PRINCIPAL INVESTIGATOR: Mark Roschewski, M.D.

STUDY TITLE: Phase 1 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid (VIPOR) for Diffuse Large B-cell lymphoma involving the Central Nervous System

STUDY SITE: NIH Clinical Center

Cohort: Treatment - Affected Patient

Consent Version: 07/10/2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

[redacted]

KEY INFORMATION ABOUT THIS RESEARCH

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). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have B-cell lymphoma in the central nervous system (CNS) that does not respond to treatment or response to treatment does not last very long or there is no standard treatment for you.

The main purpose of this research study is to learn if it is safe to give individuals with these cancers the drugs: venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (VIPOR). We also hope to learn if this combination of drugs may work in the treatment of aggressive B-cell lymphomas with involvement of the central nervous system (CNS).

The drugs in the VIPOR regimen have each been approved and used either alone or in combination to treat types of lymphoma, however, the use and combination of the drugs in this study is investigational. An "investigational drug" is a drug or combination of drugs that are being tested and is not approved in the United States by the U.S. Food and Drug Administration (FDA).

There are other drugs and treatments, such as other chemotherapy regimens, radiation therapy, single-agent targeted therapy, and/or approved forms of immunotherapy, that may be used for your disease. These can be prescribed by your regular cancer doctor if you are not in this study. These drugs all work in different ways in the body as compared to the study drugs and with different side effects. If you would prefer other drugs or treatments, you should consider not joining this study.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- Treatment will be given in cycles, each cycle is 21 days (3 weeks).
- Obinutuzumab will be given by IV infusion on days 1 and 2 of every cycle
- You will take by mouth once a day:
  - Lenalidomide on days 1-14 of every cycle
  - Ibrutinib on days 1-14 of every cycle
  - Venetoclax on days 1-14 of every cycle
  - Prednisone on days 1-7 of every cycle
- Prior to each infusion, you will receive premedication to help lessen or prevent some side effects.
- You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death. Examples of some of the side effects that you may have include: changes in blood counts (such as low red or white cells), gastrointestinal (such diarrhea, nausea, vomiting), rashes, fatigue, and infections. Since this is the first time that these drugs are being administered together, there may be side effects that we cannot predict.
- You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and to see if the treatment is having any effect on your disease. We will also collect required samples from you (including blood, bone marrow, and tumor biopsies) for both clinical and research purposes. We may also collect saliva or cheek swabs for research.
- After the study treatment has ended, we will need to see you at the NIH Clinical Center or be seen by a local oncologist periodically for up to about 10 years to assess your health and to determine what impact, if any, the study drugs may have had on your disease and then annually as your doctor feels is appropriate. If your disease worsens, or you need to start a new anti-cancer treatment, we will continue to follow-up with you by phone to see how you are doing until we complete the main research goals of the study, which we expect will take 10 years.
- Because of the possibility of potential harm to an unborn child, if you are capable of becoming pregnant or you can father children and have a partner who may become pregnant you MUST use birth control from the time you start treatment, throughout therapy (including interruptions in therapy), and for 90 days after the last dose venetoclax, 3 months after the last dose ibrutinib, 18 months after the last dose of obinutuzumab if you are a person who can become pregnant and 6 months after the last dose of obinutuzumab if you are a person who can father children, and 28 days after the last dose of lenalidomide (whichever is longer).

Just as we do not know what side effects you might have, we cannot know if you may benefit from taking part in this study. The potential benefits could include shrinking of your tumor or

lessening of your symptoms, such as pain, that are caused by cancer. If you do not benefit, this study and the results from our research will help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

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

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

In this research study, the goal is to learn if it is safe to give the drugs: venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (VIPOR) to treat individuals with your type of cancer. We also hope to learn how this combination of drugs may treat aggressive B-cell lymphomas with involvement of the central nervous system (CNS).

The drugs in the VIPOR regimen have each been approved and used either alone or in combination to treat types of lymphoma, however, the use and combination of the drugs in this study is investigational. An "investigational drug" is a drug or combination of drugs that are being tested and is not approved in the United States by the FDA.

- Venetoclax (VENCLEXTA™) is a drug that targets a specific protein in the body called BCL-2. When normal cells are damaged or old, your body tells them to self-destruct. This natural process is called apoptosis. In some lymphomas, BCL-2 may build up and prevent cancer cells from self-destructing naturally. By targeting BCL-2 with venetoclax, the process of apoptosis may be restored, allowing your body to destroy cancer cells.
- Ibrutinib (IMBRUVICA®) is a type of drug called a kinase inhibitor. Kinases are proteins inside cells that help cells live and grow. The kinases inhibited or blocked by ibrutinib inside the tumor cell may stop the growth of the tumor and may stop the function of cells in your immune system which are supporting the tumor. By blocking this, it is possible that the study drug will kill cancer cells or stop them from growing.

- Prednisone is a standard agent, often referred to as a steroid, that is given together with other medications in many lymphoma regimens. It is also commonly given as a premedication to lessen or prevent infusion-related side effects from some treatments. It is not fully known how it works in combination with treatment, but has been shown to increase cancer cell death in some lymphomas and will be used in this study.
- Obinutuzumab (GAZYVA®) is a type of drug called a "monoclonal antibody." It is believed that obinutuzumab works by targeting a specific protein in the body called CD20. CD20 is found on the surface of B-cells in the body, often in high amounts in some types of lymphoma. By using obinutuzumab to target CD20 and attach to it, it may work by causing the cell to die or by signaling your immune system to destroy the cancer cells.
- Lenalidomide (REVLIMID®) is a type of drug called an "immunomodulatory agent," meaning it can change or control the way the immune system works. It is believed that lenalidomide works by affecting the body's immune system and by directly attacking the cancer cells. Lenalidomide may work by stopping cancer cells from developing, by stopping blood vessels growing in cancer, and by helping part of the immune system to attack the cancer cells.

WHAT WILL HAPPEN DURING THE STUDY?

The screening process showed that you are eligible to participate in the study, and if you choose to be in it, you may need to have a few additional standard tests completed if not done recently. If any of the screening tests need to be repeated and show that you have become ineligible, you will not be able to continue with this study.

You will be seen at the NIH at least every 3 weeks while on the treatment to have tests to access your health. IV drug infusions will be done on Day 1 and 2 of each cycle.

You will need to have blood work taken weekly during treatment, either at the NIH or at a local physician's office with results sent in to the team.

VIPOR Treatment

Treatment will be given in cycles, each cycle is 21 days (3 weeks) for up to 6 cycles.

The treatment schedule is described below:

- Venetoclax: take by mouth once a day on days 1-14 of each cycle. Venetoclax tablets should be taken with a glass of water and should be taken with food. Do not break or chew the tablets.
- Ibrutinib: take by mouth once a day on days 1-14 of each cycle. Ibrutinib capsules should be taken with a glass of water, with or without food. Do not open, break or chew the capsules.
- Prednisone: take by mouth once a day on days 1-7 of each cycle. Prednisone tablets should be taken with a glass of water, with or without food. Do not break or chew the tablets.
- Obinutuzumab: IV infusion on days 1 and 2 of each cycle. Prior to each infusion you will receive premedication to help lessen or prevent some side effects.

- Lenalidomide: take by mouth once a day on days 1-14 of each cycle. Lenalidomide capsules should be taken with a glass of water, with or without food. Do not open, break or chew the capsules.

You will receive a supply of each of the oral medications to take at home on the days you are not seen in the clinic. Each of the oral drugs should be taken at about the same time each day, with or without food as described above. All the drugs can be taken at the once. If you do not remember to take all or any of the medications, do not make-up the dose or take extra the following day to make-up for the missed dose.

All medications should be stored at room temperature – not exposed to too high or low temperatures (that is, NOT in the refrigerator, freezer, bathroom, or in the car for a long period of time). We will ask you to bring any leftover supply of study medications to each clinic visit. You must **NEVER** share lenalidomide (or other study drugs) with someone else.

Certain medications and/ or live vaccines, need to be used with caution or avoided altogether while you are participating on this study. If any physician other than the study team prescribes a medication or vaccine for you for another condition, or you take any new over-the-counter medications, vitamins or herbal supplements, you must tell us and check with us prior to starting. This is important because the interaction of some medications may cause serious side effects and/or may still be unknown. You should also avoid grapefruit products and Seville oranges as these may affect how your body processes the study medications. Supplements such as fish oil and vitamin E preparations should be avoided. Your study team will discuss what medications to avoid during your study participation.

Study Procedures

Similar to the tests done at the beginning of the study to determine eligibility, the following will be done to see how you are doing and how cancer may be responding to treatment:

Clinical Assessments and Procedures:

- History and physical exam, including obtaining information about how you function in your daily activities, side effects and symptoms, and a review of your medications: before starting treatment, weekly, and at the end of treatment or when your disease gets worse.
- Vital signs and weight taken before starting treatment, weekly, and at the end of treatment.
- Eye Exam: during this exam you may have dilating drops placed in your eyes to enlarge the size of the pupils before starting treatment or when your disease gets worse.
- Standard blood and urine tests: before starting treatment, and before the start of every cycle
    - Tests to measure your liver, kidney, and thyroid function, white blood cells, red blood cells and platelets, and blood electrolytes (weekly each cycle as well).
    - If you are able to get pregnant and you are not already known to be pregnant, you will also have a pregnancy test done weekly for the first cycle, and at the end of treatment or when your disease gets worse (this may be done by blood or urine test).

  - To check for cytomegalovirus (CMV) and Epstein-Barr virus (EBV)- only before starting treatment.
  - If you have hepatitis B infection that is not active, will have additional monitoring for hepatitis on a monthly basis during study treatment. During the follow-up portion of the study, hepatitis monitoring will occur at each scheduled follow-up time point: End of Treatment, 30 Day Post-Treatment Safety Visit; and every 3 months for 12 months after the last cycle of therapy.

- Imaging to show all sites of disease, including CT and brain MRI and 18F FDG PET scans on cycles 1, 3, and 6 and if/when your disease gets worse:
  - Computer tomography (CT) scan, a series of x-ray images of your chest, abdomen, and pelvis.
  - 18F FDG PET scan. A Positron Emission Tomography scan or PET scan for short lets doctors see the activity of cells in specific tissues of the whole body. A sugar, which is attached to a chemical that gives off a signal, is injected into you intravenously before the scan. The scanner records the signals through the body.
  - MRI (magnetic resonance imaging): MRI uses a strong magnetic field and radio waves to take pictures of the body. We will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner for about 45 minutes. You may be asked to lie still for up to 15 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.
  - It is very important that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.
  - We may place a bar in your mouth to help keep your head still.
- Assessment to see if you are at risk for a blood clot that starts in your vein and could lead to serious problems to your blood supply (venous thromboembolism), only before starting treatment.
- A bone marrow aspiration and/or biopsy will be done prior to starting treatment, after cycle 6 if positive at baseline or when your disease gets worse. These are done by numbing your hipbone using a small needle containing local anesthesia, and then a needle will be put into the hipbone, and a small amount of bone marrow will be taken out through the needle.
- Lumbar puncture ("spinal tap") or Ommaya tap to take cerebral spinal fluid (CSF) samples. Lumbar puncture involves inserting a small needle into your lower back to sample CSF. If you have an Ommaya reservoir, an Ommaya tap is when a small needle is inserted into the small reservoir under the skin of your scalp to sample CSF.

Additional research testing

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of research only.

- Blood Samples:
  - Blood will be collected: before starting treatment, at the start of every cycle, and at the end of treatment or when your disease gets worse and during follow-up (not 30 day safety follow-up).
  - Pharmacokinetic (PK) blood samples (about 0.2 teaspoons) collected to look at levels of some of the study drugs in the body. These samples will only be collected in some patients at the request of your doctor. These samples would be done as follows:
    - Several times on day 1 of cycle 1 (up to 18 hours after receiving study drug that day).
- Tissue Samples: If tissue from your original diagnosis and/or from a procedure for your disease is available (taken either before or during the study), this may also be collected for the study.
- Cerebrospinal fluid (CSF): If an Ommaya reservoir is already in place, then CSF samples may be used for research.
- Saliva or Buccal Swab Samples: Sometimes after you start on the study and before your first dose of any study drug, a saliva sample or buccal swab sample will be collected for the study to allow us to look at your normal DNA. In some cases, this might also be done by a blood sample.
- Biopsies:

  The biopsies are an optional part of the study and you will only be asked to do so if it is felt to be safe. We will ask you to undergo a tumor biopsy at the beginning of the study, and again if your disease should come back or get worse during or after treatment on this study. The tissue is being collected for special research tests. Usually tissue can be obtained safely and comfortably with local anesthesia. If you require sedation before undergoing a biopsy, you will be informed of the risks and you will be asked to sign an additional consent prior to undergoing the procedure. Biopsies will NOT be done on this study if they require general anesthesia. We may ask that you have ultrasound and/or CT scan to help clearly locate your tumor when doing a biopsy.

  Your doctor or the study team will discuss the biopsies with you. The optional biopsies to be performed are exclusively for research purposes and will not benefit you. They might help other people in the future.

  You may agree to biopsies now and change your mind later. If at any time you do not want to have a biopsy done, please tell us. If you do not want the biopsy, this will not interfere in any way with your treatment.

A part of all biopsies done may be sent to the clinical laboratories for a standard of care evaluation to confirm the stage and grade of your disease, portions of the samples will also be used for research tests.

The following sections describe studies to be done on your samples for research:

What tests will be done on my samples?

All of your samples collected for research purposes on this study (such as the tumor and normal tissue) may be used to check for levels of some of the study drugs in the body, to look at your body's immune response to treatment, and to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. RNA (also called ribonucleic acid) carries the instructions from the DNA to the parts of your cells that make proteins.

To look at your DNA and RNA, we may do what is called "DNA and RNA sequencing." This is where we will do special tests in the lab to look at the sequence, or order, of how your DNA and RNA are put together. This is what makes you unique.

To determine which parts of the DNA and RNA have mutated, we will compare the DNA and RNA in your tumor cells to the DNA and RNA from normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA and RNA that are common to a particular type of tumor.

To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include looking in detail at the parts of the genes that produce specific proteins.

However, you should know that 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 or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described later in this consent form in the section for "Return of research results."

When you are finished taking the drugs (treatment)

When you finish taking the study treatment, you will be asked to return to the clinic or be seen by your local physician with results sent in, as soon as possible after end of treatment and at about 30 days after the end of the last cycle of treatment (this could mean two separate visits or a single visit at 30 days after the last cycle of treatment has ended). At these/this visit we will repeat most of the tests and procedures above, and see how you are doing. We will continue to contact you more frequently after this visit if you continue to experience side effects from the medications.

After this visit, we will ask you to return to clinic or be seen by your local physician with results sent in, at about the following times after treatment for as long as your disease does not recur (come back) or gets worse: every 3 months in year 1 post-treatment, every 4 months in year 2, every 6 months in year 3, and once each year in years 4-10. We may contact you by phone (or

mail, email, etc.) more frequently between visit to see how you are doing. After 5 years, we may contact you to see how you are doing for a total of 10 years after stopping treatment.

If at any time your disease recurs (comes back) or gets worse, we will ask you to return to the clinic for one more visit to repeat some of the tests and procedures above, and to have an optional tumor biopsy (if safe to do so).

After the time that your disease gets worse, we will continue to contact you by phone (or mail, email, etc.) to see how you are doing once a year for up to 10 years.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for 10 years.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 16 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Risks and side effects related to the treatment and the procedures on this study are identified below:

Venetoclax

Likely:

- Low white blood cell count (cells that help fight infection) (neutropenia)
- Low number of red blood cells that can cause tiredness and shortness of breath (anemia). May require a blood transfusion
- Low platelet count (cells that help blood to clot) (thrombocytopenia)
- Diarrhea
- Nausea
- Fatigue (feeling tired)
- Upper respiratory tract infection

Less Likely:

- Low white blood cell counts with fever (febrile neutropenia)
- Vomiting
- Constipation
- Fever (pyrexia)
- Swelling of the hands and feet (peripheral edema)
- Pneumonia
- Chemical imbalance in blood (including low potassium, high levels of uric acid, lactate dehydrogenase)
- Back pain
- Headache
- Cough
- Dizziness or fainting (syncope)
- Infection (including lower respiratory infection)
- Low levels of oxygen in the blood (hypoxia)

Rare but Serious:

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures (Tumor Lysis Syndrome)
- Liver failure (hepatic failure)
- Infertility in individuals who can father children
- Severe infection throughout the body (sepsis)

Ibrutinib

Likely:

- Low white blood cell count (cells that help fight infection) (neutropenia)
- Increase in frequency of loose or watery stools (diarrhea)
- Nausea
- Rash
- Muscle and joint pain (musculoskeletal pain)
- Bruises
- Low number of red blood cells that can cause tiredness and shortness of breath (anemia). May require a blood transfusion

Less Likely:

- Low platelet count (cells that help blood to clot) (thrombocytopenia)
- Vomiting
- Constipation
- Joint aches (arthralgia)
- Muscle spasms
- Swelling of the hands and feet (peripheral edema)
- Headache
- High blood pressure (hypertension)
- Fever (pyrexia)
- Pneumonia
- Sores in the mouth (stomatitis)
- Sinus infection (sinusitis)
- Common cold
- Skin infection

Uncommon:

- Increase in lymphocyte count (lymphocytosis)
- Increase in white blood cell counts (leukocytosis)
- Increased level of uric acid in the blood (hyperuricemia)
- Low white blood cell counts with fever (febrile neutropenia)
- Severe infection throughout the body (sepsis)
- Inflammation within the lungs that may lead to permanent damage (interstitial lung disease)
- Urinary tract infection
- Abnormal heart rhythms (see additional information below)

- Dizziness
- Blurred vision
- Nosebleed (epistaxis)
- Small red or purple spots caused by bleeding under the skin (petechiae)
- Non-melanoma skin cancer (including basal cell or squamous cell carcinoma)
- Skin redness (erythema)
- Breaking of the nails (onychoclasis)

Rare but Serious:

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures (Tumor Lysis Syndrome)
- Bleeding around the brain (subdural hematoma)
- High white blood cell count with abnormal clumping that can lead to bleeding (leukostasis syndrome)
- Swollen face, lip, mouth, tongue or throat (angioedema)
- Liver failure (see additional information below)
- Itchy rash (urticaria)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson Syndrome)
- A rare and usually fatal viral disease in the brain, Progressive Multifocal Leukoencephalopathy (PML), which may present with symptoms such as weakness, paralysis, vision loss and/or impaired speech (see additional information below)

Obinutuzumab

Likely:

- Low white blood cell count (cells that help fight infection) (neutropenia)
- Low platelet count (cells that help blood to clot) (thrombocytopenia)
- Low number of red blood cells that can cause tiredness and shortness of breath (anemia). May require a blood transfusion
- Low white blood cell counts with fever (febrile neutropenia)
- Fatigue
- Infusion reactions (see additional information below)
- Fever (pyrexia)
- Nausea
- Vomiting
- Diarrhea
- Constipation

- Decreased appetite
- Cough
- Infections, the most common include: upper respiratory tract infection, sinusitis, urinary tract infection
- General weakness (asthenia)
- Joint or muscle pain (arthralgia or musculoskeletal pain)

Less Likely:

- Low number of other white blood cells, cells that help fight infection; with or without fever (including granulocytopenia, leukopenia, lymphopenia)
- Basal cell carcinoma
- Heartburn or indigestion (dyspepsia)
- Sore throat (nasopharyngitis, pharyngitis)
- Joint aches (arthralgia)
- Pain in extremity
- Nasal congestion
- Itching (pruritus)
- Chemical imbalance in blood (including low albumin calcium, phosphate, potassium and sodium, and high levels of liver enzymes)

Rare but Serious:

- Effects on the heart (see additional information below)
- Progressive Multifocal Leukoencephalopathy (PML), a rare and usually fatal viral disease in the brain, which may present with weakness, paralysis, vision loss and/or impaired speech (see additional information below)
- In patients with a history of hepatitis B infection, taking obinutuzumab could cause hepatitis to return, which may present with worsening of fatigue and yellow discoloration of the skin or eyes (see additional information below)

Lenalidomide

Likely:

- Low number of white blood cells, cells that help fight infection; with or without fever (leukemia, neutropenia, febrile neutropenia, granulocytopenia, lymphopenia)
- Low number of red blood cells that can cause tiredness and shortness of breath (anemia). May require a blood transfusion
- Low platelets, cells that help blood to clot (thrombocytopenia)
- Blurred vision Diarrhea
- Pain (upper abdominal pain, abdominal pain, toothache)
- Constipation

- Blood clot within the pulmonary artery or vein within an organ in the body
- Nausea
- Vomiting
- Feeling weak and unwell (asthenia)
- Tiredness (fatigue)
- Swelling (peripheral edema)
- Fever (pyrexia)
- Chills
- Sore throat (nasopharyngitis, pharyngitis)
- Stuffy nose (rhinitis)
- Pneumonia or other infections (pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection, erysipelas, gastroenteritis, herpes simplex, herpes zoster, influenza, lower respiratory tract infection, sinusitis, sepsis, bacteremia)
- Weight loss
- Cataract (cloudiness in the lens of the eye)
- Insomnia (not sleeping well)
- Itching
- Chemical imbalance in blood (hypokalemia [low potassium], hypocalcemia [low calcium], hypophosphatemia [low phosphate], hypomagnesemia [low magnesium], hyponatremia [low sodium])
- Decreased appetite
- High blood sugar (hyperglycemia)
- Dizziness
- Altered sense of taste (dysgeusia)
- Headache
- Abnormal sense of touch (hypothesia)
- Indigestion/heartburn (dyspepsia)
- Shaking (tremor)
- Pain and decreased sensation in nerves (neuropathy, peripheral neuropathy, peripheral sensory neuropathy)
- Cough
- Shortness of breath (dyspnea)
- Nosebleed (epistaxis)
- Dry skin (pruritus)
- Pain including muscles, joints, and non-cardiac chest pain (pain in extremity, pain in limb, arthralgia, back pain, bone pain, muscle spasms, musculoskeletal pain, muscle cramp, chest pain, myalgia)

- Allergic reaction (rash, hypersensitivity)
- Feeling sad (depression)
- Abnormal liver lab tests (alanine aminotransferase increased, gamma-glutamyltransferase increased)

Less Likely:

- Low levels of all types of blood cells – white blood cells, red blood cells and platelets (pancytopenia)
- Heart attack (acute myocardial infarction)
- Abnormal heart rhythm (atrial fibrillation, tachycardia)
- Heart stops working (cardiac failure, congestive heart failure)
- Low oxygen to heart tissue (myocardial ischemia)
- Dry mouth
- Decreased action of intestine
- Bile flow from liver slowed or blocked (cholestasis)
- Fall
- Lowered level of consciousness with drowsiness, listlessness, & apathy (lethargy)
- Destruction of red blood cells (hemolytic anemia)
- Loss of fluids (dehydration)
- Diabetes
- Swelling of blood vessels (vasculitis)
- Redness of the skin (erythema)
- Increase in liver protein that indicates inflammation in body (C-reactive protein increased)
- Breathing disorder (respiratory distress)
- Rapid death of cancer cells where the accumulation of the contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage (Tumor Lysis Syndrome)
- Increased level of uric acid in the blood (hyperuricemia), including gout
- Iron build up in body (iron overload)
- Muscle weakness
- Cancer (acute myeloid leukemia, basal cell carcinoma, squamous cell carcinoma)
- Stroke (cerebrovascular event)
- Tingling of skin (paresthesia)
- Fainting (syncope)
- Mood changes
- Kidney injury (acute renal failure)

- Excessive sweating (hyperhidrosis)
- Bruises (contusions)
- Swelling of skin filled with blood (hematoma)
- High or low blood pressure
- Night sweats
- Blood not getting to extremities (peripheral ischemia)
- Sudden increase in tumor size (tumor flare)
- Blood cancer that causes decreased number of red blood cells, white blood cells, and platelets because they do not develop normally (myelodysplastic syndrome)

Rare but Serious:

- Inflammation of lungs (pneumonitis)
- Over and underactive thyroid (hyperthyroidism and hypothyroidism, respectively)
- Severe allergic conditions, including swelling under the skin (angioedema) and severe skin reactions involving lining of the nose, mouth, stomach and intestines or rash leading to the separation of the top layer of skin (Stevens-Johnson syndrome and toxic epidermal necrolysis, respectively)
- Release of tumor chemicals into blood (tumor lysis syndrome)

Other risks from treatment

- Prednisone:
  - Common side effects include: sleep problems (insomnia), mood changes, increased appetite (which may include gradual weight gain), acne, increased sweating, skin changes (including dry skin, thinning skin, bruising or discoloration), slow wound healing, headache, dizziness/spinning sensation, nausea, stomach pain, bloating, and changes in the shape or location of body fat (especially in your arms, legs, face, neck, breasts, and waist).
  - Rare, but serious: Changes in vision, eye pain, severe changes in mood (such as depression or extreme happiness), bloody or tarry stools, coughing up blood, pancreatitis, very low potassium, and very high blood pressure.
  - Some of these side effects are seen with prolonged and continued use of prednisone. Please contact the study staff if you are experiencing a side effect or think you might be having a severe reaction.
- Acute Graft versus Host Disease: There are reports of graft versus host disease (or "GvHD") in some patients after a bone marrow transplant where new cells attack the body which can result in abdominal pain or cramps, nausea, vomiting, diarrhea, jaundice (yellowing of skin), or skin rash. There have been reports of this in patients who received prior transplant after treatment with some of the drugs in this study.
- Allergic and infusion reactions: Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction, you might develop a rash, difficulty breathing, wheezing when you breathe, sudden low blood

pressure with light-headedness, swelling around the mouth, throat or eyes, a racing heartbeat, and/or sweating. Before starting the study drug, you must tell your study doctor about any drug allergies. You should tell a member of the study team right away if you have any allergy symptoms listed above.

- Bleeding effects: You may experience bruising or nose bleeds during dosing. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur sometimes resulting in death. If you take medicines or supplements that increase your risk of bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or medicines used to prevent or treat blood clots or stroke, some medications, including ibrutinib and obinutuzumab, may increase this risk. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib and obinutuzumab. If you have signs or symptoms of severe bleeding in or around the brain (such as sudden severe headaches, weakness in the arms or legs, difficulty speaking or understanding speech, or loss of balance) or if you have signs or symptoms of serious bleeding (such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control), please call the study team right away.
- Effects on the heart: Abnormal heartbeats (atrial fibrillation and/or atrial flutter) and worsening of heart conditions have been reported in patients treated with ibrutinib and obinutuzumab, especially when they also have a history of these and other heart conditions, including increased blood pressure, infections, or had abnormal heartbeat in the past. Atrial fibrillation/flutter is a common type of abnormal heartbeat. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of breath. If you develop any of these symptoms while on the study drug, you should tell your study doctor immediately.
- Hypertension: Hypertension, also called high blood pressure, has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. You should let the study team know if you have any of the symptoms of high blood pressure which may mean that you have developed hypertension or that your hypertension is getting worse.
- Immunization: Please discuss with the study team prior to receiving any immunizations as receiving a live vaccine during or soon following treatment could result in side effects, or make them less effective.
- Infections:
    - You may experience viral, bacterial, or fungal infections during treatment, and this has been seen with treatment with the medications used in this study. Some of these infections have led to hospitalization and death. Contact your study doctor immediately if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath – they could be signs of an infection or any other signs or symptoms of a possible infection.

- A rare and usually fatal viral disease in the brain, Progressive Multifocal Leukoencephalopathy (PML), has been reported in patients treated with ibrutinib, and obinutuzumab. If you experience symptoms such as weakness, paralysis, vision loss and/or impaired speech, you should tell the study team immediately.

- Interstitial lung disease: Interstitial lung disease is a group of lung disorders in which the tissues become inflamed and may become damaged. Interstitial lung disease is not associated with infections (e.g., bacteria, viruses, fungi) and has been reported in patients treated with ibrutinib. You should report to your physician if you have cough, any signs of new or worsening respiratory symptoms such as shortness of breath or difficulty breathing.
- Liver failure and hepatitis:
  - Rare cases of liver failure have been reported in patients treated with ibrutinib. Symptoms of liver failure include yellowing of the eyes and skin (jaundice), itching of the skin, dark colored urine, gray or clay-colored stools, confusion, nausea, loss of appetite, fatigue or diarrhea. You should tell your study doctor immediately if you have any of these symptoms which may suggest liver disease. Your study doctor may be able to diagnose and provide you required medical care.
  - In patients with a history of hepatitis B infection, taking obinutuzumab could cause it to return. You should not receive obinutuzumab or any of the study medications if you have active hepatitis B or C liver disease. We will screen you at baseline for hepatitis and monitor you during the study. You should tell your study doctor immediately if you have any of these symptoms which may suggest hepatitis: worsening of fatigue and yellow discoloration of the skin or eyes.
- Lymphocytosis and leukostasis: You may experience an increase in the number of lymphocytes, which is a type of white blood cell, in your blood (lymphocytosis). This may occur in the first few weeks of dosing and you should not assume that this increase in white blood cells means your disease became worse. This increase may last for several weeks to months. An increased number of white blood cells in your bloodstream may change the blood flow, resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in participants who received ibrutinib.
- Medication interactions:
  - If any physician other than the study team prescribes medication for you for another condition, or you take any new over-the-counter medications, vitamins, herbal supplements, or other, you must tell us and check with us prior to starting in most cases. This is important because the interaction of some medications may cause serious side effects and/or may still be unknown.
  - You should also avoid grapefruit products, Seville oranges, and starfruit as these may affect how your body processes the study medications.
- Rash: A maculopapular rash (flat, red areas on the skin with small bumps) has been commonly reported in patients treated with ibrutinib alone or in combination with other drugs. Most rashes are mild to moderate in severity and begin 2-3 weeks or longer after starting ibrutinib. There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction, or "SCAR", involving more than 50 % of the body) or rash

with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas of the body (Stevens-Johnson syndrome). These skin rashes could be life-threatening. Notify us immediately if you develop a rash that spreads quickly, or if you notice peeling of your skin, with or without ulcers or sores in your mouth.

- Secondary cancers: Patients with cancer have a higher risk of developing another or second new cancer when compared to people without cancer. These include solid tumors, skin cancer, and cancers of the blood. Participants should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers. The study team will be checking you for any possible new cancers that may develop during or following your treatment.
- Tumor Lysis Syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your study doctor may do blood tests to check for TLS.
- Blood donation: You must **NEVER** donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study.

Risks from tests and procedures

- Blood draws: The possible side effects of drawing blood include pain, bleeding, bruising, dizziness, light-headedness, fainting and, on rare occasions, local blood clot formation or infection with redness and irritation of the vein. Up to about a little over 6 tablespoons of blood may be collected at any day, up to about 16 tablespoons may be collected within 8 weeks.
- Urine collection: There are no known physical risks of collecting urine.
- Saliva Capture and/or Buccal Swab collection: There is no risk associated with the saliva capture collection. There are no physical risks with the buccal swab, but you might experience momentary discomfort.
- Tumor biopsy: 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.
- Eye Exam: During this exam you may have drops placed in your eyes to enlarge the size of the pupils (dilating drops). The drops take about 15 to 20 minutes to work and allow the back of the eye to be examined with a lamp. You may experience the effects of the dilating drops for a few hours after this exam. Your vision will likely be blurry, and you may have trouble focusing on near objects. The drops may also cause light sensitivity. The dilating drops in rare cases may also cause increased pressure in the eye, leading to nausea and pain. In some cases, you may require additional anesthesia to ensure a complete exam is possible. Your doctor will discuss the risks of any additional anesthesia if it is necessary.

- Bone marrow: 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.
- 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.
- Fluid Collection by Ommaya Reservoir: Withdrawing spinal fluid from an Ommaya Reservoir conveys a small risk of infection and a minor amount of discomfort from the needle puncture.
- Imaging:
  - CT and PET Scan: If contrast dye is used, there is a risk for allergic reaction to the dye. Participants might experience hives, itching, headache, difficulty breathing, increased heart rate, and swelling. If you are allergic to or sensitive to medications, contrast dye, iodine, or shellfish, please notify your study doctor. If you have had kidney failure or other kidney problems in the past, please notify your study doctor.
  - CSF may also be sampled by an Ommaya tap.
  - MRI

    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. In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

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 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 for gadolinium enhanced MRI scans:

Procedure: During part of the MRI you may receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for medical purposes.

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” which 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 not normal or if you received gadolinium within the previous month.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA recently 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 than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain.

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 studies.

What are the risks related to pregnancy?

If You Can Become Pregnant

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will be required to use **TWO** reliable forms of birth control, one highly effective method and one additional effective method at the same time or practice complete abstinence from heterosexual intercourse for at least 28 days before starting study treatment, during study treatment (including interruptions in therapy), and after you finish study treatment (the restricted period) as follows:

- Venetoclax: 90 days after the last dose
- Ibrutinib: 3 months after the last dose
- Obinutuzumab: 18 months after the last dose
- Lenalidomide: 28 days after the last dose

If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact the study team as soon as possible.

If You Can Father Children

You must **NEVER** donate sperm or semen while you are participating in this study and for at least 28 days after the study drugs are stopped.

If your partner can become pregnant, you will be required to use a condom **and** one highly effective method or practice complete abstinence from heterosexual intercourse throughout therapy (including interruptions in therapy), and after discontinuation of therapy (the restricted period) as follows:

- Venetoclax: 90 days after the last dose
- Ibrutinib: 3 months after the last dose
- Obinutuzumab: 6 months after the last dose
- Lenalidomide: 28 days after the last dose

There may be unknown risks to a fetus or risks we did not anticipate. If you think your partner has become pregnant during the restricted period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

If You Can Become Pregnant or Father Children

The following are the acceptable birth control methods:

Highly effective options:

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

- tubal ligation
- vasectomy

Additional effective method options:

- male latex condom
- diaphragm
- cervical cap

If you think that you or your partner is pregnant, you must stop taking the study medications and tell your study doctor or nurse **IMMEDIATELY**.

In addition, if a person that can have children is caring for you, that person should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation each year and maximum is in the first year from CT scan of the chest, abdomen and pelvis, and FDG PET scan, and 2 CT-guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 17.7 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, and ^{18}F-FDG PET scan that you get in this study will expose you to roughly the same amount of radiation as 59 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 1.8 out of 100 (1.8%) and of getting a fatal cancer is 0.9 out of 100 (0.9%).

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Privacy Risks Associated with Genetic Testing

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

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

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

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

Protections against misuse of genetic information

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

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because the knowledge gained from this study may help others in the future who have cancer.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether to be in this study, we will discuss the other options that are available to you. Instead of being in this study, you could:

- choose to be treated with radiation or with drugs already approved by the FDA for your disease
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have

learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

The results of the standard tests performed as part of the research are available to you as part of your medical record.

In addition, when we are examining your DNA, it is possible that we could find changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings":

- 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.

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic 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 that is believed to be clinically important based on medical standards at the time that we first analyze your results, we will contact you. This could be many years in the future. We will ask you to provide another sample to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered genetic counseling here at NIH (no charge) or referral to an outside genetic healthcare provider (at your expense) to discuss the results.

EARLY WITHDRAWAL FROM THE STUDY

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 worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you become pregnant
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if you had hepatitis B in the past and it becomes active again
- if the study is stopped for any reason

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.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding B-cell lymphoma, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

Will your genomic data be shared outside of this study?

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

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.

PAYMENT

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

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

REIMBURSEMENT

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

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed

after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

COSTS

Will taking part in this research study cost you anything?

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

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.

CONFLICT OF INTEREST (COI)

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

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

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

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

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 researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that,

despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

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

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that 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 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.

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. mark.roschewski@nih.gov or 240-760-6183. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

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

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

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

Signature of Witness	Print Name of Witness	Date

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

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

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