cerebrospinal fluid, or CSF) surrounding the brain. This is usually done by first placing a small reservoir (called an Ommaya reservoir) under the skin of the scalp; this reservoir is connected to a catheter that is placed through the brain itself into the fluid. This procedure is performed by a neurosurgeon under general anesthesia. These drugs may also be administered through a spinal tap (also called a lumbar puncture). Depending on how you respond to this therapy, it may be necessary to modify it and/or to also administer radiation to your brain and/or spinal cord. Each of these therapies will be discussed with you if they are needed. If this applies, you will receive this treatment for approximately 8 months and your study doctor or study nurse will explain the schedule to you before beginning the treatment.

	Day of Treatment														
	1	2	3	4	5	6	7	8	9	10	11	12	13	…	21*
Rituximab	X														
Etoposide	X →														
Prednisone	X	X	X	X	X										
Vincristine	X →														
Cyclophosphamide					X										
Doxorubicin	X →														
Filgrastim						X** →									

* This twenty-one day (21) period will be known as a "cycle" of therapy. Therapy will be repeated for a total of 6-8 cycles. As described above, during the course of treatment, you may also receive the following drugs: methotrexate, Bactrim, omeprazole, and colace.
** Filgrastim will continue to be given to you until your blood counts have reached acceptable levels. You and/or your caregiver will be taught how to give the Filgrastim injections.

Low risk disease

If you have "low risk" disease (your risk category will be determined by the treating doctor) you will receive 3 cycles (9 weeks) of Dose-Adjusted EPOCH + 2 doses of Rituximab (DA-EPOCH-RR) (two doses of rituximab per cycle). The additional dose of rituximab is given on day 5 of each cycle. The DA-EPOCH-RR will be given by intravenous (IV) infusion through a "central line," an IV catheter (or tube) placed in the large vein in your arm or in your chest. Participants will receive DA EPOCH-RR chemotherapy which consists of the following drugs: etoposide (E), prednisone (P), vincristine (O), cyclophosphamide (C), doxorubicin (H), and rituximab (R). The drug rituximab will be given by IV infusion on the first day of treatment over several hours. When the rituximab IV infusion is complete, the drugs doxorubicin, etoposide, and vincristine will each be given by continuous IV infusion over the next 4 days (that is, continuously for a total of 96 hours). The second dose of rituximab is given again (over several hours) after the 96 hour infusion ends. Cyclophosphamide will be given by IV infusion on Day 5 after you have completed the second rituximab infusion. Prednisone will be given by mouth (orally) on each day for 5 days. You will receive the drug filgrastim by subcutaneous (under the skin) injection starting on Day 6 to increase white blood cell counts. Filgrastim will be continued until your white blood counts have reached acceptable levels.

The dose of doxorubicin, etoposide, and/or cyclophosphamide may be "adjusted" up or down each cycle depending on your white blood cell count (WBC) and/or platelet count. At the beginning of each cycle, your doctors will evaluate how low your WBC and platelets went during the previous cycle and decide if your doses of doxorubicin, etoposide, and/or cyclophosphamide need to be adjusted. The DA-EPOCH-RR therapy will be repeated every twenty-one (21) days, which is known as a "cycle" of therapy.

You will be given a drug commonly known as Bactrim to be taken by mouth (orally) three times a week (for example, on a Monday-Wednesday-Friday schedule) to guard against possible infections. You will also receive a drug each day to be taken by mouth (orally) to guard against stomach ulcers. In addition, you will receive Colace, or equivalent, by mouth twice daily to prevent constipation. If constipation becomes severe, you may also receive the laxative known as lactulose.

You may receive other drugs as needed to prevent or treat problems during your treatment. If this becomes necessary, your study doctor will explain the drug, its actions and side effects.

If you have "low risk' disease, you will not receive methotrexate injected into the spinal fluid. As a safety measure, a PET scan will be performed after you have completed cycle 2. If the PET scan shows that you still have lymphoma, you will receive 4 additional cycles of DA-EPOCH-R (same treatment as the high risk group), and the PET scan will be repeated after you have completed cycle 6.

	Day of Treatment														
	1	2	3	4	5	6	7	8	9	10	11	12	13	…	21*
Rituximab	X				X										
Etoposide	X ⟶														
Prednisone	X	X	X	X	X										
Vincristine	X ⟶														
Cyclophosphamide					X										
Doxorubicin	X ⟶														
Filgrastim						X** ⟶									

* This twenty-one day (21) period will be known as a "cycle" of therapy. Therapy will be repeated for a total of 3 cycles. As described above, during the course of treatment, you may also receive the following drugs: Bactrim, omeprazole, and colace.

** Filgrastim will continue to be given to you until your blood counts have reached acceptable levels. You and/or your caregiver will be taught how to give the Filgrastim injections.

Research tests

Research studies will be performed on your blood, 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. The blood samples are collected in the beginning of the study and at the following time points while you are involved in the study: before Cycle 3, after Cycle 3 for Low Risk patients, after Cycle 6 (and after Cycle 8 if you receive 8 cycles) and on every scheduled follow-up visit.

We will not examine your tissue for anything that could have implications for an inherited gene mutation that would affect you and your family without first obtaining additional permission from you. It may be necessary to perform another biopsy of your tumor to perform important scientific research studies to better understand the biology of aggressive lymphoma, that is, how your type of lymphoma behaves. The special research studies done on this tissue will not be used to make any medical decisions, and the results of these tests will not be given to you.

OPTIONAL BIOPSY

We plan to do a tissue biopsy to learn more about your disease before you start treatment. 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.

The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor biopsy for the research tests in this study.

Yes No Initials_____

What happens after treatment is completed?

This depends on how you have responded to the therapy. If all evidence of disease has disappeared, you will be asked to return to the clinic about 30 days after the last treatment to assess your symptoms and any side effects (this may be done by phone if you cannot return to clinic), and then for follow-up exams every four (4) months for the first 2 years after completion of therapy.

If you have Burkitt lymphoma and your scans are negative at the two year post-treatment visit, you will return for one more visit at year 3. At these yearly follow up visits, you will undergo a physical examination and laboratory testing. You will not undergo a CT scan unless your study doctor determines it is clinically indicated.

If you have DLBCL or plasmablastic lymphoma and your scans are negative at the two year post-treatment visit you will return yearly. At these yearly follow up visits, you will undergo a physical examination, laboratory testing and a CT scan for up to 3 years post treatment.

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 to participate 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.

RISKS OR DISCOMFORTS OF PARTICIPATION

What side effects or risks can I expect from being in this study?

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, CAT or MRI scans, PET 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 or any other biopsies include pain, bleeding, and local infection. 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.

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.

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 don't 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 disease.

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.

Side Effects of EPOCH-R:

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.
- Tingling 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.
- A tear in the large or small bowel
- 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.

Secondary Malignancy

A number of established chemotherapy agents have an inherent risk of causing another cancer (known as a "secondary malignancy"). Certain drugs in use today, not currently known to be associated with this risk may be shown at a later time to result in the development of these secondary malignancies.

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, as well as the scans performed to assess your disease may also be very toxic to an unborn child or nursing baby.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 12months after you finish study treatment. If you are male and the partner of a woman who can become pregnant, you and your partner will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 12 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

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

Infection risks

It is important to emphasize that when you have a decreased white blood cell count you are at risk of infection. Such infections can be very serious and can even cause death if not quickly and properly treated. If you have a temperature greater than 38.3° C (101° F), you must call your doctor immediately. If your temperature is higher than 38.0° C (100.4 ° F) two times in a 24 hour period, 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.

Complications of treatment to the Central Nervous System

Complications of Ommaya insertion are uncommon when done by an experienced physician but could include infection and bleeding at the operative site or in the brain itself. Complications of lumbar puncture may include pain or bleeding at the site of needle insertion (the low back), infection, and headache. Most patients tolerate this treatment without serious side effects, although drugs placed into the brain fluid (CSF) may cause headache, stiff neck, and confusion that resolve when they are stopped. With long-term treatment, confusion and a slowing of thought processes may occur. If this treatment is necessary for you, the complications of the lumbar puncture or Ommaya insertion and chemotherapy instillation will be discussed in more detail.

Drugs used for the treatment of the Central Nervous System

- Methotrexate, when administered into the spinal fluid, may cause low blood counts and ulcerations in the mouth, stomach, and intestines. It can cause acute headache, back pain, stiff neck, and /or fever; it can also cause weakness or paralysis of certain muscles. Rarely, it can cause seizures and coma.

- Cytarabine given by lumbar puncture can cause nausea, vomiting, fever, and headaches. Rarely, it can cause weakness and seizures.

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 use many safety measures to protect your privacy. However, despite 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 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.
   - 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. It is possible that you may not respond to any of this treatment. Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn more about DA-EPOCH-R as a treatment for aggressive lymphoma. This information could help future patients diagnosed with lymphoma.

The possible benefits of taking part in the study are the same as receiving the drugs used in this study without being in the study.

RELATED RESEARCH STUDIES – BLGSP

Please note: The following section of the informed consent document is about an additional research study that is being done with people who are taking part in the main study. You may take part in this additional study if you want to. You can still be part of the main study even if you say "no" to taking part in this additional study.

The results of these research studies will not be provided to you or your doctor, nor will the results have any effect on your treatment. It is unlikely that what we learn from these studies will have a direct benefit to you. However, the information learned from these studies may benefit other patients in the future.

The results from these studies may be published, but individual patients will not be identified in these publications.

There will be no charge to you for participating in these research studies. Your samples will only be used for research and will not be sold. The research done with your sample may help to develop new products in the future.

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone is very small.

You will be asked to mark your choice by saying "yes" or "no" to several questions later in this consent form.

Purpose of the project

The purpose of this extra project, **Burkitt Lymphoma Genome Sequencing Project (BLGSP)** is to discover genetic changes associated with cancer, thus potentially leading to better prevention, detection and treatment of cancer, and perhaps other diseases as well. Body tissues are made up of cells containing DNA, which is part of the unique genetic material carrying the instructions for your body's development and function. Cancer can result from changes in this genetic material, thereby causing cells to divide in an uncontrolled way and possibly to travel to other organs. Some of the genetic changes leading to cancer are currently known, however many remain to be discovered.

The **BLGSP** is designed to identify genetic changes that can cause cancer in humans. As such, we would like to study the genetic material obtained from your tumor tissue as part of this project. We will compare the genetic material from your cancerous tissue with the genetic material from your normal tissue to find any differences that may exist. By combining information about genetic differences between normal and disease tissues along with information contained in your medical records, it may be possible to identify the genetic changes that are associated with your particular type of cancer. This same process will be performed with normal and cancerous tissues obtained from a number of other people who have agreed to participate in this research project. In this way, we expect to identify most of the genetic changes associated with many different kinds of cancer. By comparing treatment responses of patients with various cancers (through recorded medical

information), this project could also lead to more knowledge about why certain cancers respond differently to treatments. With such knowledge, future treatment options could potentially become customized to a patient's unique genetic make-up.

Collection of Samples and Medical Information

Your scheduled surgery (or surgery you already had) is/was part of the medical treatment that you agreed upon with your doctor. During surgery, cancerous tissue will be removed. Usually, when cancerous tissue is removed, very small amounts of nearby normal tissue are removed as well. Your surgery is not part of the BLGSP research project. We will receive some of these cancerous and normal tissues following your surgery.

We will collect a sample of blood (approximately 4 tablespoons), drawn from a vein in your arm, as a second type of normal tissue.

Should you object to having blood drawn, we will instead swab cells from inside of your mouth through gentle sweeping of the inner cheeks to obtain a secondary source of normal tissue.

We will also collect information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

Coding of Tissue Samples and Medical Information

Your tissues, blood or buccal (cheek swab) sample, and medical information will be labeled with a confidential project-assigned ID.

Only Dr. Roschewski at the National Cancer Institute and your main study doctor at your local hospital will have the information that matches the code to traditionally-used identifying information, such as your name, address, phone number, or social security number. Dr. Roschewski and your main study doctor will keep the information that matches the confidential code to this identifying information in a safeguarded database. Only authorized personnel, who have specifically agreed to protect your identity, will have access to this database. All materials conveyed to the BLGSP will be labeled with a project-assigned ID, removing traditionally-used identifying information, such as your name, address, phone number, or social security number. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Storage and Release of Samples and Medical Information

Your coded tissue samples will be sent to a National Cancer Institute (NCI)-sponsored storage facility. The facility will process the samples and then send portions of your samples to different types of laboratories for analysis as part of this project. One type of laboratory will analyze your DNA by a method called sequencing. Other laboratories will study your samples by different methods. The remaining tissue from your samples might be stored for an unlimited period of time for use in future research related to cancer, or perhaps in other research projects.

Information obtained from analyses performed on your coded samples and medical information will be entered into Internet-accessible databases along with information acquired from the other research participants in this project. Anonymous information from the analyses, which is nearly

impossible to trace to any individual patient, will be available to anyone in a completely public Internet database.

Information obtained from more detailed analyses, along with your confidential coded medical information, will be put into a controlled-access database. The information in this database will be available only to researchers who have received approval from an NIH Data Access Committee. In gaining access to such information, researchers have to agree to use the data only for research projects and not to ever try to use it in order to identify the donor of the material. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Please note that traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.

Recontact

In the future, we may want to obtain additional samples or follow-up information about your health or medical care. Should this be needed, a person from the NCI will contact you with an explanation of the reasons for any follow-up and to ask whether you would be interested in participating in this additional research.

Financial Compensation/Costs

You will not be paid to participate in this project. Your tissue samples and your medical information will be used for research purposes only and will not be sold. It is possible that some of the research conducted using your tissue samples or medical information will eventually lead to the development of new diagnostic tests, drugs or other commercial products. Should this occur, you will not receive any part of the profits generated from such products.

You will not incur any expenses from participating in this project

Potential Benefits of Participating in the Project

You should not expect to personally benefit from this research, aside from the knowledge that your participation will help researchers and health professionals around the world to better understand the causes of cancer and other diseases. Research projects such as this lead to better ways to prevent, detect, treat, and cure such illnesses.

Potential Risks of Participating in the Project

Physical Risks:

- There are very few physical risks associated with this project. Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually lasts only a few minutes. Every precaution will be taken to minimize these effects.

Psychological or Social Risks Associated with Loss of Privacy:

Your privacy is very important to us, and we use many safety measures to protect your privacy. However, despite 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 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 neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you (your name, address, telephone number, or social security number), technology may be developed 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 relative) in another database and be able to identify you (or your relative). It is also possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information back to you. Because some genetic variations can help to predict the current or future health problems of you and your relatives, this information may be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information could potentially be used in ways that could cause you or your family distress, such as by revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative).

There also may be other privacy risks that we have not foreseen.

While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is currently no federal law that prohibits such discrimination. We believe that the benefits of learning more about cancer and other diseases outweigh these potential risks.

Confidentiality

We will make every attempt to protect your confidentiality and to ensure that your personal identity remains anonymous. This signed consent form will be stored in a locked file that will be accessible only to authorized people involved with this project. We will carefully follow the coding, storage, and release plan explained in the *Description of the Research* section of this document.

Certificate of Confidentiality

This study has received a Certificate of Confidentiality which helps to protect your research information. The researchers involved in this study cannot be forced to disclose the identity or any information collected in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you request the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review your records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. 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.

Project Results

Your individual results from this research project will not be given back to you or put into your medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as your name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the **BLGSP** website.

Alternatives to Participating in the Project

The alternative option is not to participate in the BLGSP which is an optional part of your main study.

Voluntary Participation

The choice to participate in the BLGSP by donating your tissues and medical information is completely up to you. **No matter what you decide, your decision will not affect your medical care**.

Withdrawal from the Project

Once your coded samples have been distributed to the participating research laboratories and centers, and your information transferred to the appropriate databases, you will **not** be able to withdraw your information from this research project. However, you may be able to request the return or destruction of the tissue samples if you so desire.

Contact Information

If you have any questions about the project or your participation, please contact your main study doctor or Dr. Roschewski and 240-760-6183.

Agreeing to Participate in the Project

You have the right to receive the planned therapy on this study without participating in the optional BLGSP research study. Please read the sentence below and think about your choice. After reading the sentence, please mark your choice, sign your name, and provide the current date. No matter what you decide to do, it will not affect your care.

To participate in this research, you must agree to ALL of the following statements:

I voluntarily agree to donate cancerous tissue and normal tissue to be used for this and for other research projects.

I agree to release information from my medical records for this and for other research projects.

I agree to have my coded genetic information and coded medical information placed into Internet-accessible databases as described in the *Storage and Release of Samples and Medical Information* section of this document.

I understand that my coded genetic information and coded medical information contained in the Internet-accessible databases will be used in this and in other research projects.

I understand that there is a risk that someone in the future may be able to use information in these databases to identify me or possibly my relative(s).

I agree to be contacted in the future about my willingness to provide additional samples or follow-up information about my health or medical care if it is required.

Please sign your name here if you agree to the six statements listed above.

Your signature: _____

Date: _____

INCIDENTAL MEDICAL FINDINGS

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 during the course of this study that could be clinically relevant, we will contact you if you agree. 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 a referral to a genetic healthcare provider.

_____ I DO NOT want to be recontacted if incidental findings with potential health implications are discovered.

_____ I DO want to be recontacted if incidental findings with potential health implications are discovered. (You will be given a choice to learn or not learn about a genetic change that we find.)

ALTERNATIVE APPROACHES OR TREATMENTS

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

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

1. Getting treatment or care for your lymphoma without being in a study. For example, such treatment may include the same or other commonly-used chemotherapy drugs.
2. Participating in another research study.
3. Treatment with single drugs. This may produce very brief responses but has no beneficial effect in long-term control of the disease.

4. 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.
5. 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.

Please talk to your doctor about these and other options.

STOPPING THERAPY

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

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

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

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

CONFLICT OF INTEREST

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

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

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

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

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

We may share your specimens and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or industry sponsors of research.

We may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. The information in this database could include but is not limited to genetic information, ethnicity and sex. If your individual research data is placed in one of these repositories, it will not be labeled with your name or other information that could be used to easily identify you, and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

Your summary genomic data is being placed in an unrestricted database, so researchers will be able to access summary information about all the participants included in the study (including you), or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

In addition to the use and sharing of your specimens and data described above, we might remove any information from your specimens and data that can identify you such as name, address, or medical record number, and then use the specimens and data for additional research studies at the NIH or other places. If we do this, we might not contact you to ask your permission or otherwise inform you.

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

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

You will not receive compensation for participation in this study.

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

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

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

- If some tests and procedures performed outside the NIH Clinical Center, 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 NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

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

  The study Sponsor, the Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the

insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical 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, Mark Roschewski, M.D. at 240-760-6183 or mark.roschewski@nih.gov. *Other researchers you may call are:* Nicole Lucas, at 240-760-6252. 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