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

Study Title:	Early intervention trial of ibrutinib for patients with asymptomatic, high-risk chronic lymphocytic leukemia/small lymphocytic lymphoma
Principal Investigator:	Jennifer Woyach, MD
Sponsor:	The Ohio State University and The National Cancer Institute (NCI)

- **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?

The primary objective of this study is to determine the 2 year progression-free survival of asymptomatic, high-risk genomic CLL patients treated with ibrutinib. This study will also help to identify what the effects of the study drug are when taken with either the flu vaccine or when taken after the vaccine has already been administered, and to determine changes in the stress, anxiety and depressive symptoms, and related quality of life from patients treated with ibrutinib.

Patients with CLL having specific types of abnormalities in the leukemia cells have an especially aggressive disease with high risk for infections as the disease progresses in the first two years after diagnosis. Thus, the likelihood of their needing treatment within 2

years is high. Starting treatment earlier in these patients has the potential to prolong the time the patient can be in remission, i.e., no evidence of leukemia remaining in them. Earlier treatment also may reduce the risk of infections that they may encounter as the disease progresses

Patients enrolled on the study would be randomly placed in either one of two treatment groups of the study to either receive ibrutinib along with 3 vaccines - the pheumococcal vaccine (PREVNAR-13®), seasonal influenza virus vaccine (FLUZONE® or AFLURIA®), and Tdap (BOOSTRIX®) - (Group A) or after the 3 vaccines (Group B).

Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) Mantle Cell Lymphoma (MCL) in patients who have received at least one prior therapy, 2) Chronic Lymphocytic Leukemia (CLL)/Small lymphocytic lymphoma (SLL), 3) CLL/SLL in patients for their initial therapy with an abnormality called 17p deletion, and 4) Waldenström's Macroglobulinemia, 5) Marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy and 6) Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Ibrutinib is also known as IMBRUVICA® but will be hereafter referred to as ibrutinib or the study drug.

Patients will receive either FLUZONE® or AFLURIA® based on availability of the vaccines at OSU and seasonal availability.

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

Up to 21 patients will be enrolled on each arm of the study for a total of 42 patients expected to be enrolled at the The Ohio State University.

3. What will happen if I take part in this study?

This is a clinical trial (a type of research study). It includes only patients who are eligible and choose to take part. You may take your time to make your decision and discuss this with your family and friends. By agreeing to take part in this study, you are agreeing to comply with the study requirements.

You will be instructed on how to use a medication diary documenting each dose of medication. At scheduled visits, you will bring the medication calendar to the clinic. All bottles of study medication should be brought to each clinic visit for comparison with the medication calendar. The medication calendar for the previous time interval will be reviewed, and a new medication calendar will be given to you with each new study drug supply.

Before study enrollment, you must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-

up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

The following describes what will happen to you at each study visit.

Study Procedures

Screening Visit (within 28 days of starting treatment):
Before the study starts, you will discuss the study with your physician and will be asked to read thoroughly and sign this consent form. Only patients who meet certain requirements can participate in this study. Your study doctor is aware of all the requirements and can discuss them with you in detail. Please make sure you answer all of the questions your doctor may have so that he or she can make sure you are able to take part in this study. This will help your doctor determine whether it is safe for you to be in this study.

The following screening procedures will be completed:

- Standard of care history and physical exam, blood test (approximately 30 mins)
- You will be asked for a complete list of medicines you are taking, including supplements and vitamins.
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- An electrocardiogram (ECG), a test that measures how your heart muscle is functioning.
- If you are a woman of child bearing potential you will be required to complete a serum pregnancy test with negative results within 28 days prior to initiation of ibrutinib.
- A bone marrow sample and aspirate will be collected and part of this will be used to do laboratory research.
- A CT (computerized x-ray) scan will be performed to measure the size of the cancer in your body.

If the screening procedures show that you are eligible to continue to start treatment, and if you agree to participate in this study, you will be randomly placed to be treated on one of two treatment groups.

If you are assigned to the first group (Group A), you will take the study drug along with having an injection given intramuscularly of the Pneumococcal vaccine, Influenza and Tdap vaccines at the same time. If you are assigned to the second group (Group B), you will have in injection given intramusculary of the Pneumococcal vaccine, Influenza and Tdap vaccines the first three cycles and then take the study drug the remaining cycles. Each cycle will be for a 28-day duration and a total of 24 cycles for Group A and 27 cycles for Group B (approximately 2 - 2 ¼ years) of treatment.

You will receive enough study drug at each clinic visit according to which group you are participating in to last you until your next clinic visit. You should make all attempts to follow the treatment schedule and take the study drug at the assigned time. The study drug is stored at room temperature. Please do not freeze or refrigerate the study drug. The study drug must be taken by mouth once a day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact. Do not open capsules or dissolve them in water.

Each dose should be taken at approximately the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. Missed doses will not be made up and all the capsules from the missed dose must be returned to the clinic or hospital at the next visit. Each dose of ibrutinib should be taken

Please complete the drug diary form every day to keep track of your doses. The purpose of this form is to help you remember to take the study drug once a day. For each day, complete the date and time (including circling "am" or "pm") for when you took the study drug, and the number of capsules you took. If you experienced any symptoms that you feel might have been related to the study drug, write those down as well. Always take this form with you when you attend your visits with the clinic or hospital.

Each dose of ibrutinib can be taken with or without food; however, you should avoid taking the study drug with grapefruit juice or Seville orange juice, as they may interfere with how your body processes the study drug. 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 or supplements you are taking during the study. Be sure to tell your study doctor or study staff immediately about side effects to avoid possible harm.

If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. On the following day, you will take the study drug at the normally scheduled time. If a dose is missed for the entire day skip the missed dose and return to your normal dosing schedule. If you do not remember to take the missed dose on the same day, do not take extra pills the following day. Capsules that are missed must be returned at your next visit and not thrown away. If you do not follow the treatment schedule, or if you miss too many doses, you may be taken off the study.

Group A (study drug taken during cycles of vaccines)

Cycle 1 & 2 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (approximately 30 mins)

- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive enough study drug to last you until your next clinic visit.

Cycle 3 & 5 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (approximately 30 mins)
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive an injection given intramuscularly of the Pneumococcal vaccine PCV13 (PREVNAR-13®).
- You will receive enough study drug to last you until your next clinic visit.

Cycle 4 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (approximately 30 mins)
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive an injection given intramuscularly of the Influenza vaccine (FLUZONE® or AFLURIA®) depending on seasonal availability.
- You will receive an injection given intramuscularly of the Tdap vaccine (BOOSTRIX®).
- You will receive enough study drug to last you until your next clinic visit.

Cycle 6 thru 24 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (Cycle 18 Day 1 is the last cycle visit that the research questionnaire will be assessed) (approximately 30 mins)
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive enough study drug to last you until your next clinic visit.
- Based on how you are doing the study doctor may schedule you a bone marrow biopsy and CT scan.

Group B (study drug taken after 3 cycles of vaccines)

Cycle 1 & 3 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (approximately 30 mins)

- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive an injection given intramuscularly of the Pneumococcal vaccine PCV13 (PREVNAR-13®).

Cycle 2 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (approximately 30 mins)
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive an injection given intramuscularly of the Influenza vaccine (FLUZONE® or AFLURIA®) depending on seasonal availability.
- You will receive an injection given intramuscularly of the Tdap vaccine (BOOSTRIX®).

Cycle 4 & 5 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (approximately 30 mins)
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive enough study drug to last you until your next clinic visit.

Cycle 6 thru 27 – Day 1:

- Standard of care history and physical exam, blood test, and research questionnaire (Cycle 21 Day 1 is the last cycle visit that the research questionnaire will be assessed) (approximately 30 mins)
- Performance status (ECOG score) – The doctor will rate your ability to perform daily tasks (on a scale of 0 to 5).
- Medication diary is reviewed.
- You will receive enough study drug to last you until your next clinic visit.
- Based on how you are doing the study doctor may schedule you a bone marrow biopsy and CT scan.

End of Therapy (both Group A & B)

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. If you do not respond to the drug because your disease progresses or you have bad side effects or if you choose to stop treatment, you can undergo treatment with other agents if you are eligible or still may qualify in the future to undergo a stem cell transplant as a treatment option. No matter the reason for stopping

treatment, you will continue to be followed. Within 28 days (4 weeks) of completing treatment, your study doctor will repeat a medical history including how you are feeling and if there have been any changes in your health or medications since your last visit 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. Patients that have received 24 cycles of treatment will continue to have a blood test every 12 months as part of the research study. Additional blood tests and procedures may be requested if your study doctor feels they are medically necessary. You will be allowed a window of +/- 14 days to complete your end of study assessments.

4. How long will I be in the study?

The length of time you will be in the study will depend on if you are demonstrating clinical benefit and you will continue the study for up to 24 cycles each of 28-day duration which equals to approximately 2 years for Group A and 27 cycles for Group B (approximately 2 - 2 ¼ years) of treatment.

Duration of Follow Up

You will be followed for at least 28 (±7) days after your last dose of the study drug while on the trial treatment (i.e. the "safety follow-up period") to monitor for resolution or progression of AEs and to document the occurrence of new events unless you receive a new anticancer therapy within this period.

If you withdraw consent you are encouraged to complete the safety follow-up assessments. If you are removed from study for unacceptable adverse events you will be followed until the adverse event is stabilized or resolved.

Beyond the safety follow-up period, you will be monitored after completion of therapy until your disease progresses, or if you decide you do not want to continue to be followed. You would be responsible for any copayments/deductibles/coinsurance required by your insurance plan if you continue on commercial ibrutinib (IMBRUVICA®) after completing the study.

Criteria for Removal from Study

Your participation in this study may be stopped at any time by the study doctor without your consent because:

- The study doctor determines that your disease has worsened.
- Another illness that prevents you from taking the study drug.
- You have a serious side effect related to the study drug.
- If you elect to withdraw from study.
- If you are female and you become pregnant.
- Investigator considers withdrawal to be in your best interest.

- Diagnosis of new or secondary cancer after initiating treatment.
- If you have not followed the study procedures.

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.

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

While on this study, you are at risk for the side effects listed below. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that the researchers cannot predict. Many side effects go away shortly after the medications are stopped, but in some cases, side effects can be serious, long lasting, permanent, or fatal.

Everything possible will be done to prevent or eliminate any discomfort or risk. There may be risks and discomforts that are unknown. You may experience all, some, or none of these side effects listed. You will be asked to contact your doctor for any problems or questions that arise at any time during your treatment, so that measures can be started to prevent or decrease serious problems. If, during the course of treatment, your doctor becomes aware of additional toxic or therapeutic effects, your doctor will discuss them with you.

Side Effects For ibrutinib (IMBRUVICA®)

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 effects, occurring in at least 1 of every 5 subjects (≥ 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 count (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)
- Increase in lymphocyte count (Lymphocytosis)
- 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)
- 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)
- Bleeding in the eye (Eye hemorrhage)

Most of these side effects 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 the study drug for a short time or reduce its dose to allow you to recover from any side effects.

Bleeding

You may experience bruising or nose bleeds 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, the study drug 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 with 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. 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. 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, 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 the study drug 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 the study drug. 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 the study drug. 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 the study drug, 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 the study drug alone or in combination with other drugs. Most rashes are mild to moderate in severity and begin 2-3 weeks or longer after starting the study drug.

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, 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, also called high blood pressure, has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. 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, 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 the study drug. This interference could cause the amount of the study drug 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

The study drug may increase the risk of bleeding with any surgical procedure. Study drug should be held at least 3 to 7 days before and after surgery depending on 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, the study drug 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 the study drug 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 the study drug 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 an acceptable birth control method.

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

Women: If you become pregnant while you are on study treatment or within 1 month of your last dose of study drug 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.

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.

Side Effects for PCV13 (PREVNAR-13®)

Adults receiving the vaccine have reported redness, pain, and swelling where the shot was given. Fatigue, headache, chills, muscle or joint pain, decreased appetite, limitation of arm movement or rash have also been reported. Life-threatening allergic reactions from this vaccine are very rare.

Side Effects for Influenza Vaccine (FLUZONE®)

With a vaccine, like any medicine, there is a chance of side effects. These are usually mild and go away on their own.

Mild side effects that have been reported in adults:

- redness, pain and swelling where the shot was given
- headache
- muscle pain
- general feeling of discomfort or illness
- chills
- fever

As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.

Side Effects for Influenza Vaccine (AFLURIA®)

Mild side effects that have been reported in adults:

- redness, pain and swelling where the shot was given
- headache
- muscle pain
- general feeling of discomfort or illness

Side Effects for the Tdap vaccine (BOOSTRIX®)

Getting diphtheria, tetanus or pertussis disease is much riskier than getting Tdap vaccine. However, a vaccine, like any medicine, is capable of causing serious problems, such as severe allergic reactions. The risk of Tdap vaccine causing serious harm, or death, is extremely small.

Mild side effects may include*:*

- Pain, redness, or swelling in the arm where the shot was given
- Mild fever
- Headache
- Tiredness
- Stomach upset, including nausea, vomiting, or diarrhea
- Muscle aches and pains
- Swollen glands

In some people, these side effects may be more intense. They may temporarily interfere with daily activities. Severe swelling of the arm has been reported in three out of 100 people. About one in 250 adults who receive the vaccine develop a fever of 102 or higher.

During clinical trials, two adults developed temporary nervous system problems. It's unknown whether this was due to the vaccine or not. In rare cases, vaccination led to extreme swelling of the arm where the shot was given.

Can Adults Have Allergic Reactions to Tdap Vaccines?

Very rarely, someone may have a severe allergic reaction to an ingredient in the Tdap vaccine. This generally happens in less than one in a million doses. Most of the time, such reactions occur within a few minutes of receiving the vaccine. The following can be signs of a severe allergic reaction, called anaphylaxis:

- Behavior changes
- Breathing difficulty, including wheezing
- Dizziness
- Hoarse voice

- High fever
- Hives
- Pale skin
- Rapid heart beat
- Weakness

Contact your study doctor if you notice any of these signs after receiving the vaccines.

Other Risks Related To Study Procedures

Blood Sampling

A blood test is a laboratory analysis performed on a blood sample that is drawn from a vein in the arm using a needle. The possible side effects of drawing blood include pain, bleeding, bruising, light-headedness, fainting and, on rare occasions, local blood clot formation or infection with redness and irritation of the vein.

Bone Marrow Sampling

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.

CT Scans

A CT scan is a computerized x-ray that gives your study doctor clearer pictures of the inside of your body. You lie on a narrow, motorized table that slides through the opening into a tunnel. Straps and pillows may be used to help you stay in position. While the table moves you into the scanner, detectors and the X-ray tube rotate around you. Each rotation yields several images of thin slices of your body. You may hear buzzing, clicking and whirring noises.

You may be required to have CT scans regularly to monitor your disease while you are in this study. The known risks associated with CT 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. CT scans also expose you to radiation; the amount depends on the number of body areas scanned. The amount of radiation exposure you will have in the course of this study will be about the same as allowed radiation exposure limits for radiation workers. Too much radiation over time can lead to the development of second cancers or leukemia.

Magnetic resonance imaging (MRI)

You may have an MRI scan performed only if you cannot have a computed tomography scan (for example, you have a documented allergy to IV and oral contrast that is used for CT scan). When having an MRI scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (who have claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell the study doctor. S/he may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete. You will also need to tell the study doctor if you have any metal in your body, since you would not be able to get the MRI scan.

ECG

Up to 12 self-adhesive electrodes (small blunt pieces of metal) will be attached to your skin on your arms, legs and chest using sticky pads. The areas where the electrodes will be placed will be cleaned; some areas may need to be shaved. Some skin irritation can occur where the electrodes are placed. Once the electrodes are placed, the test will begin. The test is completely painless and takes less than a minute to perform. After the test, the electrodes are removed. Rarely, a reaction to the electrode tape may cause redness or swelling of your skin.

Additional side effects

You may have all, some, or none of the listed side effects of the study drug, the vaccines, or the procedures done for this study. 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.

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

There is no guarantee that this treatment will benefit you. This 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. If you choose not to take part in any of those treatment options, you have the right to choose supportive care. Supportive care is when you decide not to treat your cancer, but instead decide to treat your symptoms in a manner that will keep you as comfortable as possible.

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

Most of the care you receive on this study is considered routine care for your disease. This means you would have a similar schedule for physician appointments, lab work and scans even if you were not participating in a study. You and/or your insurance company will be billed for the routine physician visits, various blood tests, CT scans, bone marrow biopsy and aspirate and medication treatments given before and while being treated with the study drug. You will be responsible for any copayments/deductibles/coinsurance required by your insurance plan while on study.

The costs of the vaccines, giving them to you and processing research blood samples will be paid by the study. The study agent, ibrutinib, will be provided at no cost to you by Pharmacyclics LLC (the company who manufactures ibrutinib), for up to 24 cycles for Group A and 27 cycles for Group B. If your doctor recommends that you continue on commercial ibrutinib (IMBRUVICA®) after completing the maximum number of cycles for your Group, the cost of the ibrutinib will be billed to you and your insurance plan.

Before taking part in this study, you should learn which research-related care will be provided without charge, which costs will be billed to your insurance and which costs will be your responsibility. To find out more about this, you can ask your study doctor, the study staff or your insurance provider. You may also ask to speak to a financial counselor about the costs of this study.

Additional funding for this study will also be provided by The National Cancer Institute (NCI).

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

You will receive a $50 travel stipend upon completion of each research visit. If the visit happens to extend over the course of several days, you would be reimbursed the $50 only one time per each cycle and not for each individual day which will be reimbursed after the completion of the research visit. By law, payments to subjects are considered taxable income.

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.

Pharmacyclics, its collaborators and affiliates may study your data and tissue, blood, or other specimens collected from you. Your tissue, blood or other specimens may be used for any purpose including research, which may lead to the development of medical products such as devices, or new drugs or patentable processes and procedures. You will not be compensated for any patents or discoveries that may result from your participation in this research. Your signature on this form indicates that you understand and accept this.

13. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related personal 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 (FDA);

- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The National Cancer Institute (NCI);
- Pharmacyclics LLC (the manufacturer of ibrutinib), their collaborators (e.g. Janssen Biotech, Inc.), and their affiliates; 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.

The results of this study may be disclosed in a publication or presentation. However, your name and other identifying information will not be disclosed.

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: Pharmacyclics LLC, the study drug supporter of this research, its affiliates, and any persons or companies that are:
  - Working for or with the supporter (e.g. Janssen Biotech Inc.); or
  - Owned by the supporter.
- 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 you may contact ***Dr. Jennifer Woyach, The Ohio State University Comprehensive Cancer Center 455D Wiseman Hall, 410 W. 12th Ave Columbus, OH 43210, (614) 685-5667.***

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
Suite 500, 1590 N. High St.
Columbus, OH 43201
Ph: 614-293-4477

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact ***Dr. Jennifer Woyach, The Ohio State University***

Comprehensive Cancer Center 455D Wiseman Hall, 410 W. 12th Ave Columbus, OH 43210, (614) 685-5667

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)**
Relationship to the 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