The Ohio State University Consent to Participate in Research

Study Title:	A Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Genetic Risk-Stratified Relapsed and Refractory patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) and B-cell Prolymphocytic Leukemia (B-PLL)
Principal Investigator:	Kami Maddocks, M.D.
Sponsor:	The Ohio State University

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

1. Why is this study being done?

This is a clinical trial, a type of research study, involving treatment with an investigational (experimental) drug called PCI-32765, a "kinase inhibitor". "Kinases" are proteins that are inside of cells and help them to live and grow. The specific kinase inhibited or blocked by this study drug is believed to help blood cancer cells grow and live. By inhibiting or "blocking" the activity of this kinase, it is possible that the study drug may be able to kill the cancer cells or stop them from growing.

From here on out, we will refer to PCI-32765 as ibrutinib or the "study drug".

This study will involve treating patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or B-cell prolymphocytic leukemia (B-PLL) that has not responded to or has relapsed after standard treatment. Patients will be treated with single agent ibrutinib as a pill. We want to find out how effective ibrutinib is at treating your CLL, SLL, or B-PLL and all the effects, good and/or bad, treatment with this drug has on you and your cancer. Ibrutinib has been 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) CLL/SLL patients including those with 17p deletion or a *TP53* mutation, 3) Waldenström's Macroglobulinemia, 4) marginal zone lymphoma (MZL)for patients who require systemic therapy and have received at least one prior anti-CD20 based therapy, and 5) chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Ibrutinib is currently under investigation in various indications as a single agent and in combinations. The FDA approved name for Ibrutinib is IMBRUVICA®.

During this study, your blood will be tested periodically to determine how the study drug affects your cancer cells. Other specialized blood tests will also be performed periodically to see the way your cancer cells are responding to the drug and they way your immune system responds to the drug.

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

Up to 161 patients will be enrolled on this study which will be conducted at 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 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.

A single course of the study drug or "cycle" is 28 days. If you tolerate the study drug and your study doctor feels that your cancer is stable or responding to the study drug or that you are benefiting from the study drug, you may continue to receive treatment until your disease progresses or unacceptable drug-related toxicity occurs. You will visit the clinic weekly for the first month of treatment (Cycle 1), followed by monthly evaluations for the next five months, and then you will be required to visit the clinic every 3 months with monthly blood draws and phone follow-up through 24 months with one of the investigators on the study. Patients enrolled on this study prior to June 1st, 2013 will continue on the prior evaluation schedule which was monthly until Cycle 3 and then every 3 months.

You will receive enough study drug at each clinic visit 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 should be stored at room temperature. You will take 420 mg of the study drug (3 capsules) once a day with 8 ounces (240 ml) of water. You should take

the study drug around the same time each day. 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.

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. 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:

Pre-treatment Evaluation

To find out if you qualify for the study, you will undergo several tests and procedures, as well as a complete medical examination. 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.

- You will be asked about your medical history, including any eye symptoms you may have, and demographics (including your sex, age, race/ethnicity). If you have moderate or severe eye symptoms, you may receive an eye exam. At the time of the early clinical studies, changes in the eye were considered a potential risk based on laboratory studies and studies in animals. However there have been no similar side effects seen in (over 1200) patients treated to date, therefore effects on the eye are no longer considered a risk. However, in this study we will continue to monitor eye problems. Be sure to report any eye or visual problems you may have to your study doctor.
- 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, beta-2-microglobulin, direct and indirect Coombs, immunoglobulins, cytogenetics, and liver function tests).
- A urine sample will be collected for routine laboratory tests.
- If you are a woman of child bearing potential you will be required to complete a serum pregnancy test with negative results within 10-14 days of treatment.)
- Women of childbearing potential and men must agree to use adequate contraception for at least 14 days prior to the study and for the duration of participation.
- Electrocardiogram (EKG), a recording of the electrical activity of your heart.
- A CT (computed tomography) 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 study 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 (an extra amount of bone marrow, about 2 teaspoons, will be collected for research).
- Research Blood Draws: Approximately 33 ml (7 teaspoons) of blood will be taken for research purposes.
- Questionnaire: Information including age, race, marital status, social support, social contacts and reports of recent stressful events will be obtained to measure emotional distress, depressive symptoms and quality of life. This questionnaire should be completed during the screening process. It will be administered as a paper questionnaire to you during your evaluation and should take approximately 30 minutes to complete.

During the Study

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

Cycle 1-Day1:

- You will need to stay in the study doctor's office (clinic or hospital) for approximately 6-8 hours.
- Prior to the first treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Routine Blood Tests (Complete Blood Count, test of blood chemistries – various substances in the blood, test of kidney function, and liver function tests) will be done prior to treatment.
- Approximately 24 ml (5 teaspoons) of blood will be collected 2 hours after taking the study drug to determine how the study drug affects your cancer cells.
- Approximately 56 ml (11 teaspoons) of blood will be collected prior to treatment to better understand how your cancer cells respond to the drug.

- Questionnaire: Information including age, race, marital status, social support, social contacts and reports of recent stressful events will be obtained to measure emotional distress, depressive symptoms and quality of life. It will be administered as a paper questionnaire to you during your evaluation and should take approximately 30 minutes to complete.

Cycle 1-Day2:
Approximately 24 ml (5 teaspoons) of blood will be collected prior to taking the study drug.

Cycle 1-Day8:
- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Routine Blood Tests (Complete Blood Count, test of blood chemistries – various substances in the blood, test of kidney function, and liver function tests) will be done prior to treatment.
- Approximately 24 ml (5 teaspoons) of blood will be collected prior to taking the study drug to determine how the study drug affects your cancer cells.

Cycle 1-Days 15, 22:
- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Routine Blood Tests (Complete Blood Count, test of blood chemistries – various substances in the blood, test of kidney function, and liver function tests) will be done prior to treatment.

Cycle 2-Day1:
- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Questionnaire: Information including age, race, marital status, social support, social contacts and reports of recent stressful events will be obtained to measure emotional distress, depressive symptoms and quality of life. It will be administered as a paper questionnaire to you during your evaluation and should take approximately 30 minutes to complete.
- Routine Blood Tests (Complete Blood Count, test of blood chemistries – various substances in the blood, test of kidney function, and liver function tests) will be done prior to treatment.

- Approximately 56 ml (11 teaspoons) of blood will be collected prior to treatment to better understand how your cancer cells respond to the drug.

Cycle 3 –Day 1:

- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Questionnaire: Information including age, race, marital status, social support, social contacts and reports of recent stressful events will be obtained to measure emotional distress, depressive symptoms and quality of life. It will be administered as a paper questionnaire to you during your evaluation and should take approximately 30 minutes to complete.
- Routine Blood Tests (Complete Blood Count, test of blood chemistries – various substances in the blood, test of kidney function, and liver function tests) will be done prior to treatment.
- Approximately 24 ml (5 teaspoons) of blood will be collected prior to taking the study drug to determine how the study drug affects your cancer cells. Blood draws to detect immune system function will be done after 2 months, 5 months and then every 6 months after that until progression of disease.
- CT scans will be done after 2 months of treatment, after 5 months of treatment and then every 6 months after that until disease progression.
- Bone marrow biopsy will be performed once your disease is no longer able to be detected by physical examination, blood tests or CT scans to document that you have responded to treatment and will not be required again.

Cycles 4-5-Day1:

- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Routine Blood Tests (Complete Blood Count) will be done prior to treatment.

Cycle 6 –Day 1: through the end of therapy-Day1 every 3 months:

- Prior to treatment your physician will again assess you with a complete medical history, including how you are feeling and if there have been any changes in your health or medications since your last visit.
- A physical examination including weight and vital signs (blood pressure, pulse, respiratory rate and temperature) will be measured.
- Questionnaire: Information including age, race, marital status, social support, social contacts and reports of recent stressful events will be obtained to measure emotional distress, depressive symptoms and quality of life. It will be administered as a paper questionnaire to you during your evaluation and should take approximately 30 minutes to complete.

- Routine Blood Tests (Complete Blood Count, test of blood chemistries – various substances in the blood, test of kidney function, and liver function tests) will be done prior to treatment.
- Approximately 24 ml (5 teaspoons) of blood will be collected prior to taking the study drug to determine how the study drug affects your cancer cells. Blood draws to detect immune system function will be done after 2 months, 5 months and then every 6 months after that until progression of disease.
- CT scans will be done after 2 months of treatment, after 5 months of treatment and then every 6 months for the first 24 months and then only at the discretion of the treating physician.
- Bone marrow biopsy will be performed once your disease is no longer able to be detected by physical examination, blood tests or CT scans to document that you have responded to treatment and will not be required again.

Additional blood samples may be needed depending on if your cancer relapses or to confirm response status.

Additional blood tests, x-rays, and procedures may be requested if your study doctor feels they are medically necessary.

At the End of Treatment

You may stop treatment with the study drug for several reasons: because your cancer is not responding to this treatment, because the treatment has caused too many side effects, or because you choose to stop treatment. 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 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. CT scans will be repeated at this time. Additional blood tests, x-rays, and procedures may be requested if your study doctor feels they are medically necessary.

Continued Follow-up

You will be followed for two years after you have completed the study drug treatments. You will be followed every three months with a medical history and physical examination and complete blood counts. Your study doctor will also ask about any side effects of your treatment. Other laboratory tests, procedures, and x-rays will be done if your study doctor thinks they are medically necessary.

4. How long will I be in the study?

You may continue to receive treatment with the study drug indefinitely if you show no signs of worsening disease and do not suffer from dangerous side effects. After you complete your treatment with the study drug, we would like to keep track of your medical condition for up to 2 years. You will be seen and examined by your study doctor every 3 months to monitor how well your disease responded to this treatment, to make sure that any side effects have resolved, and to find out if you have developed any unexpected side effects.

5. Can I stop being in the study?

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

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

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

Ibrutinib (IMBRUVICA®)

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 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 hand and feet (Peripheral neuropathy)
- Dizziness
- Urinary Tract Infection

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)

Side effects that have been seen 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)

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. Also 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, 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 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 2-3 weeks or longer after starting ibrutinib.

There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction or “SCAR”, 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 causal relationship with 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

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 now and 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.

Reproductive effects

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

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

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

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

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

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

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

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

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 of study procedures

Blood Sampling

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 numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow biopsy. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. As the bone marrow liquid is taken from the bone, there may be a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all patients experience discomfort.

The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.

CT scans

You will be required to have CT scans regularly to monitor your disease while you are in this study. CT scans expose you to radiation; the amount depends on the number of body areas scanned. Too much radiation over time can lead to the development of second cancers or leukemia. Your study doctor will inform you regarding the amount of radiation exposure you will exposed to during each CT scan and may ask you to sign a separate consent form for the CT 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. 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.

Magnetic Resonance Imaging (MRI)

There is no radiation risk associated with ultrasound or MRI. However, an MRI could be very dangerous if you have certain objects or devices implanted in your body, such as a pacemaker, insulin pump, ear implant, joint replacement, permanent dentures, piercings, or shrapnel. You must tell the study doctor or study staff about any objects that you know are implanted or embedded in your body.

Other risks

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 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. You should get medical help and contact the study doctor or study staff right away if you have any of these or any other side effects whether or not you think they are related to the study drug.

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

There is no guarantee that this treatment will benefit you. This treatment regimen may also be harmful to you. However, the benefits could be an easing of symptoms, decrease in the

amount of cancer suggestive of improvement in your cancer, prolonged disease-free remission and/or survival or increased knowledge about this cancer treatment in patients with CLL/SLL/B-PLL. 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. 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;
- Pharmacyclics (the manufacturer of ibrutinib), its affiliates and it's collaborators (e.g. Janssen Biotech, Inc.), their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

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

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

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

Pharmacyclics LLC, its affiliates, and its collaborators (Janssen Biotech, Inc) 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.

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

Under normal circumstances you would have physician appointments and undergo similar lab and scan procedures on the same schedule. It is known as standard of care, and therefore you and/or your insurance company will be billed for the 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 co-pay/deductibles required by your insurance plan while on study.

The study agent, ibrutinib, will be provided free of charge by Pharmacyclics LLC the pharmaceutical company who manufactures the study drug, while you are participating in this study.

The tests that are exclusively done for the research will not be billed to you or your insurance company. These research charges include: (PK) blood testing, as well as your screening ECG, urinalysis, and pregnancy test.

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

You will not be paid to take part in this study.

12. What happens if I am injured because I took part in this study?

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

STUDY DRUG PROVIDER LIABILITY
If the injury was caused by a defect in the study drug ibrutinib, then Pharmacyclics LLC, the provider of the study drug, will pay the reasonable costs for necessary medical treatment that are not covered by your medical insurance provided you have followed the directions of the study doctor. This commitment for free medical treatment does not include treatment for any other complications or illness that you may experience during this study, which do not result from your participation in the study.

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

13. 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.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact ***Dr. Kami Maddocks***
A350C Starling Loving Hall, 320 West 10th Avenue, Columbus, Ohio 43210.
Telephone: 614-293-1395.

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 ***Dr. Kami Maddocks***
A350C Starling Loving Hall, 320 West 10th Avenue, Columbus, Ohio 43210.
Telephone: 614-293-1395.

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