The Ohio State University Consent to Participate in Research and HIPAA Research Authorization

Study Title: Obinutuzumab, Ibrutinib, and Venetoclax for Relapsed and Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Principal Investigator: Kerry A. Rogers, MD

Sponsor: The Ohio State University

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

You are being asked to participate in this study because you have been diagnosed with CLL.

This is a phase Ib/II study designed to test the safety and efficacy of three cancer drugs, ibrutinib, obinutuzumab and venteoclax at different doses to subjects with CLL (chronic lymphocytic leukemia).

While doing this, researchers hope to discover what effects, if any, the study drugs have on people when given at the same time and to determine the dose and schedule of each drug to be administered.

Another purpose of the study is to study how these drugs affect CLL cancer cells and the immune system of CLL patients. This will be studied using special laboratory tests on blood samples taken during the course of treatment. These research blood draws are described below.

In this investigational study, researchers may utilize drugs which have not been approved by the FDA, or have not been approved by the FDA for use in your type of cancer. The FDA stands for Food and Drug Administration. The Food and Drug Administration is a federal governmental body within the U.S. Department of Health and Human Services. This office is charged with protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, medical devices, most of our nation's food supply, all cosmetics, and products that give off radiation.

Obinutuzumab is a monoclonal antibody which can increase cell death in CLL cells. Although this drug has been FDA approved for the treatment of CLL, its use in this study is considered experimental because it is being combined with venetoclax and ibrutinib.

Venetoclax is an oral tablet which inhibits certain biological pathways in the body that are associated with increased resistance to chemotherapy drugs. This drug has not yet been approved by the FDA and is therefore considered an experimental drug.

Ibrutinib is a cancer drug which has been FDA approved to treat both CLL and mantle cell lymphoma. Ibrutinib is an oral capsule which inhibits certain biological pathways in the body to cause CLL cell death. Although this drug has been FDA approved, its use in this study is considered experimental because it is being combined with venetoclax and obinutuzumab.

2. How many people will take part in this study?
A total of 87 patients will participate in this study at The Ohio State University.

3. What will happen if I take part in this study?
By agreeing to take part in this study, you are agreeing to comply with the study requirements.

After signing this consent form, you must complete a pre-treatment evaluation. During this evaluation, you will be required to complete multiple tests to determine whether or not you are eligible to participate in this study. If you are found to be eligible you may begin the study.

A single course of the study drug or "cycle" is 28 days. Because this is a dose escalation study, the amount of each drug that you take may be changed up, down or not at all.

If you tolerate the study drugs (obinutuzumab, venetoclax, and ibrutinib) and your study doctor feels that your cancer is stable or responding to the study drug, or that you are otherwise benefiting from the study treatment, you may continue to receive treatment until your disease progresses or unacceptable drug-related toxicity occurs up to the completion of cycle 14. The treatment schedule is designed to end after Cycle 14 as the study is designed to allow patients to discontinue treatment by this time. After treatment ends, patients enrolled on the study will continue to be followed for at least one year after the last patient is enrolled. For participants

enrolling after 11/1/2018, you will not be allowed to continue ibrutinib after completing study treatment. If you need to continue taking ibrutinib after cycle 14 for any reason you will be removed from the study.

As outlined below, you will visit the clinic for evaluation and/or treatment at least monthly for as long as you are on the study receiving active treatment.

Pre-treatment Evaluation

If you decide you want to be in this study and you sign the consent form, you will be asked to have a medical evaluation done in order to determine if you qualify for the study. These exams, tests and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. If you meet all of the requirements, you will be enrolled in the study.

A description of tests and visits required for the medical evaluation are listed below:

- Medical history
- You will be asked for a complete list of medicines you are taking, including supplements and vitamins.
- Physical examination (including vital signs, height and weight, measurement of lymph nodes, liver, spleen)
- Routine blood tests: complete blood count, test of blood chemistries (various substances in the blood), liver function tests, beta-2-microglobulin (a chemical marker of CLL activity), Coomb's test (a test to see if your body makes antibodies to red blood cells), immunoglobulin levels (tests to measure the levels of blood proteins that fight infection), and cytogenetic studies (tests to see if there are abnormal chromosomes in the CLL cells, and liver function tests).
- If you are a woman of childbearing potential you will be required to complete a serum pregnancy test with negative results within 7 days of treatment.)
- Women of childbearing potential and men must agree to use adequate contraception for at least 2 months for women and 3 months for men prior to the study and for the duration of participation.
- An ECG (electrocardiogram), a record of electrical activity of the heart.
- An MUGA/Echocardiogram, a sonogram image of your heart.
- A CT (computed tomography) or MRI (magnetic resonance imaging) scan will be performed to measure the size of the cancer in your body.
- A CT scan is a computerized x-ray that gives your doctor clearer pictures of the inside of your body. CT scans are routine procedures used to help doctors diagnose and follow the size and location of your cancer.

- Bone marrow biopsy and aspirate will be performed to measure how much cancer is left in your bone marrow. An additional 5 mL (1 teaspoon) of bone marrow will be obtained for research purposes.
- Research blood draws (about 40 mL or 10 teaspoons of blood) will be performed for pharmacodynamic (PD) studies (special lab tests to understand what the study drug does to the body).
- Quality of life surveys will be completed.

Study Drug Administration

Ibrutinib
You will receive your dose of study drug (ibrutinib) orally once a day every day at approximately the same time every day. You will receive enough ibrutinib to last you until your next clinic visit (enough for a full cycle). You should make all attempts to follow the treatment schedule and take the drug at the assigned time.

If you miss a dose of ibrutinib, it can be taken up to 6 hours after the scheduled time. On the following day, you should return to taking the drug at the normally scheduled time. If more than six hours have passed since the regularly scheduled time you take the drug, you should just skip the dose and resume taking the drug at the next scheduled time. The missed dose will not be made up.

Ibrutinib and Venetoclax can be taken at the same time as long as they are taken with meals as described above and below.

Venetoclax
You will receive your dose of study drug (venetoclax) orally once a day every day within 30 minutes after the first meal of the day or the completion of a low-fat breakfast (a meal which 30% of the total caloric content of the meal is from fat). You will receive enough venetoclax to last you until your next clinic visit (enough for a full cycle). You should make all attempts to follow the treatment schedule and take the drug at the assigned time.

If you miss a dose of venetoclax, it can be taken up to 8 hours after the scheduled time. On the following day, you should return to taking the drug at the normally scheduled time (ensuring that the missed dose is taken with food). If more than eight hours have passed since the regularly scheduled time you take the drug, you should just skip the dose and resume taking the drug at the next scheduled time. The missed dose will not be made up.

During the venetoclax dose escalation portion of this study you may be required to stay overnight in the hospital for monitoring depending on your risk group or your assigned dose level.

Obinutuzumab
You will receive your dose of study drug (obinutuzumab) by infusion during your clinic visits. The first dose of obinutuzumab will be administered as a split infusion over two days. Two additional doses of obinutuzumab are given during clinic visits on days 8 and 15 of cycle 1. After the first cycle you will receive this infusion on day one of each cycle through cycle 8.

During the Study
If you qualify for the study, you will start treatment with the study drug as an outpatient on the schedule described in detail below. While receiving treatments with the study drug your physician will continue to monitor your health and the status of your disease.

Cycle 1 Day 1
- Prior to the first treatment a member of your treating team (physician, nurse practitioner, or physician assistant) will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including height and weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Routine blood tests (complete blood cell count, blood chemistries)
- Quality of life surveys to be completed.
- Obinutuzumab will be given by infusion.

Cycle 1 Day 2
- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit as well as take your vital signs.
- Routine blood tests (complete blood cell count, blood chemistries)
- Obinutuzumab will be given by infusion.

Cycle 1 Day 8
- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- Vital signs (blood pressure, pulse, respiratory rate and temperature) will be taken.
- Routine Blood Tests (Complete Blood Count, and test of blood chemistries – various substances in the blood).
- Quality of life survey to be completed.
- Obinutuzumab will be given by infusion.

Cycle 1 Day 15
- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.

- Vital signs (blood pressure, pulse, respiratory rate and temperature) will be taken.
- Routine blood tests (complete blood cell count, blood chemistries)
- Quality of life survey to be completed.
- Obinutuzumab will be given by infusion.

Cycle 1 Day 22

- A member of your treating team will assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- Vital signs (blood pressure, pulse, respiratory rate and temperature) will be taken.
- Routine blood tests (complete blood cell count, blood chemistries)
- Quality of life survey to be completed.

Cycle 2 Day 1

- Prior to treatment a member of your treating time will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood cell count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected for research purposes prior to taking the study drugs.
- Quality of life survey to be completed.
- Obinutuzumab will be given by infusion.
- Ibrutinib will be given orally. You will continue to take a dose of ibrutinib once a day for the rest of the week.

Cycle 2 Day 8

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit as well as take your vital signs.
- Routine blood tests (complete blood cell count, blood chemistries)
- Quality of life survey to be completed.
- Ibrutinib will be given orally. You will continue to take a dose of ibrutinib once a day for the rest of the week.

Cycle 2 Day 15

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit as well as take your vital signs.
- Routine blood tests (complete blood cell count, blood chemistries)
- Quality of life survey to be completed.
- Ibrutinib will be given orally. You will continue to take a dose of ibrutinib once a day for the rest of the week.

Cycle 2 Day 22

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit as well as take your vital signs.
- Routine blood tests (complete blood cell count, blood chemistries)
- Quality of life survey to be completed.
- Ibrutinib will be given orally. You will continue to take a dose of ibrutinib once a day for the rest of the week.

Cycle 3

During Cycle 3, you will begin taking the third drug used in this study: venetoclax. If your study doctor believes that you are at increased risk for complications because of the amount of disease you have or your kidney function, you may be required to stay overnight in the hospital during one or more visits so you can be more closely monitored.

Cycle 3 Day 1

- Prior to treatment a member of your study team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood cell count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Quality of life survey to be completed.
- Obinutuzumab will be given by infusion.
- Ibrutinib and Venetoclax will be given orally.

Cycle 3 Day 2

- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit as well as vital signs recorded.
- Routine blood tests (complete blood cell count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Ibrutinib and Venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of the week.

Cycle 3 Day 8

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood cell count, blood chemistries)

- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Quality of life survey to be completed.
- Ibrutinib and Venetoclax will be given orally.

Cycle 3 Day 9

- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit as well as vital signs recorded.
- Routine blood tests (complete blood cell count, blood chemistries)
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of the week.

Cycle 3 Day15

- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood cell count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Quality of life survey to be completed.
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of the week and/or the rest of this cycle, depending on your assigned dose of venetoclax.

Cycle 3 Day 22

- Depending on your assigned dose of venetoclax, this visit may not be required.
- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood cell count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Quality of life survey to be completed.
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of the week and/or the rest of this cycle, depending on your assigned dose of venetoclax.

Cycle 3 Day 29

- Depending on your assigned dose of venetoclax, this visit may not be required.

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood cell count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of the week and/or the rest of this cycle, depending on your assigned dose of venetoclax.

Cycle 4-8 Day 1

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Quality of life survey to be completed.
- Obinutuzumab will be given by infusion.
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of this cycle.

Cycle 9 Day 1

- Prior to treatment a member of your treating team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Routine blood tests (complete blood count, blood chemistries)
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Bone marrow biopsy and aspirate will be performed to measure how much cancer is left in your bone marrow. An additional 5 mL (1 teaspoon) of bone marrow will be obtained for research purposes.
- A CT or MRI scan will be performed to measure the size of the cancer in your body.
- Quality of life survey to be completed.
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of this cycle.

Cycles 10-14 Day1

- Prior to treatment a member of your study team will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be completed.
- Routine blood tests (complete blood count, blood chemistries).
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- Ibrutinib and venetoclax will be given orally. You will continue to take one dose of each medication daily for the rest of each cycle.

Cycle 14 Day 28 (For people starting treatment after 11/1/2018)

- Prior to completing your study medications you will have an assessment for how well these medications worked.
- Routine blood tests (complete blood count, blood chemistries).
- Approximately 40 ml (10 teaspoons) of blood will be collected prior to taking the study drug for research purposes.
- A CT or MRI scan will be performed to measure the size of the cancer in your body.
- Bone marrow biopsy and aspirate will be performed to measure how much cancer is left in your bone marrow. An additional 5 mL (1 teaspoon) of bone marrow will be obtained for research purposes.
- A lymph node biopsy if there is enough lymph node tissue to perform a biopsy. This will involve inserting a needle into the lymph node tissue to take a sample for research.

Additional blood tests, x-rays, and procedures may be requested if your doctor feels they are medically necessary. Anyone starting treatment after 11/1/2018 will not complete the quality of life surveys.

At the End of Treatment:

You may stop treatment with the study drug for several reasons: because your cancer is not responding to this treatment, because the treatment has caused too many side effects, or because you choose to stop treatment. No matter the reason for stopping treatment, you will continue to be followed.

Within 30 days (4 weeks) of completing treatment, your study doctor or other member of the treating team will repeat a medical history and perform a physical examination, including measurements of your lymph nodes, liver, and spleen. You will also have routine laboratory tests that are part of the regular care for patients with your cancer. Approximately 40 ml (10 teaspoons) of blood will be collected for research purposes. For patients who have completed cycle 14, bone marrow biopsy and aspirate samples will be repeated at this time to find out how much cancer is left in the bone marrow. Samples will be sent for routine studies, and approximately 5 mL (1 teaspoon) of bone marrow will be collected for research purposes. CT or MRI scans will also be performed to measure the size of cancer in your body. Additional blood tests, x-rays, and procedures may be requested if your doctor feels they are medically

necessary. If you are continuing on ibrutinib treatment after Cycle 14, you will continue seeing your doctor for visits and blood tests as part of regular care for people taking this medication.

Changes due to the COVID-19 Pandemic

Due to the COVID-19 pandemic it may not be safe for you to travel to the Ohio State University for study visits or for you to undergo planned tests. This means that some of your study visits may be conducted by telemedicine (video or telephone). In some cases, if your doctors feels it is safe, you will not be asked to have planned lab work. In some cases tests, such as CT or MRI scans or bone marrow biopsies, will not be done as planned. When you are not able to come for a planned study visit due to the COVID-19 pandemic oral study medication will be shipped to you, rather than given to you at your clinic visit. Any of these things can be discussed with your doctor at any time to make sure that you received the safest medical care possible and to minimize disruptions to your study treatment.

Additional Questions and Research Testing Related to the COVID-19 Pandemic

We are trying to understand the impact of CLL treatment on the immune system and how this may affect illness related to SARS-CoV-2, the virus that causes COVID-19. For that reason you may be asked questions about if you have had COVID-19, behaviors that put you at risk for contracting COVID-19, and some of the blood collected for research may be used to test for evidence of infection with SARS-CoV-2. As these are research tests and not validated clinical tests you will not receive the results of this testing.

Follow-Up

You will be required to have a clinic visit to be seen by the study staff at least once every three months for 2 years and then every 6 months until your disease progresses, start of a new CLL therapy, death, or the study closes. Your study doctor may request additional tests, including a bone marrow biopsy, and/or scans if he or she believes that your disease is starting to relapse. If you have confirmed progression of your disease, peripheral blood and bone marrow aspirate (if a bone marrow biopsy is done per your study doctor) will be collected for research purposes if you have a visit at OSU.

If you are doing well after the study and unable to return to the Ohio State University for visits you and your doctor can decide that you will follow with a local doctor who specialized in Hematology and Oncology and have records sent to the Ohio State University for study purposes. Your doctor has to agree that this is a safe option for you. In that case you have to be seen by your local doctor every 3 months for the first 2 years, and every 6 months thereafter. If you are still enrolled in the study and taking ibrutinib you have to return to the Ohio State University at least once every 12 months to remain in the study.

As long as you agree to remain in the study and the study is open you will be in follow up for survival. This would mean someone contacting you every 6 months to find out if you are alive. This may be at an appointment, or by phone, or e-mail, particularly if you are in remote follow-up. This will continue as long as the study is open, even if you have started a new

treatment for your CLL. If you were previously removed from the study, you will be asked to re-enter the study only to follow your survival status.

You will also be offered the option to have additional tubes of blood collected for research that is being done on people who completed treatment. This is completely optional and you may say "yes" or "no" to this request for additional blood when asked. These will be 2 tubes of blood and they may be collected at your visit to the Ohio State University or if you are being seen at a local hospital or clinic they may be collected there and mailed to the Ohio State university. This research is to learn more about immune function after finished treatment.

☐ I refuse for collection of additional optional research blood samples collection as described above.
☐ I agree for collection of additional optional research blood samples collection as described above.

We will also ask you questions about your history of COVID-19 testing, exposure to SARS-CoV-2 (the virus that causes COVID-19), and any vaccines you may have had.

Genetic Testing
In addition to the above testing, subjects in Cohort 3 may have analysis performed on blood, marrow, and tissues samples. This includes detailed genomic, biochemical, and epigenetic assessment of the residual tumor cells and microenvironment persisting at end of therapy for comparison to baseline tumor features. Detailed assessment of the cellular and innate immune cell numbers at serial time points may be performed as well.

Whole genome sequencing may be performed. No genes known to cause a hereditary disease will be specifically tested. Since whole genome sequencing may be done it is a possibility that a gene known to cause a hereditary disease will be incidentally discovered. The genetic testing is done to compare germline sequences to tumor (CLL) sequences to look for genetic changes that are responsible for resistance to the CLL treatment being studied in the clinical trial. Since we may perform germline sequencing it is possible we will uncover a genetic change responsible for an inherited disease or that has health implications for you. If any clinically actionable mutations are identified, your provider will be informed of these results and they may refer you for clinical genetic testing and counseling if incidental findings are identified.

4. How long will I be in the study?
You may continue to receive treatment with the study drugs (venetoclax, obinutuzumab, and ibrutinib) for up to 14 cycles as long as you show no signs of worsening disease and do not suffer from dangerous side effects. You will be seen and examined by your doctor or other member of the treating team at least monthly to monitor how well your disease responded to this treatment, to make sure that any side effects have resolved, receive study drug, and to find out if you have developed any unexpected side effects.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. It is important to tell your doctor if you are thinking about stopping or decide to stop so any risks from the treatment can be evaluated and your doctor can inform you what follow-up care and testing could be most helpful for you. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

While you are taking part in this study, you are at risk for the following side effects. You should talk to the researcher and/or your medical doctor about these side effects. There also may be other side effects that are not known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after treatment is stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death.

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

Below are the known common or serious side effects of the drugs used in the study. In addition to the side effects of the individual agents the rare (occurring in <2% of patients) but serious side effect of reversible cerebral vasospasm syndrome (RCVS) has been seen with this combination of drugs. RCVS is a condition effecting the blood vessels in the brain that can result in headaches, neurologic problems such as numbness, weakness, or difficulty with thinking or speech, and in rare instances seizures. RCVS is treatable with medications and in many cases a short stay in the hospital is required for treatment.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions about your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies

cannot ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.

Venetoclax

Before you start taking venetoclax, tell your doctor if:
• You have heart, kidney, or liver problems
• You have fever or other symptoms of infection
• You have recently received or are scheduled to receive a vaccine
• You are pregnant or plan to become pregnant
• You are breastfeeding or plan to breastfeed
• You are taking medicines given by your doctor or on your own. Certain medicines and supplements may increase or decrease the amount of venetoclax in your blood.

Very common: occurs in 1 or more out of 10 patients (≥ 10%)

• Upper respiratory tract infection – signs include runny nose, sore throat, or cough

• Pneumonia

• Low number of white blood cells (neutrophils), sometimes with fever. A decreased number of white blood cells may increase your risk of infection including serious infections that may lead to death.

• Diarrhea

• Nausea or vomiting

• Constipation

• Feeling tired

• Low number of red blood cells (anemia). A decreased number of red blood cells may result in weakness and fatigue. In severe cases, a blood transfusion may be necessary.

Common: occurs in between 1 or more patients out of 100 to less than 10 patients out of 100 (≥ 1% TO ≤ 10%):

• Urinary tract infection
• Very serious infection in your blood (sepsis)

• Low number of lymphocytes (another type of white blood cell). A decreased number of white blood cells may increase your risk of infection including serious infections that may lead to death.

• Tumor lysis syndrome (described below; may experience fever, chills, nausea (feeling sick to your stomach), vomiting, diarrhea, confusion, shortness of breath, irregular heartbeat, unusual tiredness, muscle pain, joint discomfort and/or seizure.)

• Higher level of phosphorous (hyperphosphatemia)

• Higher level of uric acid/urate (hyperuricemia)

• Higher level of potassium (hyperkalemia)

• Lower level of calcium (hypocalcemia)
• Higher level of creatinine (blood creatinine increase

Uncommon; occurs in between 1 or more patients out of 1,000 and less than 10 patients out of 1,000 (≥ 0.1% TO < 1%)

- Cystitis (inflammation or infection of the bladder)
- Reduced levels of uric acid in the blood
- Reduced levels of hemoglobin in the blood
- Infection
- Pneumonia legionella (lung infection caused by a type of bacteria)
- Anorexia (loss of appetite)

Medications to avoid:
Use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase due to the potential for increased risk of tumor lysis syndrome. It is very important to tell your doctor of any medications you are on.

Serious infections
Some infections (for example lung infections or infection in the blood) that require treatment in hospital have been reported in patients receiving venetoclax treatment, some of which have resulted in death. The risk of such infections is higher in patients receiving venetoclax plus other anti-cancer treatments (combination therapy). It should be noted that the risk of infection itself is common with certain types of cancer (particularly blood cancers). Your doctor may also advise you to take other measures to reduce your chance of developing an infection. If you notice fever or other symptoms of infection, notify your doctor or nurse right away.

Tumor Lysis Syndrome
Treatment with venetoclax in cancer subjects has been associated with nausea, decreases in lymphocytes and neutrophils (two different types of white blood cells), anemia (decrease in the number of red blood cells), thrombocytopenia (decrease in platelets), and tumor lysis syndrome (TLS).

TLS is a problem that can occur when cancer cells break down and the body has to get rid of the broken up cell parts. Sometimes your body can't remove the cell parts quickly enough, so the levels of some products in your blood, such as salts and acids, can rise. This can happen especially in subjects with large tumors or a high number of white cells in the blood.

TLS can lead to serious problems such as effects on your kidney and heart (including abnormal heart rhythms) or seizures. These side effects can result in needing kidney dialysis (a special machine to remove toxins from the blood) or be fatal. If you develop TLS, your doctor will closely monitor and treat you as needed to try to prevent these complications.

In some subjects with cancer, after receiving the initial dose of venetoclax or after receiving a higher dose of venetoclax than previously received, blood tests have shown TLS. In addition, two deaths in subjects who experienced TLS have been reported after receiving venetoclax, and 1 subject with TLS has needed dialysis. Subjects with CLL (particularly with large lymph nodes) and mantle cell lymphoma may be at higher risk than other non-hodgkin's lymphoma (NHL) subjects for these complications after receiving venetoclax.

Your study doctor will ask you to drink plenty of fluids. Depending on your risk for developing TLS, your doctor will give you medication prior to starting treatment with venetoclax to help your body process the remnants of the CLL cells that are produced following treatment. You may receive allopurinol (a pill to be started several days before your first dose of venetoclax) or rasburicase (an IV infusion to be started prior to your first dose of venetoclax). Allopurinol is a drug and rasburicase an enzyme; they both help the body to deal with these breakdown products in different ways.

If laboratory changes that suggest you may be developing TLS are seen, further hospitalization and/or extra blood tests or special monitoring (such as monitoring of your heart rhythm) may be recommended by your study doctor.

You may experience abnormal blood counts, especially decreased white blood cells (lymphopenia and neutropenia) and red blood cells (anemia), and infections when receiving venetoclax. You will be carefully monitored and, if necessary, treated with appropriate medications should these occur.

If your white blood cells are low, you may be at risk from infection. The time taken for your white blood cells to come back to normal levels in the body may be very long (i.e., 6 months to 1 year or longer).

Be sure to tell your study doctor if you develop any of the following during the study: fever, sweats, chills, flu-like symptoms, cough, shortness of breath, feeling very tired, vomiting, nausea (feeling sick to your stomach), diarrhea, irregular heartbeat, muscle aches, skin rashes or sores, burning when you urinate, cloudy urine, or urinating more often than normal.

Some subjects with CLL who have been treated with venetoclax, have developed an aggressive form of lymphoma (cancer of the lymph node). These subjects had received several previous chemotherapy treatments. The CLL cells of some of the subjects had abnormal DNA (genes), which put them at higher risk of developing this condition. It is unknown if venetoclax has contributed to these cases. Aggressive lymphomas can occur in approximately 10% (1 out of 10) of patients with advanced CLL.

Side effects observed in pre-clinical studies

Side effects that have been seen in pre-clinical studies in animals are reported below. Some of these side effects have been also observed in clinical trials, where patients with cancer have been treated with venetoclax. It is not clear, at this time, if venetoclax treatment is causing the

side effects to happen or if they are caused by other medical conditions that the patients were having at the same time or had in the past.

- Decrease in sperm cells in male dogs. It is unknown how long this decrease may last. It could be permanent. This may affect the ability of a man taking venetoclax to father a child. If you are a man who is planning to have children in the future, you should consider sperm banking before receiving treatment on this study.

- Areas of hair color change (to white or gray) without changes in the skin or eye color.

- Proteins blocked by venetoclax may be involved in protecting the ear against hearing loss. As a precaution, you should wear ear plugs or other appropriate hearing protection when involved in a loud activity.

The meaning of these findings in pre-clinical animal studies to humans is unclear. You will be watched closely for signs of these and other potential side effects.

Vaccination

You should not receive a live vaccine before (4 weeks before is recommended, may vary with protocols based on background disease population and/or combination agent), during, or after treatment with venetoclax until your doctor tells you it is okay. If you are not sure about the type of immunization or vaccine, ask your study doctor. These vaccines may not be safe and/or may not work as well during treatment with venetoclax. Your study doctor will provide further information on the non-live vaccines that you can receive while on study.

Obinutuzumab

Obinutuzumab has been tested in over 1900 subjects to date. The side effects of obinutuzumab appear generally similar to rituximab (a similar drug that has been approved and widely used as a treatment for lymphomas and leukemia).

It is important that you understand that the effects of obinutuzumab and other monoclonal antibodies may persist for a long time after the treatment stops. Also, the side effects of the treatment can appear up to 1 year after the infusions are completed (see the information about infections and pregnancies).

Common Side Effects (Occurring in 10 or more out of 100 people) of obinutuzumab

Infusion-Related Reactions

You may develop infusion-related effects such as fever, chills, and shivering especially within the first 2 hours of the first obinutuzumab infusion. Before the infusion, your doctor will recommend that you take acetaminophen (e.g., Tylenol®), which reduces fever and chills, and antihistamines (e.g., diphenhydramine) to help prevent any allergic reactions. Your doctor may also give you a corticosteroid to help prevent any infusion-related reactions. Other

infusion-related effects that you may experience are rash, blisters and itching of the skin, sickness, tiredness, dizziness, headache, breathing difficulties, cough, sensation of the tongue or throat swelling, itchy, runny nose, nausea, vomiting, diarrhea, flushing, irregular heart rate, high or low blood pressure, and tumor pain. Pre-existing heart conditions such as angina pectoris or congestive heart failure may get worse. If you experience any of these symptoms during obinutuzumab administration, your doctor may slow down or temporarily or permanently stop the infusion. Your study doctor may also give you some drugs to treat these symptoms. After the symptoms improve, the infusion may be continued. If you develop a severe reaction, especially a severe breathing difficulty, you may need additional tests on your blood or an X-ray of your chest. The infusion of obinutuzumab will not be started again unless your doctor is sure that you have recovered completely from the reaction. In the event of a severe reaction, you may be withdrawn from the study. The frequency of such reactions decreases with subsequent infusions. Because of the possibility of a reaction like this, you will be monitored closely by your doctor and study research staff during each infusion and for a time afterwards.

Abnormal Laboratory Tests

You may experience a severe drop in neutrophils (a type of white blood cell that fights infection). Your blood counts will be monitored regularly. As part of your disease, your bone marrow (the soft inner part of your bone that is the factory producing blood cells) may not be working properly, and if you have low levels of neutrophils, medication may be given to help the body increase the number of neutrophils. You may also experience a severe drop in your platelet count (cells that help stop bleeding). If you have a low platelet count, transfusion may be required to increase the number of platelets and to reduce the risk of bleeding. If this happens to you, then your study doctor may ask you to remain in hospital to allow for more frequent blood tests and transfusions if required.

Infection

B cells (a type of white blood cell or lymphocyte) help the body fight infection. Therefore, the removal of B cells by obinutuzumab may increase your risk of infection. Some infections can be serious, which may mean you have to go into hospital for treatment with IV antibiotics. Serious infections can sometimes be fatal. To further reduce any risk of infection, your study doctor will ask you to keep good oral hygiene. This means keeping your mouth clean by brushing and flossing on a regular basis. By doing this, you will prevent the build-up of plaque (the sticky film of bacteria and food that forms on the teeth), which will help prevent tooth decay and gum disease and infections. Your study doctor may ask you to visit your dentist for a dental check-up prior to study treatment. It is very important that if you experience any symptoms likely to be due to an infection (e.g., fever, chills, sore throat, coughing up phlegm, loin/kidney pain, pain when you urinate or pass water, feeling weak, giddy, or generally very unwell), that you contact your study doctor and/or study nurse right away. You will need to be seen by a doctor to check your health and start antibiotics if necessary. You will be given a study card, which you should keep with you at all times, which warns any doctor you see to check for signs of infection.

If your white blood cells are low, you may be at risk from infection. The time taken for your white blood cells to come back to normal levels in the body may be very long (i.e., 6 months to 1 year or longer).

Less Common Effects (Occurring in 5 to 10 of 100 People)

These include swelling (edema), joint pain, tumor pain or swelling; cough; weight loss; decrease in appetite; and difficulty breathing. You might also experience changes in blood tests because of the rapid destruction of tumor cells (TLS). Your study doctor will ask you to drink plenty of fluids. Depending on your risk for developing TLS, your doctor will give you medication to help your body process the remnants of the CLL cells that are produced following treatment. These medications will start prior to initiating treatment with obinutuzumab.

Rare but Serious Effects (Occurring in Fewer Than 5 of 100 People)

These include severe infusion-related reaction with symptoms similar to an allergic reaction (hives, severe breathing difficulties, extreme decrease in blood pressure, or shock). A severe allergic reaction needs treatment and may require you to go into hospital for a short period of time. Very rarely (less than 1 in 100,000 cases), a very serious reaction could be fatal. Cases of fatal bleeding have been reported in patients treated with obinutuzumab. Most of these occurred during the first cycle.

Finally, obinutuzumab has rarely been associated with perforation (a hole or tear) of the gastrointestinal tract (esophagus, stomach, or intestines). This has never been documented in patients with chronic lymphocytic leukemia but has occurred in the treatment of other lymphomas.

Other Risks with Obinutuzumab

- When you receive obinutuzumab, there is small chance that your immune system might develop antibodies against the drug. If you develop these special antibodies, it may affect your body's ability to respond to other drugs of a similar type.

- Other side effects such as anxiety, sleeplessness, joint pain, weight loss, and decrease of appetite have been reported in clinical studies with obinutuzumab.

If you have had hepatitis B in the past, treatment with obinutuzumab may increase the risk of the hepatitis B infection coming back. Blood samples will be taken before you enter the study to test for hepatitis B. If the tests show that you have active infection or have had an infection in the past, you will not be allowed to take part in the study.

A blood sample will also be taken to assess whether you have another form of hepatitis, called hepatitis C. If this test is positive, you will not be allowed to enter into the study unless a different confirmatory test (called HCV RNA) is negative. State law requires that the results of positive tests for hepatitis be reported to a local health agency.

In rare cases, some patients may develop serious viral infections or, occasionally, have a flare-up of an old infection. In some cases, these infections may occur over 1 year after the treatment is completed and result in death. A very rare and severe viral infection called progressive multifocal leukoencephalopathy (PML), which causes brain damage and is almost always fatal or causes severe disability, has occurred in patients with cancer treated with monoclonal antibodies, including obinutuzumab. This disease can occur in cancer patients even if they do not receive anti-cancer treatment. You should tell your study doctor/study research staff immediately if you have memory loss, trouble thinking, difficulty with walking, or loss of vision.

Ibrutinib

You may develop side effects while participating in this study. You should tell the study doctor about any side effects that you develop.

The side effects listed below have been reported by patients who have received ibrutinib in clinical trials.

The most common side effects, occurring in at least 1 of every 5 patients (≥ 20%), have been:

- Occurrence or increase frequency of loose or watery stools (Diarrhea)
- Muscle and bone pain (Musculoskeletal pain)
- Nausea
- Low white blood cell count (cells that help fight infection) (Neutropenia)
- Low platelet count (cells that help blood to clot) (Thrombocytopenia)
- Bleeding (Haemorrhage)
- Rash
- Fever (Pyrexia)
- Common cold (Upper Respiratory Tract Infection)

Side effects that have been seen in at least 1 of every 10 (≥ 10%) patients include:

- Pneumonia
- Constipation
- Swelling of the hands or feet (Oedema peripheral)
- Muscle spasms
- Vomiting
- Joint aches (Arthralgia)
- Sores in mouth (Stomatitis)
- Headache
- High Blood pressure (Hypertension)
- Skin infection
- Weakness, tingling, numbness, and pain from nerve damage, usually in the hands and feet (Peripheral neuropathy)

- Dizziness
- Urinary tract infection
- Indigestion (Dyspepsia)

Side effects that have been seen in at least 1 of every 100 (≥ 1%) patients include:

- Sinus Infection (Sinusitis)
- Increased level of uric acid in the blood (Hyperuricemia)
- Abnormal heart rhythm (Atrial fibrillation)
- Non-melanoma skin cancer
- Blurry vision (Vision blurred)
- Low white blood cell counts with fever (Febrile neutropenia)
- Severe infection throughout the body (Sepsis)
- Redness of the skin (Erythema)
- Increase in white blood cell counts (Leukocytosis)
- Breaking of the nails (Onychoclasis)
- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Heart failure (Cardiac failure)
- Itchy rash (Urticaria)

Side effects that have been seen in less than 1 of every 100 (<1%) patients include:

- Increase in white blood cell count (Lymphocytosis)
- 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)
- Inflammation of the fatty tissue underneath the skin (Panniculitis)
- Swollen face, lip, mouth, tongue or throat (Angioedema)
- High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- Liver failure (Hepatic failure)
- Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachyarrhythmia).
- Bleeding in the eye (Eye hemorrhage)

Most of these side effects listed above have been mild to moderate in severity; however severe side effects have occurred. Some side effects have been severe enough to lead to study drug discontinuation, dose modification or reduction, hospitalization, disability and sometimes death.

You should tell your study doctor or medical team about any side-effects you are having. Your study doctor may be able to give you medications to help treat the side effects and prevent them from becoming worse. Your study doctor may also choose to stop ibrutinib for a short time or reduce its dose to allow you to recover from any side effects.

Bleeding

You may experience bruising or nosebleeds during treatment with ibrutinib. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur, sometimes resulting in death. If you take other 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, ibrutinib may increase this risk. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided while taking ibrutinib. Call your study doctor 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.

Effects on the heart

Abnormal rapid and/or irregular heart rhythm (atrial fibrillation, atrial flutter, and/or ventricular tachyarrhythmia) have been reported in patients treated with ibrutinib, especially when they also have heart conditions, increased blood pressure, infections, have diabetes, or had abnormal heartbeat in the past. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart, dizziness, weakness, feeling light-headed, shortness of breath, chest discomfort or fainting. Ibrutinib can also potentially cause an abnormally slow heart rhythm by effective the heart rhythm generator, which is called sinus node dysfunction. This slow heart rate can also cause dizziness, weakness, feeling light headed, or feeling short of breath. If you develop any of these symptoms while on the study drug, you should tell your study doctor immediately.

Infections

You may experience viral, bacterial, or fungal infections during treatment with ibrutinib. 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, vomiting, jaundice, feel tired or feel short of breath - these could be signs of an infection. Your study doctor may start or continue medication to help prevent or treat an infection.

A rare and usually fatal viral disease in the brain, Progressive Multifocal Leukoencephalopathy (PML), has been reported in patients treated with ibrutinib in combination with rituximab and in patients who were previously treated with rituximab. If you experience symptoms such as weakness, paralysis, vision loss and/or impaired speech, you should tell your Study Doctor immediately.

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 treatment and you should not assume that this increase in white blood cells means that your disease is worsening. This increase may last for several weeks to months. 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 patients treated with ibrutinib. Your study doctor will monitor your blood counts and may administer additional therapy as needed. Talk to your study doctor about what your test results mean.

Decreased blood counts

Severe decreases in white blood cells, red blood cells, and platelets (neutropenia, anemia, and thrombocytopenia) were reported in subjects treated with ibrutinib. If you experience symptoms such as fever, weakness, or easy bruising and/or bleeding, you should tell your Study Doctor immediately.

Allergic reactions

Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction to ibrutinib, 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 the Study Doctor right away if you have any allergy symptoms listed above.

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. You should notify your study doctor 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.

Non-Melanoma Skin Cancer and Other Cancers

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and may be related to the use of ibrutinib. Other cancers have been reported such as solid tumors and blood cancers, the relationship to the use

of ibrutinib is unknown. You should tell your study doctor if you develop a new cancer while in the study.

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.

Hypertension

Hypertension is also called high blood pressure, and 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. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your study doctor 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. Your study doctor may adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Liver Failure

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, and 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.

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.

Interference with other drugs/food

Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body processes ibrutinib. This interference could cause the amount of ibrutinib in your body to be higher or lower than expected. It is also possible that taking the study drug with your regular medications or supplements, including fish oil,

Vitamin E, or other vitamins, may change how your regular medications, or your regular supplements, work. It is very important that you avoid grapefruit juice and Seville oranges and tell the study doctor about all medications, supplements, or herbal medicine like St. John's wort that you are taking during the study. You should notify your study doctor immediately about any side effects to avoid possible harm.

Drug interruption for any surgical procedures

Ibrutinib may increase the risk of bleeding with any surgical procedure. Ibrutinib should be held at least 3 to 7 days before and after surgery depending upon the type of surgery and the risk of bleeding. Please contact your study doctor if you have any planned surgical procedures. For emergency surgical procedures, ibrutinib should be discontinued (stopped) after the procedure until the surgical site is reasonably healed (not oozing fluid).

Please contact your study doctor as soon as possible and your study doctor will tell you when to stop ibrutinib and when to restart it following a surgical procedure.

In addition to the risks listed above, there could be unknown or unexpected side effects associated with the use of ibrutinib. You will be told in a timely manner, verbally and in writing, of any new information, findings, or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

You may have all, some, or none of the listed side effects of ibrutinib. Your study doctors and nurses will check you closely for side effects. You may receive medicines or other treatments to prevent or reduce some of these effects. Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think they are related to the study drug.

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Reproductive effects

The effects of ibrutinib on a developing baby are unknown; therefore women who are pregnant or nursing are not allowed to be in this study. Nobody knows what these risks are right now. Some drugs cause women to have their babies prematurely (early) or to have babies with birth defects.

Women: If you are able to have children, you must use a highly effective method of birth control and a barrier method, or sexual abstinence (which is defined as refraining from all aspects of sexual activity), while taking study treatment, as well as for 1 month after you stop taking study treatment, to prevent pregnancy in either you or your partner, unless your partner is sterilized. A "highly effective method of birth control" is defined as a method that has a low failure rate (i.e., less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with 2 hormones, some intrauterine devices (IUDs). If you are

using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (e.g., condoms) must be used.

Men: You must use a barrier method while on treatment with ibrutinib and for 3 months after the last dose of treatment to prevent pregnancy of your partner. You should not donate sperm while you are taking the study drug and for 3 months after you stop taking the study drug.

Note: Some birth control pills may not work when you are taking certain drugs. If you have any questions about this, please discuss this with the study doctor.

Be aware that you can still become pregnant even if you use a highly effective method of birth control.

Women: If you become pregnant while you are on study treatment or within 1 month of your last dose of ibrutinib you must notify the study staff. If you become pregnant on the study, you must immediately stop taking the study treatment. The Sponsor will continue to collect information about your pregnancy and the birth of your baby even after study treatment is stopped.

Men: If your partner becomes pregnant while you are on study treatment, or within 3 months of your last dose of ibrutinib, you must notify the study staff. The study staff will discuss this with you further.

Breast-feeding

It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, breast-feeding should be discontinued during ibrutinib treatment.

Additional Risks

Blood drawing risks:
There may be bruising, bleeding or inflammation at the sites where blood samples are taken. Care will be provided to avoid these complications.

Bone marrow biopsy risks:
A bone marrow biopsy and aspiration is a procedure in which an area of the hip is numbed with an anesthetic drug (similar to a shot of Novocain before dental work), and a needle inserted into the numbed area. A small sample of bone marrow and fluid is withdrawn through the needle. Complications related to bone marrow aspirations and biopsies may include bleeding (inside or outside the body), pain, bruising, blood clots and infection. Care will be taken to avoid these complications.

Lymph Node Biopsy (for participants after 11/1/2018):
Tissue biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with your doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Genetic testing will be performed on your tumor tissue retrieved during the biopsies.

Imaging (CT and MRI scans):
The known risks associated with CT and MRI scans include the rare occurrence of allergic reactions to the contrast dyes injected into a vein during the scan. Such allergic reactions can involve itching, rash, or in severe cases, difficulty in breathing and dangerous lowering of blood pressure. If you have known allergic reactions to imaging contrast agents, you should let your study doctor and radiologist know. Additionally, these scans are associated with exposure to vary small amounts of radiation.

ECG (Electrocardiogram):
There are very rare chances of developing allergic dermatitis (itching, redness of skin) due to electrodes used for ECG examination.

Reproductive risks:
You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

If you or your partner becomes pregnant while you are on the study, or within 30 days of your last dose of study drug, you must notify the study staff immediately. The study staff will discuss this with you immediately. If you become pregnant on the study, you must immediately stop taking the drug.
For more information about risks and side effects of these or any other tests and procedures, always ask your doctor or another member of your health care team.

7. What benefits can I expect from being in the study?
There is no guarantee that this treatment will benefit you. This treatment regimen may also be harmful to you. However, the benefits could be an easing of symptoms; decrease in the amount

of cancer suggestive of improvement in your cancer, prolonged disease-free remission and/or survival or increased knowledge about this cancer treatment in patients with CLL. This information could benefit patients in the future.

8. What other choices do I have if I do not take part in the study?
You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate in this trial, other treatments you qualify for will be discussed with you.

Other treatment options may include:
- Getting treatment or care for the subject's cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care.

The quality of care you receive will not be affected if you choose not to participate in this study.

9. What are the costs of taking part in this study?
The study drugs Obinutuzumab and Venetoclax will be provided to you free of charge. You will not be charged for any tests or procedures that are for research purposes. You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research study.

You and / or your insurance company will be billed for the costs of routine tests and procedures in the usual manner. You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage. You will be responsible for any charges not reimbursed by your insurance company. Some insurance companies will not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

10. Will I be paid for taking part in this study?
You will not be paid to take part in the study.

11. What happens if I am injured because I took part in this study?
If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Medical Center.

If you are injured as a result of your participation in this study, you may obtain immediate care at the Ohio State University Medical Center. The cost of this treatment will be charged to you or your insurance company. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study. The Ohio State University has no funding set aside for the payment of health care expenses for this study.

By signing this consent form, you will not be waiving any of the legal rights which you otherwise would have as a subject in a research study.

12. What are my rights if I take part in this study?
If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

13. Will my study-related information be kept confidential?
Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):
- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsors (Genentech**)** supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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

14. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:
  HIV / AIDS
  Hepatitis infection
  Sexually transmitted diseases
  Other reportable infectious diseases
  Physical exams
  Laboratory, x-ray, and other test results
  Diaries and questionnaires
  The diagnosis and treatment of a mental health condition
- Records about any study drug you received;

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office record;
- Others: Genentech, the study drug sponsor of this research and any persons or companies that are:
  - Working for or with the sponsor; or
  - Owned by the sponsor.
- OSUCCC Data and Safety Monitoring Committee (DSMC).

IV. Your information may be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact:

Kerry A. Rogers, MD
458 Wiseman Hall
400 W 12th Ave
Columbus, Ohio 43210
Phone: 614-366-9338 24 hrs: 614-293-8000 ext. 5806

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

For HIPAA privacy concerns:

Medical Center Office of Compliance & Integrity
1590 N. High St. Suite 500
Columbus, OH 43201
Ph: 614-293-4477
Email: privacyoffice@osumc.edu

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact:

Kerry A. Rogers, MD
458 Wiseman Hall - CCC
410 W 12th Ave
Columbus, Ohio 43210
Phone: 614-366-9338 24 hrs: 614-293-8000 ext. 5806

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
	AM/PM
Relationship to the subject	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM

Date and time