PRINCIPAL INVESTIGATOR:	Christopher Melani, M.D.
STUDY TITLE:	**Treatment and Natural History Study of Lymphomatoid Granulomatosis**
STUDY SITE:	**NIH Clinical Center**
Cohort:	Affected patient
Consent Version:	01/27/2021

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.

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 enrolled is a minor then the term "you" refers to "you and/or your child" throughout the remainder of this document.

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 Lymphomatoid Granulomatosis (LYG). The purpose of this study is to learn about LYG and its treatments.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A total of 105 people will be enrolled in this study.

DESCRIPTION OF RESEARCH STUDY

This is a study of interferon and/or chemotherapy for the treatment of lymphomatoid granulomatosis (LYG). There is no standard treatment for your disease. In this study, the selection of your therapy will depend on the type of your disease and past treatment. If you have LYG without signs of aggressive LYG, you will receive interferon. Interferon is an approved drug that is being tested as a treatment for your disease. Interferon is a protein which your body naturally produces. If you do not respond to interferon and/or have aggressive LYG, you will receive EPOCH-R chemotherapy (each letter stands for one of the drugs used in the combination). If you have disease after receiving interferon and/or EPOCH-Rituximab (EPOCH-R), you may receive rituximab by itself or with interferon. Your physician may make changes to this treatment approach if your disease does not adequately respond.

EPOCH-R is a combination of drugs which seem to have a high degree of effectiveness in patients with other types of lymphomas. Rituximab is a special kind of drug called an antibody which binds to a specific molecule (called CD20) present on most B-cell lymphomas. EPOCH-R contains drugs which are standard for the treatment of lymphomas. Because higher doses of chemotherapy may increase the benefit, the doses of several drugs in EPOCH-R may be increased on each cycle if you tolerated them on the previous cycle. However, EPOCH-R has not been previously tested in patients with LYG. If you respond to EPOCH-R but still have disease present after its completion, you will receive interferon after the chemotherapy is completed. An important part of this study is to understand the features of LYG. Therefore, to help us understand this disease better, we will try to obtain a biopsy of one of your lesions. Although the results of this biopsy may not directly benefit you, it may help in our future understanding of the disease.

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

In order to determine if you are eligible for this study, several tests need to be done. This period of evaluation may take up to three weeks and may be done on an outpatient basis. Evaluation may include some or all of the following tests: standard blood tests, 24 hour collections of urine, tests of lung and heart function, computerized tomography (CT) scans, MRIs if you have disease in your central nervous system (CNS), nuclear medicine scans of the body (called a PET scan), bone marrow biopsies and biopsies of suspected areas of tumor using CT guidance.

Interferon treatment

If you receive interferon, you administer this drug to yourself as an injection under the skin three times a week. While you are receiving interferon, you will be followed in the clinic every 2-12 weeks, depending on how you are tolerating and responding to the interferon. We will evaluate your disease with CT scans MRI (if you have CNS disease) every month for the first 6 months, then every 3 months. In addition, PET scans will be done before you start study therapy and after you have completed interferon therapy. The dose will be increased as tolerated over the next several months to a dose that is effective and tolerated by you. You will receive interferon on a chronic basis, for a year past the time your disease goes away, depending on your response.

EPOCH-R chemotherapy treatment

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 a large vein your arm or chest. Patients who receive dose adjusted (DA) EPOCH-R chemotherapy will receive 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). 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 depending on your white blood cell count. 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.

The DA-EPOCH-R therapy will be repeated every twenty-one (21) days, which is known as a "cycle" of therapy, for a total of 6 cycles. Following the fourth and sixth treatment cycles (approximately weeks 12 and 18) of DA-EPOCH-R, your doctor will evaluate you with blood tests, CT, and MRI scans (if you have CNS disease). In addition, PET scans will be done before you start study therapy and after you have completed study therapy.

	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.

Hepatitis B Testing and Prophylaxis:

As part of our study, we will test you for infection with Hepatitis B. We will tell you what the results mean and if you will require more frequent testing for Hepatitis B and need to take medicine to prevent Hepatitis B reactivation while on the study.

If you need to take medicine, you will take one, such as entecavir, by mouth every day until 12 months after your last chemotherapy.

EBV Testing:

As part of our study, we will test you for infection with Epstein-Barr virus. We will tell you what the results mean and if you will require more frequent testing for Epstein-Barr virus.

OPTIONAL BIOPSY

The biopsy to be performed may be done using CT guidance and is exclusively for research purposes and will not benefit you. It might help other people in the future. Biopsies for experimental purposes will not be done on children. We may request biopsy after you sign consent document.

If you agree to have the optional biopsy, you will be asked to sign a separate procedure consent before you have the procedure.

Treatment of disease in the nervous system

LYG may spread to the central nervous system (CNS) which includes the brain and spinal cord. In some cases, the disease in the CNS will respond to interferon. However, it may be necessary to treat the CNS with chemotherapy which usually includes the instillation of one of chemotherapy drugs (methotrexate and 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.

When you are finished taking the drugs

About 30 days after the last dose of interferon or DA-EPOCH-R, someone will contact you by phone if you are not seen in the clinic to see how you are doing and collect information about any symptoms or side effects you may be having. You will then continue to be followed in the clinic with visits, scans, and labs about every 3 months during year 1, about every 4 months for year 2, about every 6 months for year 3, and then once a year for years 4 and 5. After 5 years, we will continue to see you in the clinic or contact you by phone at least yearly, and you will have scans and other tests only as needed.

BIRTH CONTROL

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment and during study

treatment. If you think that you or your partner is pregnant, please contact the study doctor before taking any further study treatment or undergoing any imaging scans.

Effective forms of birth control include:

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

RISKS OR DISCOMFORTS OF PARTICIPATION

You will have a blood drawn from a vein. This may require a needle stick in your arm or hand, or if you already have an IV catheter in place, we may be able to draw through that. The amount of blood we will draw is up to 5 tablespoons of blood may be drawn before treatment, and at 2, 4, 8, and 12 weeks and every 3 months thereafter for research studies. Blood draws may cause pain, redness, bruising or infection at the site of the needle stick. Rarely some people faint. The study team member may apply numbing cream to the area so that the needle stick won't hurt as much Biopsies of tumor will be done with local or general anesthesia. The tumor biopsies are being performed for two reasons; first to confirm your diagnosis and second to perform research tests on the tumor. Biopsies requiring major surgery (opening the chest or abdomen) will only be done if necessary for medical care and will not be done for experimental purposes. It is important for you to understand that in some cases, biopsies of tumor may be done primarily for experimental purposes. Biopsies for experimental purposes will not be done on children, however, biopsies to confirm diagnosis may be done.

In order to receive EPOCH-R chemotherapy, you will need to have a central venous catheter. This is catheter is placed under the skin of the chest wall and enters a major vein in the chest. There are several types of catheters including those which must be removed after each cycle of chemotherapy (temporary type) and those which may be kept for the duration of therapy (permanent type). These options will be discussed with you. The risks associated with placing some catheters include pain, bleeding, infection and collapsed lung. The long term risks of the catheter include infection, and clotting of your veins. 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 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 symptoms that you experience while taking part in the study.

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

Side Effects of Interferon

Likely:

- Flu-like symptoms with headache, fever, chills, muscle and joint aches
- Redness, pain and swelling at the injection sites
- Lowered white blood cell count that may lead to infection
- Lowered platelets which may lead to an increase in bruising or bleeding
- Lowered thyroid function which may require replacement with an oral medication
- Increase in the liver enzymes
- Gastrointestinal symptoms such as nausea, taste change, and constipation
- Weight loss
- Change in mood such as depression, agitation, anxiety or short temper
- Severe fatigue
- Neurological symptoms such as numbness in your hands and feet, and memory loss
- Decreased sexual function for men

Rare, but serious:

- Fainting
- Hemophagocytic syndrome, a process where your body destroys its own blood cells
- Increased blood clotting
- Heart abnormalities
- Seizure
- Lung infiltrates

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
- 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 Risks

- **Drugs used for the treatment of the 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. It can cause seizures and coma. Other side effects it can cause are usually associated with intravenous administration rather than intrathecal (lumbar puncture administration), but these include liver function abnormalities, inflammation and scarring of the lungs, inflammation of the tissue covering the heart, and severe skin reactions.
  - Cytarabine given by lumber puncture can cause nausea, vomiting, fever, and headaches. Rarely, it can cause weakness and seizures. When given into the spinal fluid, it does not usually cause systemic toxicity, but we will monitor you for low blood counts, and liver function abnormalities, which can occur with cytarabine when given by vein.
- **Secondary malignancy (EPOCH-R):**

  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. 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. If you are a woman

and become pregnant while on this study, treatment will be stopped immediately. A safety visit will be completed within 30 days following the stop of treatment and then you will be taken off the study.

- **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 are receiving EPOCH-R, and 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.

  Interferon may also cause decreases in WBCs. However, these are usually not associated with severe infections. Because interferon itself causes fever, you should not be concerned if you have a fever after the interferon. However, if you have a persistent fever (more than 12 hours after your interferon dose), you should call your doctor.

  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. For more information about risks and side effects, ask your study doctor**.**

- **Complications of treatment in the Central Nervous System (CNS):**

  Complications of Ommaya insertion are uncommon when done by an experienced group 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 becomes necessary for you, the complications of the lumbar puncture or Ommaya insertion and methotrexate instillation will be discussed in more detail.

- **Hepatitis B Reactivation**

  Hepatitis B reactivation has occurred in patients treated with DA-EPOCH-R. Signs of hepatitis B reactivation may include: fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, clay colored bowl movement, joint pain and yellowing of the skin and/or eyes (jaundice). It may lead to long-term health problems, including liver damage, liver failure, liver cancer, and even death.

- **Risks of Lumbar Puncture:**

The lumbar puncture may cause pain at the site where the needle goes in and the spinal fluid is taken. There is a small risk of infection or bleeding. After the lumbar puncture you may get a headache. About a third of adults report a headache after an LP. To minimize the risk of a headache, the doctor will use a small needle and may prescribe bed rest for one or more hours after the procedure. If a headache occurs, it is usually mild and can be controlled by bed rest, drinking lots of fluids and a pain pill, such as acetaminophen. Rarely, the headache is severe and may require additional treatment with a "blood patch". In this procedure, a small amount of your own blood is injected into the lumbar puncture site. This procedure is generally effective in stopping the headache. A rare but serious complication of a LP, if it is done when the pressure inside the head is higher than normal (such as when a brain tumor is present), is known as medullary herniation which can result in death. Increased intracranial pressure is very unlikely to be present. The LP will not be done if there are any clinical indications that you have increased intracranial pressure, a skin infection in the lower back area, or bone malformation of the lower back (including severe scoliosis) which would make a LP difficult. To minimize these risks, the lumbar puncture procedure will be performed by a medical professional specifically trained to do this procedure.

- **Biopsy Risks:**

Once treatment is complete as part of follow-up assessments, you may agree to the biopsy now and change your mind later. If at any time you do not want to have a biopsy done, please tell us, it will not affect your care. If you agree to have the biopsy, you will be asked to sign a separate procedure consent before you have the procedure(s). The likely side effects include discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion. Bleeding from the site of the needle insertion is a less likely risk. Rarely, significant infection or bleeding from this procedure, allergic reaction to the anesthetic, or formation of a scar at the site of needle entry occurs. If you will have sedation with the procedure, these risks will be discussed with you prior to the procedure. You will be asked to sign a separate consent form prior to any biopsy procedure.

- **Risks of Bone Marrow Aspiration:**

These procedures usually cause only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site. A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow biopsy. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. As the bone marrow liquid is taken from the bone, there may be a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all patients experience discomfort. The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.

- **Risks of Radiation Exposure:**

If you receive Interferon

During your participation in this research study, you may be exposed to radiation from up to eight (8) CT scans and two (2) PET Scans to assess your disease and up to one (1) optional CT guided each year. The amount of radiation exposure from these procedures is equal to approximately 12.4 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." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans that you get in this study will expose you to roughly the same amount of radiation as 41.3 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is *1.2* out of 100 (1.2%) and of getting a fatal cancer is *0.6* out of 100 (0.6%).

If you receive DA-EPOCH

During your participation in this research study, you may be exposed to radiation from up to four (4) CT scans and two (2) PET Scans to assess your disease and up to one (1) optional CT guided each year. The amount of radiation exposure from these procedures is equal to approximately 7.2 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." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans that you get in this study will expose you to roughly the same amount of radiation as 24 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.7 out of 100 (0.7%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

- **Risks related to MRIs:**

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

- **Risks related to Gadolinium enhanced MRI**

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes. It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

Risks: The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level. Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not

clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your study.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

As a result of participating in this investigational treatment program, you will receive evaluation and treatment of your LYG. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. In addition, the knowledge gained from this study may help others in the future who have cancer.

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. Treatment with other chemotherapy.
2. Radiation treatment may control tumor growth in local areas such as lymph nodes, bones and lung. However, this approach will not effectively treat disease which is outside the area that is being irradiated.
3. Surgery can be used to remove disease from local areas but is not useful for long-term control when the disease has spread.
4. If you decide to have no therapy for your disease, therapy may be started at a later time. However, in general, waiting to start therapy may decrease your potential benefit to therapy.
5. If your disease has progressed, you also have the option to receive no further treatment and seek only treatments that will make you comfortable.

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
- if you become pregnant

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 cannot 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, 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 purpose. 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 the research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

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

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 are 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.

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

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, Christopher Melani, M.D., 240-760-6057, christopher.melani@nih.gov . 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

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Signature of Parent/Guardian *(as applicable)*	Print Name of Parent/Guardian	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Witness:

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: _____.