PRINCIPAL INVESTIGATOR:	Christopher Melani, M.D.
STUDY TITLE:	Phase 1 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid in Combination with Polatuzumab (ViPOR-P) in Relapsed/Refractory B-cell Lymphoma
STUDY SITE:	NIH Clinical Center
Cohort:	Standard Affected Subject
Consent Version:	08/05/2026

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Christopher Melani, M.D.
Phone: 240-760-6057
Email: christopher.melani@nih.gov

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 relapsed and/ or refractory B-cell lymphoma including aggressive diffuse large B-cell lymphoma (DLBCL) and its subtypes or indolent B-cell lymphomas- excluding mantle cell lymphoma (MCL), and chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL). You have received at least one other type of cancer treatment before that did not work.

The purpose of this study is to learn if it is safe to give the drugs polatuzumab and venetoclax in combination with ibrutinib, prednisone, obinutuzumab, and lenalidomide to patients with your disease. We also hope to begin to learn about how these drugs may work together to treat B-cell lymphomas.

Although each is approved and used either alone or in combination to treat types of lymphoma, the use and combination of the drugs in this study is investigational. An "investigational drug" is a drug or combination of drugs that is 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 that may be used for your disease, and 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, such as alternative chemotherapy regimens, radiation therapy, single-agent

targeted therapy and/or approved forms of immunotherapy, you should consider not joining this study.

Prior to taking part in this study, we will find out if you are fit, which is called screening. If you are not, you will be taken off the study.

The screening portion will include checking your health history, taking a complete physical exam, performing blood and urine tests, electrocardiogram, and a review of a biopsy sample that you might have given before or we will take a fresh bone marrow biopsy, and imaging (such as CT and/or MRI, and PET/CT scans).

There is no benefit to you from the screening itself; however, it is required to take part in the main study, which does offer the possibility of benefit.

You may choose not to have screening done and receive care for your cancer from your regular doctor. However, to take part in the main study, screening must be performed. The risks from the screening tests include those associated with blood draws, bone marrow aspiration/biopsies, and radiation from imaging procedures. These risks are similar to those from tests you would receive prior to starting any treatment for your cancer.

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

- In the first part of the study (dose escalation portion), we want to find out the highest dose of polatuzumab and venetoclax that is safe to use with ibrutinib, prednisone, obinutuzumab, and lenalidomide. We will test increasing doses of polatuzumab and venetoclax in small groups of patients. We also want to find out what kind of side effects these medications might cause. After the first part is done, we will enroll additional patients in a second part of the study (dose expansion portion) to learn more about whether these study medications can shrink your tumor(s).
- If you are eligible to receive treatment, the study drugs will be given as follows for up to 6 cycles of 21 days each. You will take lenalidomide and ibrutinib by mouth once each day on days 1-14 of each cycle. You will take venetoclax by mouth once each day on days 2-14 of each cycle. Prednisone will be taken by mouth once each day on days 1-7 of each cycle. Obinutuzumab will be given by IV infusion on days 1 and 2 of each cycle. Prior to each infusion you will receive premedications to help lessen or prevent some side effects. Polatuzumab will be given by IV infusion on day 2 of each cycle. You will come to the NIH on days that you receive medications by IV.
- 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 5 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. After 5 years, we will want to see you annually to monitor your disease status until your disease gets worse or you start need to start a new anti-cancer treatment. If your disease worsens, or you start need to start a new anti-cancer, 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 4-5 years.
- Because of the possibility of potential harm to an unborn child, if you can become pregnant or you can father a child and your partner is able to become pregnant you MUST use birth control from the time you start treatment, throughout therapy (including interruptions in therapy), and for 18 months after the last dose study drug if you can become pregnant or for 6 months after the last dose of study drug if you can father a child and your partner is able to become pregnant.

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. 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 treatments they would want to receive. 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.

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?

B-cell lymphoma is a cancer of certain white blood cells (called lymphocytes) that are found in lymph nodes and the cancer affects the lymphatic system. The lymphatic system helps to fight infections and disease. In this research study, the goal is to learn if it is safe to give the drug polatuzumab in combination with venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide to patients with relapsed and/ or refractory B-cell lymphoma including aggressive

diffuse large B-cell lymphoma (DLBCL) and its subtypes and indolent B-cell lymphomas-excluding mantle cell lymphoma (MCL), and chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL).

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

Additional information about each of the study drugs in the ViPOR-P study (V: venetoclax; i: ibrutinib; P: prednisone; O: obinutuzumab; and R: lenalidomide or REVLIMID® and, P: polatuzumab or POLIVY™) is below:

- 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 the cancer, and by helping part of the immune system to attack the cancer cells.
- Polatuzumab (POLIVY™) is a type of drug called an "antibody-drug conjugate," which means the drug is made of an antibody linked to an agent that is toxic to cells. The

antibody targets a specific protein in the body called CD79b which is found on the surface of B cells, and when the antibody binds to it, the drug-conjugate is taken into the cell and the toxic agent is released in the cell, killing the cancer cell.

All participants in this study will receive each of these drugs so that we can learn more about the side effects when given together. We also hope to begin to learn about how these drugs may work together to treat B-cell lymphomas.

WHAT WILL HAPPEN DURING THE STUDY?

Before you begin the study

We will perform tests and procedures to find out if you are able to participate. All of these tests or procedures are part of your regular care and may be done even if you are not being considered to join the study. If you have had some of these tests or procedures recently, they may or may not have to be repeated. The following tests and procedures are needed to determine whether you are eligible for this trial:

- Medical history: A complete review of your medical history, including obtaining information about your diagnosis and previous treatments, and reviewing information about your other conditions. If you have medical records from another clinic or hospital, you will be asked to get copies of these records, or your study doctor may be able to request them on your behalf.
- Physical exam: This will include taking your vital signs (temperature, blood pressure, heart rate, breathing rate), seeing how you function in your daily activities, any current symptoms of your condition and a review of all medications that you take
- Standard blood and urine tests:
  - Tests to measure your liver, kidney, and thyroid function, white blood cells, red blood cells and platelets, and blood electrolytes
  - Tests to measure how well your blood clots (also called coagulation studies)
  - If you are an individual who is able to get pregnant and you are not already known to be pregnant, you will also have a pregnancy test done. This may be done by blood or urine test. You will not be able to participate if you are pregnant.
  - Tests routinely done in patients with your type of cancer to confirm the status of your disease
  - To check for Hepatitis B and C infection. As part of our study, we will test you for infection with Hepatitis B and C. 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 dose of study therapy.
  - To check for HIV infection: As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV, you will not be able to participate in this study. We will tell you

what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection

- Imaging to show all sites of disease, including CT and/or MRI scans and PET/CT scan
  - CT (Computed Tomography) scan: The CT scanner is a donut-shaped machine that uses x-rays to make computer pictures of the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan, and you will be told to hold your breath. The scan itself will only take a few minutes, and the entire visit will take about 30 minutes.
  - MRI (Magnetic Resonance Imaging): An MRI makes pictures of the inside of your body using strong magnets instead of x-ray energy. At the time of each scan, you will be asked to fill out a screening form to verify that it is safe for you to have the scan. You will also be asked to remove any metallic objects you are wearing (for example, watches, earrings, or piercings). We may ask you to change into a hospital gown. Then, you'll be asked to lie on a narrow bed that will move into the MRI scanner. The scanner is a long, narrow tube that is open at each end. Once you are comfortable, the table will be moved into the scanner. You will need to lie still on the table during the scan. The scan will take about 90 minutes to complete. You will hear normal "hammering" or clicking and squealing noises during the scan. We will give you earplugs or earmuffs to muffle the sound. You will be able to communicate with the technician running the scan the entire time. We will also give you an emergency button to squeeze at any time if you want the scan to stop. During part of the MRI you may receive gadolinium, a contrast agent, through an intravenous (IV) catheter. It will be done for medical purposes.
  - PET (Positron Emission Tomography) Scan: The PET scanner is a donut-shaped machine that uses x-rays combined with a dose of a radioactive material (tracer) to make computer pictures showing the inside of your body. Before the scan, we will give you an injection (shot) of radioactive material into your arm. After the shot, you will need to wait for about 30 minutes for the material to be absorbed by your body. After 30 minutes, you'll lie on a narrow, padded table. We will position your body for the scan. The scan itself is painless and won't make much noise. During the scan, you will need to lie very still. The scan will take about another 30 minutes to complete.
- An electrocardiogram (EKG) of the heart will be done to check the electrical activity and the function of your heart
- 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)
- A sample of tissue from any previous surgery or biopsy will be tested at NCI to confirm your diagnosis, stage, and status of your disease. If no tissue is available, then a biopsy will need to be performed. Usually, tissue can be obtained safely and comfortably with local anesthesia. However, some participants may require conscious sedation. Conscious

sedation is usually given to help someone relax and minimize discomfort. It can be given as a pill, a shot, an IV or even inhaled. You may have to wait up to an hour to start feeling the effects, depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. We will monitor you throughout the procedure.

We will remove you from the study if the tests show you are unable to participate.

ViPOR-P Treatment

You will be seen at the NIH at least every 3 weeks while on the study, and on Days 1 and 2 of every cycle to receive some of the medications by intravenous (IV) infusion-- a small plastic tube is put into a vein in your arm to give you the medication.

Treatment will be given in a series of up to 6 cycles. Each cycle is 21 days (3 weeks).

In order to confirm that the doses are safe, patients will be enrolled and start treatment on study in groups as follows:

- Dose escalation part: First, a group of 3-6 study participants will receive, ibrutinib, prednisone, obinutuzumab, and lenalidomide at fixed doses together with polatuzumab and venetoclax at the starting doses. The doses of polatuzumab and/or venetoclax will be escalated (or increased) in a new group of 3-6 patients, as long as there were no safety issues in the first group. If there are no safety issues in the second group, the dose of polatuzumab and/or venetoclax will be increased again in ongoing groups of 3-6 patients for as long as it is safe to do so, and until the best or highest dose of polatuzumab and venetoclax planned for this study is found. Each group of patients will be monitored closely for side effects by the study staff closely for at least 3 weeks before enrolling the next group and/or moving on to the next doses.
- Dose expansion part: Once the highest safe doses of polatuzumab and venetoclax given together with ibrutinib, prednisone, obinutuzumab, and lenalidomide are found, then the next part of the study will begin. In this part of the study, patients will receive the safest doses of the study drugs as determined in the dose escalation part of the study to learn more about this drug combination and its effect on the treatment of B-cell lymphomas.

The treatment schedule for each study drug is described in more detail here:

- Venetoclax: This is an oral drug, taken by mouth once each day on days 2-14 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: This is oral drug, taken by mouth once each 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: This is an oral drug, taken by mouth once each 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: This is a drug given by IV infusion on days 1 and 2 of each cycle. Prior to each infusion you will receive premedications to help lessen or prevent some side effects.
- Lenalidomide: This is an oral drug, taken by mouth once each 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.
- Polatuzumab: This is a drug given by IV infusion on day 2 of each cycle. On the day of the first dose, you will need to stay in the day hospital for at least 90 minutes after the IV and so that we can monitor your vital signs and laboratory blood tests. If you do not have bad side effects after the first dose, you will only need to be monitored for 30 minutes after the rest of the infusions.

All study participants will take the same doses of ibrutinib, prednisone, obinutuzumab, and lenalidomide. Your dose of polatuzumab and venetoclax will be assigned depending on what dose level is open at the time of your enrollment during dose escalation or the maximum tolerated dose during the dose expansion portion.

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. 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). You will be given a drug diary to help you remember the schedule and to record each dose that you take, if you choose to do so. We will ask you to bring this diary and 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 all together 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. You 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 repeated at least once each cycle, unless otherwise noted, to see how you are doing and how the 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, before the start of every cycle, and at the end of treatment or when your disease progresses
- Vital signs will be taken: before starting treatment, on Day 1 and 2 of every cycle and at the end of treatment or when your disease progresses
- 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 (on Day 8 and 15 of every cycle as well).
  - Tests to measure how well your blood clots (also called coagulation studies, only before the start of every cycle)
  - If you can get pregnant and you are not already known to be pregnant, you will also have a pregnancy test done at least twice each cycle (this may be done by blood or urine test, on Day 15 also).
  - Tests routinely done in patients with your type of cancer to confirm the status of your disease
- Imaging to show all sites of disease, including CT and/or MRI scans: before cycles 3 and 5 and at the end of treatment or when your disease progresses. PET scans will be done if needed to confirm response.
- A bone marrow aspiration and/or biopsy will be done prior to starting treatment to confirm the stage and status of your disease and will be repeated at the end of study treatment if needed to confirm response, if and only if other tests show a complete response. 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.
- Lenalidomide – Revlimid REMS™ Program Participation

  You have been informed of the risk of birth defects. If you can get pregnant, you agree not to become pregnant while taking lenalidomide. For this reason, lenalidomide is provided to patients under a special distribution program called REVLIMID REMS®.

  In order to participate in this study, you must register into and follow the requirements of the Revlimid REMS™ program of Celgene Corporation. This program provides education and counseling on the risks of lenalidomide, including fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling every 28 days, or more frequently dependent on treatment regimen, during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate for you and take telephone surveys regarding your compliance with the program.

  By signing this consent, you understand and agree to receive counseling and to comply with the pregnancy precaution requirements of the REVLIMID REMS™ program. You will be registered in the REVLIMID REMS™ program.

In order to obtain lenalidomide free of charge from Celgene, your name, address, phone, date of birth and the fact that you are participating in this trial will be disclosed to Celgene and its agents or vendors that supply lenalidomide and administer the REVLIMID REMS® program. By signing this consent form, you agree to this disclosure.

The study staff will provide you with more information about this program. It is required of all patients who receive lenalidomide whether on or off a study.

Research Sample Collection

- Blood Samples:
  - Blood (about 3.2 tablespoons) will be collected for laboratory studies: before starting treatment, and at the start of every cycle, and if at any time your doctor thinks you have responded or may have progressed during or after treatment.
  - Some patients will also be asked to have pharmacokinetic (PK) blood samples (about 1 teaspoon each) 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 2 of cycle 1 (up to 6 hours after receiving study drug that day), including once the next day; as well as on day 8 of cycle 1 prior to and about 2 hours after dosing on 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.
- Saliva or Buccal Swab Samples: Sometime 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 progress during or after treatment on this study. The tissue is being collected for special research tests.

  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.

  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.

- Tumor Biopsy: 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. Usually, tissue can be obtained safely and comfortably with local anesthesia. However, some participants may require conscious sedation.

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.

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

To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA 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 growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and 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 result sent in, about 30 days after the last dose of study treatment. At 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 progress: 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 4-5. 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 the rest of your life.

If at any time your disease is felt to have gone away completely (complete response), we may ask you to come to the clinic in between visits. If at any time your disease recurs (comes back) or progresses, 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 progresses, we will continue to contact you by phone (or mail, email, etc.) to see how you are doing for the rest of your life, or until the study is closed (whichever is sooner).

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for at least 5 years. After this time, we may continue to contact you until we complete the main research goals of the study, which we expect will take 4-5 years.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 51 people get the study drugs 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.

There is also a risk that you could have side effects from the study drug(s)/study approach.

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.

- Some side effects could happen with any drug you receive though they may be more frequent in some drugs than others. These include:
    - Allergic reaction or infusion reaction (if the drugs are given by IV). Allergic and infusion reactions may include a rash, hives, fever, difficulty breathing, nausea, and low blood pressure. You may experience pain at the site where the IV was inserted. Although usually reversible with treatment, it can be severe or life threatening.

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.

The information below shows the most common and the most serious side effects doctors know about each study drug. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you:

Venetoclax (VENCLEXTA™)

VERY COMMON (some may be serious) In 100 people receiving Venetoclax, more than 10 may have:

- Low white blood cell count (cells that help fight infection)
- Low red blood cell count
- Low platelet count (cells that help blood to clot)
- Diarrhea
- Nausea
- Feeling tired
- The study treatment may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Vomiting
- Cough
- Swelling of the hands and feet
- Muscle and/or bone pain

COMMON (some may be serious) In 100 people receiving Venetoclax 1 to 10 may have:

- Low white blood cell counts with fever
- Constipation
- Fever

- Chemical imbalance in blood (including abnormally low or high potassium, high levels of uric acid, and/or low level of calcium, and high levels of phosphates)
- Pain (such as back pain)
- Headache
- Abnormal kidney test (possible kidney damage)
- Dizziness
- Low levels of oxygen in the blood
- 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)
- Severe infection throughout the body

Rare but Serious:

- Liver failure
- A second cancer related to the treatment of your first cancer. This usually occurs years after treatment for the first cancer.

Ibrutinib (IMBRUVICA®)

COMMON (some may be serious) In 100 people receiving ibrutinib, more than 20 may have:

- Condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Nausea
- Rash
- Muscle and/ or bone pain
- Diarrhea
- Abdominal pain
- Bruising
- Bleeding
- Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion.
- Feeling tired
- The study treatment may cause low blood cell counts (white blood cells). A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Low number of platelets count, which may cause bleeding and bruising
- Muscle spasms

- Headache
- Fever
- Mouth blisters/sores

Rare (some may be serious):

- Irregular heartbeat
- The study drug may cause you to develop another type of cancer.
- Liver damage
- 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)
- Heart failure

Obinutuzumab (GAZYVA®)

Very Common (in 10 people receiving obinutuzumab one or more may have):

- Condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Low number of platelets, which may cause bleeding and bruising
- which may cause bleeding and bruising
- Low number of red blood cells that can cause tiredness and shortness of breath
- Low number of other white blood cells, cells that help fight infections; with or without fever
- Feeling tired or having no energy
- Fever
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased appetite
- Cough
- Runny Nose
- Infections, the most common include: upper respiratory tract infection, sinusitis and urinary tract infection
- Pain (such as joint, muscle, back, bone, or chest)
- Itching
- Herpes virus infections such as oral herpes (cold sores) or herpes zoster (shingles)

- Headache
- Hair loss
- Trouble sleeping

Common (In 100 people receiving obinutuzumab, 1 to 10 may have):

- Low number of other white blood cells, cells that help fight infection; with or without fever
- Other cancers (such as basal cell carcinoma or squamous cell carcinoma of the skin)
- Heartburn or indigestion
- Sore throat
- Stuffy nose
- Hemorrhoids
- Stuffy Nose
- Heart beats too fast or too slow
- Increased weight
- Anxiety and/or depression
- Loss of bladder control or pain when urinating
- High blood pressure
- Chemical imbalance in blood (including low albumin calcium, phosphate, potassium and sodium, and high levels of liver enzymes)
- Tumor Lysis Syndrome (see additional information below)

Rare but Serious:

- Effects on the heart (see "Other Risks from Treatment" below)
- Hole in your gastrointestinal tract
- Progressive Multifocal Leukoencephalopathy (PML) (see additional information below)
- In people 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)
- Condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion.

Lenalidomide (REVLIMID®)

<u>Likely:</u>

- Low number of white blood cells, cells that help fight infection; with or without fever
- Low blood count
- Low platelets, cells that help blood to clot

- Vision blurred
- 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
- Tiredness
- Swelling
- Fever
- Chills
- Sore throat
- Stuffy nose
- Pneumonia or other infections
- Weight loss
- Cataract
- Insomnia (not sleeping well)
- Itching
- Chemical imbalance in blood (low potassium, low calcium, low phosphate, low magnesium, low sodium)
- Decreased appetite
- High Blood Sugar
- Dizziness
- Altered sense of taste
- Headache
- Abnormal sense of touch
- Indigestion/heartburn
- Shaking
- Pain and decreased sensation in nerves
- Cough
- Shortness of breath
- Nosebleed
- Dry skin
- Pain including muscles, joints, and non-cardiac chest pain

- Allergic reaction
- Feeling sad
- Abnormal liver lab tests

Less Likely:

- Low levels of all types of blood cells – white blood cells, red blood cells and platelets
- Heart attack
- Abnormal heart rhythm
- Heart stops working
- Low oxygen to heart tissue
- Dry mouth
- Decreased action of intestine
- Bile flow from liver slowed or blocked
- Fall
- Lowered level of consciousness with drowsiness, listlessness, & lethargy
- Destruction of red blood cells
- Loss of fluids
- Diabetes
- Swelling of blood vessels
- Redness of the skin
- Increase in liver protein that indicates inflammation in body
- Breathing disorder
- 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, including gout
- Iron build up in body
- Muscle weakness
- Cancer (acute myeloid leukemia, basal cell carcinoma, squamous cell carcinoma)
- Stroke
- Tingling of skin
- Fainting
- Mood changes
- Kidney injury
- Excessive sweating
- Bruises

- Swelling of skin filled with blood
- High or Low blood pressure
- Night sweats
- Blood not getting to extremities
- Sudden increase in tumor size
- Blood cancer that causes decreased number of red blood cells, white blood cells, and platelets because they do not develop normally

Rare but Serious:

- Swelling of lungs
- Over and underactive thyroid
- Severe allergic conditions, including swelling under the skin) 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 or an allergic condition that can lead to low blood pressure, breathing difficulty, and rapid heartbeat
- Release of tumor chemicals into blood (tumor lysis syndrome)
- Small intestinal blockage
- Bleeding into the stomach and intestine
- Low blood oxygen

Polatuzumab (POLIVY™)

Likely:

- Condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing
- Low number of platelets (cells that help blood to clot), which may cause bleeding and bruising
- Low number of red blood cells that can cause tiredness and shortness of breath
- Condition affecting the nerves supplying the arms and legs. Typically, the feet and hands are involved first. If sensory nerves are involved, numbness, tingling, and pain are felt, and if motor nerves are involved you will experience weakness
- Diarrhea
- Fever
- Decreased appetite
- Infections, may include: pneumonia or other infections (such as fungal pneumonia, herpes simplex, herpes zoster, upper respiratory tract infection, COVID, cytomegalovirus, urinary tract infection, or skin infection)
- Vomiting
- Weight decrease

- Chemical imbalance in blood (such as low potassium, low albumin, low calcium, low magnesium or low phosphate)
- Abnormal liver lab tests
- Dizziness
- Low number of other white blood cells, cells that help fight infections; with or without fever
- Feeling tired, feeling weak and having no energy
- Nausea
- Constipation

Less Likely:

- Joint aches
- Swelling of lungs
- Severe infection throughout the body
- Abnormal digestive blood test (possible inflammation of the pancreas
- Eye side effects like bleeding in the tissue lining the eye , teary eyes , blurred vision, double vision, painful red eyes and bleeding in the eye
- Cough and/or shortness of breath
- Pain, such as abdominal pain
- Rash, itching, dry skin
- Muscle spasms, body aches
- Sores in the mouth and esophagus, which may be painful and cause difficulty swallowing
- Swelling (arm/leg)
- Chills
- Brain infection that damages nerve tissue (see additional information below)
- Abnormal kidney tests (possible kidney damage)
- Irregular heartbeat
- Tumor Lysis Syndrome (see additional information below)
- Digestive system bleeding
- To leak out of the vein during an infusion or injection. This may cause damage to local tissues.

Prednisone:

Common side effects (some may be serious) In 100 people receiving prednisone, more than 20 and up to 100 may have:

- Difficulty sleeping

- Swelling of the body, tiredness, bruising
- Mood swings
- Increased appetite and weight gain in the belly, face, back and shoulders
- Loss of bone tissue
- High blood pressure which may cause headaches, dizziness, blurred vision

Occasional side effects (some may be serious) In 100 people receiving prednisone, from 4 to 20 may have:

- Cloudiness of the eye, visual disturbances, blurred vision, glaucoma
- Infection
- Diabetes
- Low levels of potassium in the blood, which can cause abnormal heart rate. This could cause an irregular heartbeat, which can be serious and life threatening.
- A tear or a hole in the bowels which may cause belly pain or that may require surgery
- Low levels of potassium in the blood, which can cause an abnormal heart rate, which can be serious and life threatening
- Damage to the bone which may cause broken bones, joint pain and loss of motion

Other risks from treatment

- 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.
- 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 called Disseminated Intravascular Coagulation (DIC). 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 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, polatuzumab 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. The maximum amount of blood that will be drawn at a single timepoint on study is approximately 6.5 tablespoons. The maximum amount of blood that will be drawn over 8 weeks on the study is approximately 28 tablespoons.
- 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, the most common risks of conscious sedation last up to a few hours after being given can include drowsiness, feeling slow or sluggish, low blood pressure, headache, and nausea.
- 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.
- Electrocardiogram (EKG): Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the EKG.
- Urine collection: There are no physical risks or discomforts associated with urine collection.
- Cheek swab and saliva collection: There are no physical risks involved with the cheek swab or collection of saliva.
- Imaging as applicable:
    - 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.
    - MRI (magnetic resonance imaging): You might be at risk for injury from the MRI magnet if you have some kinds of metal in your 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 tell us. You will be asked to fill out 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 you enter the MRI scan room.

If you are afraid of confined (small, cramped) spaces, you may get anxious during an MRI. If you have back problems, you may have back pain or discomfort from lying in the scanner.

The noise from the scanner is loud enough to damage your hearing, especially if you already have hearing loss. We will give you 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:

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 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: 30 days after the last dose
- Ibrutinib: 1 month after the last dose
- Obinutuzumab: 18 months after the last dose
- Lenalidomide: 28 days after the last dose
- Polatuzumab: 9 months 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.

Individuals 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 you are the partner of a person who 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: 1 months after the last dose
- Obinutuzumab: 6 months after the last dose
- Lenalidomide: 28 days after the last dose
- Polatuzumab: 6 months 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.

All study participants must be registered into the mandatory Revlimid REMS™ program.

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, individuals of childbearing potential that might be caring for you 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 up to six CT scans of the neck, chest, abdomen and pelvis, and up to two ^{18}F-FDG PET scans, and two CT-guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 11.8 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 39.3 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%).

Psychological or Social Risks Associated with Return of Incidental Findings

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

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

Privacy Risks Associated with Return of Incidental Findings

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

Protections against misuse of genetic information

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

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

The aim of this study is to see if this combination of treatment is safe to give to patients with B-cell lymphoma. We also hope to learn more about how effective or not this combination of medications may be in treating patients. 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.

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 or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with surgery, 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.

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

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

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

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 believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to 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 a referral to a genetic healthcare provider 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 any of the study drugs may become unavailable
- if new information shows that another treatment would be better for you

- if you do not follow the study rules
- if the study is stopped for any reason

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

After therapy is stopped, we would like to see you for a safety visit 30 days after your last dose.

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

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Celgene Corporation, and Genetech Inc., or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand cancer, 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 identifiable specimens and data to be stored and used by the study team for future studies as described above.

_____ Yes _____ No

Initial Initial

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

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code, (not with your name or other information that could be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will be widely available to anyone who wants it.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

I give permission for my **de-identified** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In some cases, it may help other researchers to know that the specimens or data were collected from you (i.e., they will have your identifiers). If we share your identity with other researchers, their study will be reviewed and approved by an Institutional Review Board who will make sure that the study team is protecting your confidentiality.

I give permission for my **identifiable** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

Information about all the people (including you) in this study may be combined to create what is called summary information. The summary information may be placed in a database and shared in scientific publications. This information will help the researchers understand if some patterns are more common than others among everyone who was a part of this study. The summary information will be available to anyone without the need for any permission. The risk of anyone identifying you based on this information is very low.

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

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 who 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 that no one will 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.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. 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 is already complete, the information from that research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH as long as the study is open. When this study is closed, we may keep the data and any samples that are leftover for future research indefinitely.

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?

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.

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.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (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.

Celgene is providing lenalidomide for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Celgene.

Genentech Inc. is providing venetoclax, obinutuzumab and polatuzumab for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Genentech Inc.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, Center for Cancer Research or their agent(s)
- Qualified representatives from Celgene, the pharmaceutical company who produces lenalidomide.
- Qualified representatives from Genentech, the pharmaceutical company providing venetoclax, obinutuzumab and polatuzumab

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 Privacy Act helps keep your NIH medical information confidential. In some cases, it is different from the Certificate. Under 42 U.S.C. § 282, NIH is authorized to collect the data for this study. This data is covered by an NIH Privacy Act System of Records Notices: 09-25-0200, Clinical, Basic and Population-based Research Studies of the National Institutes of Health and 09-25-0099, Clinical Research: Patient Medical Records. Sometimes the Privacy Act allows sharing your information without your permission. An example is if Congress requests it.

Information may also be shared for some research. It can be given to some federal and state agencies. It can be used for HIV partner notification, or for infectious disease, abuse, or neglect reports. It may be shared with tumor registries, for quality and medical reviews. It may also be shared if NIH is involved in a lawsuit or event of a suspected or confirmed breach. However, NIH will only release medical record information if allowed by both the Certificate 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, Christopher Melani, MD, christopher.melani@nih.gov, 240-760-6057. 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

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

NOTE: The witness must be fluent in both the language of the participant and the language of the investigator. The interpreter may also serve as the witness, however the investigator obtaining consent may not serve as the witness. Document the use of an interpreter in the medical or research record. Refer to Policy 301 for details.