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

Study Title:	Daratumumab and Ibrutinib for Symptomatic, Treatment-Naïve CLL: A Phase 1b Proof-of-Concept Study
Principal Investigator:	Jennifer Woyach, MD
Sponsor:	Janssen Pharmaceuticals 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 take part in a research study (also known as a clinical trial). This is a consent form and it has details about the study that your doctor will explain if you decide to take part. We are asking you to take part in this study because you have previously untreated chronic lymphocytic leukemia (CLL).

This is a study to evaluate the safety and effectiveness of two cancer drugs, daratumumab and ibrutinib in patients with previously untreated CLL.

While doing this, researchers hope to discover what effects, if any, the study drugs have on people when the drugs are taken together for people with previously untreated CLL.

In this investigational study, researchers may utilize drugs which have not been approved by the Food and Drug Administration (FDA) for use in your type of cancer. Ibrutinib is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CLL. Although this drug has been FDA approved, its use in this study is considered experimental because it is being combined with daratumumab. Daratumumab is approved by the U.S. FDA for the treatment of patients with multiple myeloma.

2. How many people will take part in this study?

A total of 31 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.

Because the safety of the combination has not before been assessed, the study will be conducted in 2 stages. Depending on which stage of the study you are in the doses of the drugs may be different.

Treatment will be delivered in cycles of 28-day length. Daratumumab will be administered intravenously at the approved dose (16 mg/kg) and schedule beginning during Cycle 1 and continuing through Cycle 12. Ibrutinib will be administered orally once daily at the approved dose for CLL (420 mg) beginning during Cycle 2. Ibrutinib will continue until disease progression unless side effects are intolerable.

Your tissue samples called specimens (such as blood and tumor) will be collected by the nursing staff. The samples will then be sent to the clinical trials processing laboratory, and studies will be performed in the Experimental Hematology Laboratory at OSU unless otherwise noted. Samples not immediately used will be stored at OSU for future study to examine mechanism or response to this novel combination. These samples will only be used for research associated with this trial.

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, Hepatitis B and C, hepatitis B virus DNA (HBV DNA), 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 child bearing 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).

Study Drug Administration

Daratumumab

Daratumumab is given as an infusion. The daratumumab infusion will be intravenously administered at the appropriate initial infusion rate. Incremental escalation of the infusion rate will be considered only if the previous infusion of daratumumab was well-tolerated.

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.

Tests and Observations During the Study:

During the study, you will have examinations, laboratory studies, and other studies in the following intervals:

	Cycles 1 and 2				Cycles 3 through 6		Cycles 7 through 12	Cycle 13+
Day	1	8	15	22	1	15	1	Day 1 Every 12 weeks
Physical Examination	X				X		X	X
Routine laboratory studies	X	X	X	X	X	X	X	X
Bone Marrow Biopsy							Day 1 cycle 7	Day 1 cycle 13 and at time of complete response
CT (or MRI) Scans							Day 1 cycle 7	Day 1 cycle 13 and every 6 months for 2 years

If you stop therapy for a reason other than disease progression, you will continue to be followed every 12 weeks with laboratory studies and physical exam until the time that your CLL progresses.

4. How long will I be in the study?

If you agree to participate, your involvement will last as long as your disease does not progress and you continue to agree to be involved in the study. All patients, including those discontinuing for unacceptable adverse events, will be followed for safety and disease assessments until initiation of alternative CLL-specific therapy, disease progression, death, withdrawal of consent for further follow-up, or until no more than 2 years after the last patient completes planned therapy. In conclusion you will be in the study for approximately 3 years.

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. Your decision will not affect your future relationship with The Ohio State University. Please contact your study coordinator or Dr. Jennifer Woyach at 614-685-5667 or 614-293-8000 (24 hours) if you wish to withdraw your consent.

In addition, Dr. Jennifer Woyach may stop you from taking part in this study at any time:

- If it is in your best clinical interest,
- If you do not follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

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

Any drug has risks and side effects which may vary from person to person. Side effects may be mild or very severe. Most side effects will go away after treatment is stopped, but some may be long lasting. Side effects seen on research studies can result from a patient's disease, the drug under study, other drugs you are taking, other diseases you have, or a combination of these. This section gives you the information known so far about side effects seen with daratumumab.

Daratumumab

As of 15 November 2023, approximately 6,034 patients with multiple myeloma and other various conditions, have been treated with daratumumab IV *(intravenous, directly into the*

vein) or SC *(subcutaneous, underneath the skin of the abdomen). Of these 6,034 patients about 2,163 received daratumumab*) alone, *and about 4,100 patients received daratumumab* or in combination with other therapies.

Daratumumab

Daratumumab is commercially approved for the treatment of multiple myeloma and AL amyloidosis, a rare disease that occurs when an abnormal protein, called amyloid, builds up in your organs and interferes with their normal function. For AL amyloidosis it is currently approved by the FDA (United States) in combination with three medications: bortezomib, cyclophosphamide and dexamethasone.

Not all the possible side effects and risks related to daratumumab are known. New side effects may happen. You will be watched closely and you will receive appropriate care if side effects happen. Please tell your study doctor if you have any of the side effects described below or any other ones not listed. You will be told of any new findings that may affect your decision to continue in this study.

The following side effects are observed when daratumumab was given to patients with multiple myeloma, either alone or in combination with other drugs.

Very common side effects with daratumumab (affects 1 in 10 patients or more).

- Infusion related reaction (see separate section)
- Infection of the upper respiratory tract such as nose, sinuses throat or upper airway, including influenza and flu like symptoms
- Infection of the lower airway (bronchitis)
- Infection of the lung (pneumonia)
- Low platelets, may increase the risk of bleeding and bruising
- Low red blood cells (anemia)
- Low white blood cells (including neutrophils and lymphocytes); may increase the risk of getting an infection (see also separate section below)
- Decreased potassium in the blood
- Decreased appetite
- Sleeplessness (insomnia)
- Abnormal sensation including numbness/tingling of hands, feet or limbs (sensory neuropathy, paresthesia)
- Headache
- High blood pressure
- Cough
- Shortness of breath, including wheezing
- Constipation
- Diarrhea
- Nausea
- Pain in the belly (abdomen)
- Vomiting

- Rash, a noticeable change in the texture or color of your skin
- Muscle spasms
- Swelling of hands, feet or limbs
- Fatigue, or lack of energy
- Weakness, lack of strength
- Fever
- Pain in the bones and muscles such as back pain or chest pain
- Joint pain

Common side effects with daratumumab (affects 1 in 100 patients or more and fewer than 1 in 10 patients).

- Urinary Tract infection
- COVID-19
- Sepsis (a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs)
- Hypogammaglobulinemia, a condition with your immune system in which not enough gamma globulin proteins (also known as antibodies) are produced. Decreases in gamma globulin proteins can increase the risk of infections
- High blood glucose levels
- Low blood calcium levels
- Loss of body fluids, also known as dehydration
- Irregular heartbeat
- Chills
- Fluid in lungs (pulmonary edema)
- Dizziness
- Fainting
- Inflammation of the pancreas (pancreatitis)
- Itchy skin
- Low blood pressure (hypotension)
- Weight loss

Uncommon side effects with daratumumab (affects in 1,000 patients or more and fewer than 1 in 100 patients).

- Cytomegalovirus infection (see separate section on infections below)
- Liver infection (hepatitis) in those patients who are carriers of the hepatitis B virus
- Interference with pre-transfusion blood testing (see Indirect Antiglobulin Testing below)

<u>Infusion Related Reactions</u>

An antibody is a large protein that is generated as part of the normal immune system to neutralize foreign objects such as bacteria and viruses. Daratumumab is an antibody designed to specifically target and eliminate a specific harmful object in your body, in this case cancerous plasma cells. A non-local side effect to daratumumab that occurs

during or shortly after an administration (IV or SC) is completed (when the medicine is given into a vein) is called an infusion-related reaction. Infusion-related reactions were reported in approximately half of all patients treated with daratumumab IV. *These reactions can be life-threatening and fatal outcomes have been reported when given IV. In patients treated with daratumumab SC, infusion-related reactions were reported in about 9% of the patients. Reactions* usually occurs with the first administration and during or within the first few hours after the start of the administration.

Signs and symptoms of infusion-related reactions may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, low blood pressure or high blood pressure and fluid in the lungs (pulmonary edema). Most of the observed infusion-related reactions so far were mild or moderate, and ended by temporarily stopping the administration and/or giving medicines to treat the side effect. Tell your doctor right away if you have above mentioned symptoms.

If you have a breathing problem now or have had breathing problems in the past (like chronic obstructive pulmonary disease (COPD) or asthma), you should tell your study doctor. Also, if you start to have breathing problems while you are on the study you should tell your study doctor right away. You may be asked to see a doctor who takes care of patients with airway diseases, and additional medicines for airway problems may be given to you. Your doctor will explain how these additional medicines should be taken. Get emergency medical help if you have any of the following: hives, wheezing, difficulty breathing, swelling of your face, lips, tongue, or throat or pain in chest.

Severe reactions have occurred, including narrowing and obstruction of the respiratory airway (bronchospasm), low level of oxygen, shortness of breath, high blood pressure, swelling in the throat and fluid accumulation in the lungs (pulmonary edema), and complaints of the eyes, such as fluid in the eye (choroidal effusion), blurry vision (acute myopia), and increased pressure in the eye or eye pain (acute angle closure glaucoma). In addition, heart attack (myocardial infarction) have also occurred when daratumumab is given through the vein. Your study doctor and their staff will be ready to treat such a reaction in case it happens. In the future, you should tell any doctor you visit that you received daratumumab (an antibody) in this research study and if you had an allergic reaction including anaphylaxis, the worst case of allergic reaction.

<u>Anaphylactic Reaction</u>
Anaphylactic reaction is a serious allergic reaction that can develop quickly (in minutes to a few hours) and may cause death. Usually a combination of the following side effects occurs: an itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, and low blood pressure. This type of reaction is for example seen when one is allergic to a bee sting or certain foods like peanuts.

Anaphylactic reactions were rarely reported when commercially available daratumumab was used outside of clinical trials (also called postmarketing experience). The reported cases of anaphylactic reaction were believed to be a more severe form of infusion related reactions. More than 150,000 patients globally have been treated with daratumumab. Anaphylactic reaction has not been reported in clinical studies; therefore, the frequency is not known.

Please inform your doctor immediately if you experience any of these signs and symptoms.

The sponsor will continue to monitor infusion-related reactions and make changes to the way daratumumab is administered and/or recommend additional medications as necessary.

In this study, the following will be done to reduce the chance of a daratumumab infusion-related reaction:

- You will get medications, including steroids, acetaminophen and antihistamine, before the administration
- If you have a reaction, the administration will be paused and/or the symptoms treated as needed. Dependent on the reaction, the administration may continue at a slower rate. If you have a life-threatening reaction, you will need to stop further treatment with daratumumab and your doctor will discuss alternative treatments with you.
- If you are considered higher risk for breathing problems (for example COPD, asthma), you may also get medications, including inhaled steroids, after the administration.
- You may stay overnight in the hospital after the administration so medical staff can check you

<u>Immunogenicity</u>
Immunogenicity is the ability of cells/tissues to provoke an immune response and is generally considered to be an undesirable physiological response. In order for daratumumab to be absorbed into the body when injected under the skin, it is combined with a substance called recombinant human hyaluronidase PH20 (rHuPH20). rHuPH20 is a substance that breaks down hyaluronic acid, these have long been used to increase the absorption of drugs, like daratumumab, under the skin and into the blood stream. Some patients who receive rHuPH20 may develop antibodies directed to the PH20 hyaluronidase; approximately 5% of the general population has these antibodies even without ever having been exposed to rHuPH20. Antibodies are a blood protein produced in response to foreign substances in the body. Antibodies combine chemically with substances which the body recognizes as alien, such as bacteria, viruses, and foreign substances in the blood. In clinical trials, there have not been any links between the development of these antibodies and any negative effects. Antibodies to rHuPH20 could, in theory, interact with human sperm (location of the PH20 hyaluronidase in the body). It is unknown whether these antibodies may interfere with conception or fetal development in humans. Extensive animal studies do not indicate harmful effects due to rHuPH20 or

antibodies developed in response to treatment with rHuPH20 in regards to male or female reproduction. Studies have been performed with doses of rHuPH20 higher than those in this study.

Blood Cell Effects

Daratumumab can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever or any symptoms of decreased platelet counts such as bruising or bleeding.

Infection

Different kinds of infection have been seen in patients receiving daratumumab. Most of them are upper respiratory tract infections. *If you have an infection now, have a history of frequent infections, or if you feel sick, you should tell your study doctor right away. Signs of an infection may include fatigue, headache, fever, chills, aches and pains, coughing, congestion, chest tightness, or shortness of breath.* Majority of the observed infections so far were mild or moderate. Severe infection such as pneumonia from bacteria, influenza virus, respiratory syncytial virus, and COVID-19, and sepsis has also been reported. Your doctor may also recommend other medications to potentially prevent or reduce the risk of COVID-19 infection or severe infection. It is important to tell your study doctor right away if you are diagnosed with COVID-19 (even if you have no or only minor symptoms) or have been exposed to someone with COVID-19 infection. It is also important to continue general infection prevention practices such as washing hands, wearing masks, social distancing, and avoiding public transportation or travel as much as possible.

Cytomegalovirus (CMV) is a kind of herpesvirus which usually produces very mild symptoms in an infected person that infects 50-85% of adults in the US by age 40 and is also the virus most frequently transmitted to a child before birth. Persons with symptoms have prolonged fever and mild liver inflammation. Once a person becomes infected, the virus remains alive and usually dormant within that person's body for life. Recurrent disease rarely occurs unless the person's immune system is suppressed due to therapeutic drugs or disease.

Certain infections with viruses, such as shingles (Herpes Zoster Virus) and cytomegalovirus and liver infection (hepatitis B virus) have been observed with daratumumab. Your doctor will tell you about how to prevent the Herpes Zoster Virus infection. Severe liver infection, including cases resulting in death, have occurred in patients who are carriers of hepatitis B virus. Patients who have had prior exposure to hepatitis B virus are at increased risk of recurrence of the virus. Your doctor will test you for the hepatitis B virus before beginning treatment on this study [or if you are already on the study and have been receiving treatment for less than 6 months]. If you test positive for the virus, you will be closely monitored for signs of infection during daratumumab treatment and until 6 months after the last dose of daratumumab, and you will be treated, if appropriate, by your doctor.

Indirect Antiglobulin Testing

If you need a blood transfusion, tests are performed on your blood so that suitable donor blood can be given for a transfusion. Daratumumab treatment will affect one of these tests known as an indirect antiglobulin test (IAT; also known as an indirect Coombs test).

Therefore, an IAT will be done before you receive daratumumab, and the result placed on the patient identification wallet card you will carry for this study. Before a blood transfusion, you should show the wallet card and tell all your health care providers that you are taking daratumumab and that it interferes with pre-transfusion blood testing. You should do this during the entire period that you are receiving daratumumab and for at least 6 months after your daratumumab administration or for as long as your study doctor recommends.

When daratumumab is given at the same time with other drugs, some side effects of these drugs may happen more often or may be more severe. There may be other unexpected side effects.

What about birth control and pregnancy during the study?

The effects of daratumumab on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. If you are a woman, taking part in the study might harm your unborn child or breast-fed baby. Thus, you must agree not to become pregnant while you are in this study. Also, you cannot take part in this study if you are pregnant or breastfeeding a child. If you are a man, the effect of daratumumab on your sperm is unknown.

If you are a woman and becoming pregnant is a possibility, you will be required to undergo a pregnancy test prior to taking daratumumab. Both male and female patients must use effective methods of birth control during the course of the study and for 3 months after stopping daratumumab.

The type of birth control you use must be discussed with, and approved by, the study doctor before you begin the study. If you are female and become pregnant during the study, you must tell the study doctor immediately.

If you are a woman:

- You must not donate eggs during the study and for 3 months after your last dose of study drug.

If you are a man:

- The effect of the study drug on your sperm is unknown.
- You must not donate sperm during the study and for 3 months after your last dose of study drug

Your study doctor will discuss with you and the sponsor if it is in your best interest to continue or stop some or all treatments.

The study doctor will advise you about your medical care. We will ask you to allow us to collect information about your pregnancy and the health of your baby. If you are male, you should advise your study doctor if you father a child while participating in this study. The doctor will advise you on medical attention for your partner should this be necessary. We will ask for your partner's permission to collect information about the pregnancy and health of the baby.

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 and from post-marketing sources.

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

- Occurrence or increase in 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 specific white blood cell counts (Leukocytosis, Lymphocytosis)
- Breaking of the nails (Onychoclasis)
- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Increased level of "creatinine" in the blood (blood creatinine increased)
- Heart failure (cardiac failure)
- Itchy rash (Urticaria)

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

- 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)
- Itchy rash (Urticaria)
- 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)
- Temporary or permanent decrease of brain or nerve function due to reduced blood flow to the brain (mini-stroke or stroke)
- Tender or painful bumps or ulcers on the skin, sometimes with a fever (neutrophilic dermatoses)
- Bleeding in the eye (Eye hemorrhage)
- Inflamed blood vessels in the skin, which may lead to a rash (cutaneous vasculitis)

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) and heart failure, including some fatal events, 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. Tell your study doctor immediately if you have any symptoms of heart problems such as feeling as if your heartbeat is fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, swollen legs, or you faint.

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 specific 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. In rare cases, 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 to 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.

Stroke
Cases of stroke, with and without changes in heartbeat rhythm and/or hypertension have been reported with the use of ibrutinib. Some of these cases have led to death. Seek immediate medical attention if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

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.

Side effects for Ibrutinib (Imbruvica®) and Daratumumab (Darzalex®) combination studies:

Side effects of unknown frequency:

- Visual Disturbances or Ophthalmic Events

Other Side Effects

Possible Risks and Discomfort Associated With Drawing Blood
During this study, small amounts of blood will be drawn from a vein in your arm for laboratory tests that allow your doctors to see how you are doing. Drawing blood may

cause pain where the needle is inserted, and there is a small risk of bruising and/or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.

Bone Marrow Aspiration and Biopsy (Removal of Tumor Tissue)
You will be required to undergo regular bone marrow aspirations and biopsies as part of this study. As with any procedure, there are risks and discomforts. You may feel some amount of pain or discomfort during the aspiration or biopsy, including slight, stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness at the biopsy site. If a conscious sedation medication is used, you will not feel pain during the procedure because you will be asleep. Your study doctor will explain the details of the procedure and the risks to you, depending on how the bone marrow aspirate and biopsy will be obtained.

Other risks include redness, swelling, excessive bleeding, bruising, or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site.

Possible Risks and Discomfort Associated With Computed Tomography Scans
CT scans are special X-ray tests used to study the internal organs and bones of your body, and they may be necessary for measuring your response to this treatment. You would likely undergo these scans even if you were not participating in this research study because your doctor would need to monitor your disease. If during the screening period there is no evidence of CLL outside of the bones and bone marrow, then you will not need regular CT scans.

You will be exposed to radiation from CT scans approximately every 16 weeks. During this study, the total radiation dose to your whole body will be about 126 millisieverts (mSv; a measurement of radiation received), which is 252% of the 50-mSv annual whole-body limit for adult radiation workers (i.e., the amount of radiation that is not expected to be harmful over a 1-year period). Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life. Since the effects of radiation can build up over time, it is important to know your past radiation exposure. If you have been exposed to radiation through CT scans, X-rays, or other means in the past 12 months, please inform study personnel. If it is determined that your prior radiation exposure exceeds current guidelines, it is possible that you will not be allowed to participate in this study.

As part of the CT scan, a contrast agent may need to be taken by mouth and/or injected into your vein to make certain organs and disease sites visible on the scan. Oral contrast may cause side effects such as nausea, constipation, diarrhea, and abdominal bloating. Pain, bruising, redness, swelling, or infection may occur at the site where a needle is inserted to administer the contrast material into your vein. It is normal to experience a

warm, flushing feeling when the contrast material is given. You may have an allergic reaction to the contrast material that may cause rash, hives, shortness of breath, wheezing, and itching, and rarely may cause your heart to stop beating ("cardiac arrest"). The use of contrast material during these tests would be a normal part of measuring your response to therapy, even if you were not participating in this research study.

Possible Risks and Discomfort Associated With MRI Scans

MRI scans are specialized imaging procedures that are necessary for measuring your response to this treatment. For most patients, the risks or side effects associated with undergoing MRI are minimal. An MRI scan does not involve ionizing radiation like conventional X-rays. Instead, images are generated using a magnetic field and radio signals. Because an MRI scanner uses strong magnets, you cannot have any metal implants in your body to have an MRI scan. People with an artificial heart valve, metal plate, pin, or other metallic objects in their body (including gun shot or shrapnel) are not eligible for MRI scans. Study personnel will ask you questions to make sure you can safely have an MRI scan.

There may be some anxiety and claustrophobia (fear of being in small places) associated with the scanner. Staff at the imaging center use techniques to help reduce these feelings in patients. Your study doctor may also prescribe mild sedatives or anti-anxiety drugs to help manage your symptoms. As part of the standard MRI scan, a contrast agent containing gadolinium is injected into your vein to enhance visibility. The risks associated with the contrast agent include mild nausea, headache, hives, temporary low blood pressure, chest pain, back pain, fever, weakness, and seizures. There have been reports of a severe and potentially fatal condition known as nephrogenic systemic fibrosis (a scarring condition that can lead to kidney failure) that has occurred in some patients who received gadolinium-based contrast agents. This has not been seen in patients with normal working kidneys or mild problems in kidney function. Prior to study entry, your study doctor will run tests to determine if your kidneys are working properly to make sure the contrast agent is safe for you.

Possible Risks Associated With Loss of Privacy

Although your genetic information will not contain any personal identifying information, there is a very small risk that it could be linked to an outside public database and used to help identify you and your blood relatives. Because some genetic differences can help to predict future health problems experienced by you or your blood relatives, this information might be of interest to health care providers, life insurance companies, and others. It is possible that your genetic information could be used in ways that would cause you or your family distress, such as by revealing that you or a blood relative carries a genetic disease. Your privacy is very important, and Roche uses many safeguards to protect your privacy. However, there is no guarantee that your identity will never become known. Refer to the "Will my medical and personal information be kept private?" section for information about laws that protect against certain genetic discrimination.

Reproductive Risks

The effects of ibrutinib or daratumumab 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 3 months 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 or daratumumab 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 3 months of your last dose of ibrutinib or daratumumab you must notify the study staff. If you become pregnant on the study, you must immediately stop taking the study treatment. Your doctor 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 or daratumumab, you must notify the study staff. The study staff will discuss this with you further.

Breast-feeding
It is not known whether ibrutinib, daratumumab or their 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 these drugs, breast-feeding should be discontinued during study treatment.

7. What benefits can I expect from being in the study?

If you decide to take part in this study, there is no guarantee that you will receive any benefits from this study. Taking part in this study may or may not cause your health to improve. Information from this study may help doctors learn more about ibrutinib and daratumumab as treatments for cancer. This information could help other people who have a similar medical condition 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. You can get treatment for your CLL without participating in this study, or pursue other research studies. Please discuss options with your doctor.

9. What are the costs of taking part in this study?

Daratumumab, is the study drug and will be provided by Janssen. Ibrutinib study drug is FDA approved for your disease and will be billed to you and/or your insurance in the usual manner.

Participation in this study will **not** eliminate costs associated with routine clinical care of your CLL. You or your insurance company is responsible for paying for procedures, tests, and any medications that are considered standard care for CLL. The costs of the standard care will be billed in the usual manner and the co-payments, deductibles and co-insurance required by your insurance company will still apply. If you have questions regarding what is covered by your insurance company please feel free to contact your insurance company.

If you have questions regarding the research procedures and tests, please speak with your doctor or research coordinator.

10. Will I be paid for taking part in this study?

No, you will not be paid or reimbursed for taking part in this 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 Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this 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 company supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

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:
  - Physical exams
  - Laboratory, x-ray, and other test results
  - Diaries
- Records about any study drug you received

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

Study doctor 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: Janssen Scientific Affairs, LLC, OSUCCC Data and Safety Monitoring Committee (DSMC).

IV. Your information <u>may</u> 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, or if you feel you have been harmed as a result of study participation, you may contact:

Jennifer Woyach, MD
455A Wiseman Hall
Columbus, OH 43210
Ph: 614-685-5667
24 hrs: 614-293-8000

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact *Medical Center Office of Compliance & Integrity Suite 500, 1590 N. High St., Columbus, OH 43201. Phone number 614-293-4477, email privacyoffice@osumc.edu.*

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.

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

Jennifer Woyach, MD
455A Wiseman Hall
Columbus, OH 43210
Ph: 614-685-5667
24 hrs: 614-293-8000

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 combined consent and HIPAA research authorization form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	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