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

Study Title:	A Dose Escalation Study of Selinexor (KPT-330), a Selective Inhibitor of Nuclear Export, and Ibrutinib, a Bruton's Tyrosine Kinase Inhibitor, in Patients with Relapsed and Refractory Chronic Lymphocytic Leukemia or Aggressive Non-Hodgkin Lymphoma
Principal Investigator:	Jennifer Woyach, M.D.
IND Sponsor/Institution:	The Ohio State University
Selinexor Drug Provider:	Karyopharm Therapeutics Inc.

- **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 phase I study designed to test the safety of the combination of two cancer drugs, Ibrutinib plus Selinexor at different doses in subjects with the following types of cancer:

- CLL (chronic lymphocytic leukemia)
- SLL (small lymphocytic lymphoma)
- PLL (prolymphocytic leukemia) or
- Aggressive NHL (non-hodgkin lymphoma).

You are being asked to participate in this study because you have been diagnosed with one of the cancers listed above.

When ibrutinib and selinexor are combined in the lab and in animal studies, the two drugs appear to work better when given together. Mice with cancer that no longer responds to treatment with ibrutinib respond to treatment with selinexor. During this study researchers hope to discover what effects if any, the study drugs have on people when given at the same time and also to determine the dose and schedule of each drug to be administered.

Outside of the goals described above, researchers are also interested in studying how these drugs affect CLL cancer cells specifically, and the immune system of CLL patients. This will be studied using special laboratory tests on blood samples taken during the course of treatment. These research blood draws are described below.

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

Selinexor is an oral cancer drug which when taken, inhibits certain biological pathways in the body that allow for the spread of your type of cancer and also induce cancer cell death. This drug has not yet been approved by the FDA and is therefore considered an experimental drug.

Ibrutinib is also a cancer drug which works similarly to Selinexor, but inhibits a different biological pathway to stop cancer cell growth. Although Ibrutinib has been FDA approved to treat MCL or mantle cell lymphoma and CLL, its use in this study is considered experimental because it is being combined with Selinexor and it has not been FDA approved to treat NHL SLL or PLL

For patients enrolled into cohort 3, who will already be taking ibrutinib prior to the study, the use of testing for minimal residual disease, and using minimal residual disease to guide therapy is investigational.

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

Up to 48 patients will participate in this study at The Ohio State University and University of Utah.

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

While you are part of this study, the research staff will follow you closely to check whether you have any problems that need medical care. By agreeing to take part in this study, you are agreeing to:

- Finish all of the study requirements as listed below in the sections titled "Before you begin the study" and "During the study".
- Keep all of your appointments and follow all instructions given to you by the study doctor or staff.
- Tell the study doctor about any new medications you begin taking after signing this consent form. This includes medicines you buy without a prescription, so called "over the counter" medicines.
- Inform the study doctor of any problems or side effects you may experience while on the study.
- Ask questions about anything you do not understand.
- Tell the research staff if your telephone number or address changes.
- Tell your regular doctor about your participation in this study.

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

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.

- Review of your medical history, medications, and previous treatments
- Assessment of your activity level (This is also called performance status)
- 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, blood pressure, heart rate, and temperature)
- Information regarding prior HIV or hepatitis testing. If you have been tested before the doctor will want to know these results.

- Routine Blood Tests:
    - Blood tests
    - Blood counts
    - Kidney and liver function tests
    - Hepatitis B and C
    - HIV
    - A blood test that can find cancer cells if they are currently in your blood
    - A blood test that checks for any abnormal markers that cancer cells might make
    - If you are a woman who could become pregnant (still has periods), you will have a pregnancy test.
    - If you have CLL, a blood test that will look at the genes of your cancer cells.
- An ECG (electrocardiogram), a record of electrical activity of the heart.
- A CT (computed tomography) or PET (positron emission tomography)-CT scans will be performed to measure the size of the cancer in your body.
    - A CT scan is a computerized x-ray that gives your doctor clearer pictures of the inside of your body. CT scans are routine procedures used to help doctors diagnose and follow the size and location of your cancer.
    - PET-CT is a new method that combines two scanning techniques in one test procedure. It is often used to diagnose cancer, measure cancer progression, and evaluate the response to treatment. During the PET procedure, you will be injected with a small amount of radioactive glucose. This substance is easily eliminated from the body either through radioactive decomposition or via the urine. A PET scan may cause you to feel "closed in" while lying in the scanner. However, the scanner is open at both ends and an intercom allows you to talk with doctors and staff. If you feel ill or anxious during scanning, doctors and/or technicians will give comfort or the scanning will be stopped. The PET-CT scan exposes your body to radiation. The radioactive solution does not remain in your system for a long period of time. However, you should wait 2 hours before holding an infant or getting close to a pregnant woman to avoid exposing them to radiation. You should drink fluids after the scan to help remove the solution from your system.
- Bone Marrow Biopsy and Aspirate (an extra amount of bone marrow, about 1 teaspoon, will be collected for research).
    - This is a test done in the clinic. You do not have to stay in the hospital for this test. You will lay on your stomach or side. A small needle will be used to numb the back side of your hip bone with a medication called lidocaine. Another needle will be placed into your hip bone and fluid inside the bone will be taken out. Then, another needle will be placed into the same spot in your hip bone and a small piece of the bone will be taken out.

- Research Buccal Swab (a swab will be taken of the inside of your cheek to look at the genes of your normal cells)
- Ophthalmologic exam or eye exam to examine your vision and clarity of vision

During the Study

If you are found to be eligible you may begin the study. Before treatment, you will start medications that will help you with some of the side effects that are possible. These medications treat nausea and loss of appetite or energy.

Cohort 1 and 2

One cycle of treatment lasts 28 days or about one month. You will start the selinexor first, which is a pill that you will take by mouth one day per week. Selinexor should be taken with at least 120ml (about 4 ounces) of fluid such as water or juice. The first day of treatment (Cycle 1, Day 1), you will have blood drawn before you take the selinexor, and 30 minutes, 1 hour, 2 hours, 4 hours, and 8 hours after you take the first dose. You will need to come back the next day (Cycle 1, Day 2) to see how you are doing and for another lab test.

After one week of treatment (Cycle 1, Day 8), you will start the ibrutinib, which is a pill that you will take every day. Patients who are on ibrutinib at study entry are not required to discontinue ibrutinib for any period of time. Patients continuing on ibrutinib should take ibrutinib days 1-28 starting of Cycle 1. You will also have an examination and blood drawn at this visit.

For the third week of treatment, you will return on the first day of the week (Cycle 1, Day 15), for an examination. You will have blood drawn before you take the selinexor, and 30 minutes, 1 hour, 2 hours, 4 hours, and 8 hours after you take the first dose. You will need to come back the next day (Cycle 1, Day 16) to see how you are doing and for another lab test.

For the fourth week of treatment, you will return on the first day of the week (Cycle 1, Day 22), for an examination and blood draw.

During the second and third cycles, you will need to come back every other week on Days 1 and 15 of both cycles to have an examination to see how you are doing and to have your blood drawn.

During the fourth through the sixth cycles, you will need to come back once a month on Day 1 of all cycles to have an examination to see how you are doing and to have your blood drawn.

From the seventh cycle on, you will need to come back every three months on Day 1 of those cycles to have an examination to see how you are doing and to have your blood drawn.

Number of Required Visits and Timing of the Visits									
Cycle*	1					2-3		4-6	7±
Day	1	2	8	15	16	1	15	1	1

Total Visit # for Each Cycle	6	2	1	1±
* One cycle = 28 days; ±One visit every 3 months.				

At each visit or the indicated visit, you will have the following tests:

Exam/Test	**Time**
Physical Exam	Before each treatment
Assessment for Side Effects to Treatment	At any time during treatment
Routine Blood Tests*	Before each treatment
Research Blood Tests*	Before each treatment
CT scan or PET Scan	Cycle 2, Day 1; Cycle 4, Day 1; Cycle 7, Day 1±
Bone Marrow Biopsy	This test will only be done if all cancer cells have been cleared from your blood.
*Amount of blood taken will range from 1-9 teaspoons at each test ±Starting with Cycle 7, CT/PET scans will be done every 3 months for one year and then every 6 months after this time.	

Cohort 3
One cycle of treatment lasts 28 days or about one month. You will start the selinexor first, which is a pill that you will take by mouth one day per week. Selinexor should be taken with at least 120ml (about 4 ounces) of fluid such as water or juice. The first day of treatment (Cycle 1, Day 1), you will have an examination to see how you are doing and have blood drawn.

After one week of treatment (Cycle 1, Day 8), you will start the ibrutinib, which is a pill that you will take every day. Patients who are on ibrutinib at study entry are not required to discontinue ibrutinib for any period of time. Patients continuing on ibrutinib should take ibrutinib days 1-28 starting of Cycle 1.

During the second and third cycles, you will return on Day 1 of each cycle for an examination to see how you are doing and to have your blood drawn.

You will not have any study visits during the fourth and fifth cycles.

During the sixth through twelve cycles, you will return once every three cycles (Day 1 of Cycle 6, Cycle 9, and Cycle 12) for an examination to see how you are doing and to have your blood drawn.

You will not have any study visits during the thirteenth cycle.

From the fourteenth cycle on, you will need to come back on Day 1 every three cycles for an examination to see how you are doing and to have your blood drawn. At the fourteenth cycle only, you will have a bone marrow biopsy and aspirate performed.

Number of Required Visits and Timing of the Visits

Cycle*	1		2-3	6-12	14+
Day	1	15	1	1	1
Total Visit # for Each Cycle	2		1	1±	1±
* One cycle = 28 days; ±One visit every 3 months.					

At each visit or the indicated visit, you will have the following tests:

Exam/Test	**Time**
Physical Exam	Before each treatment
Assessment for Side Effects to Treatment	At any time during treatment
Routine Blood Tests*	Before each treatment
Research Blood Tests*	Before each treatment
CT scan or PET Scan	Cycle 14, Day 1±
Bone Marrow Biopsy	Cycle 14, Day 1
*Amount of blood taken will range from 1-9 teaspoons at each test ±Starting with Cycle 14, CT/PET scans will be done every 3 months	

At the End of Treatment

You may stop treatment with the study drug for several reasons:

- because your cancer is not responding to this treatment
- because the treatment has caused too many side effects
- or because you choose to stop treatment.

No matter the reason for stopping treatment, you will continue to be followed. Within 30 days (4 weeks) of completing treatment, or the start of a new anticancer therapy, your 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. An ophthalmologic exam or eye exam will be performed to examine your vision and clarity of vision. Bone marrow biopsy and aspirate samples will be repeated at this time, for patients who relapse or for patients who have a complete response. Approximately 40 ml (10 teaspoons) of blood will be collected for research purposes from patients that relapse or have a complete response. Residual nodal material may also be collected at this time for patients who have a complete response or relapse. Additional blood tests, x-rays, and procedures may be requested if your doctor feels they are medically necessary.

4. How long will I be in the study?

Response Follow Up:

You will be required to have a clinic visit to be seen by the study staff at least once every six months until your disease progresses, an alternative therapy is started, death or the study closes.

You can remain on the study unless your cancer worsens, you have side effects that you cannot accept, you develop another medical problem that prevents you from taking the treatment, or you no longer want to participate.

If you stop the study because of a side effect to the treatment, you will be seen by your regular doctor until the side effect goes away.

5. Can I stop being in the study?

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

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions about subjects which you normally do not discuss
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may not request your genetic information from this research.
    - Health insurance companies and group health plans may not use your genetic information when making decisions about your eligibility or premiums.
    - Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

  All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies cannot ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage

or benefits for health care services. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect your or your blood relatives could be found during a study. Results obtained from genetic testing will generally not be disclosed to the patient or the treating physician.

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

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

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- It is possible that side effects of the combination of selinexor and ibrutinib may interfere with ability to receive standard ibrutinib therapy.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The information below shows the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you

Selinexor

You may experience certain unwanted effects and symptoms as a result of treatment with Selinexor.

Side effects of Selinexor (KPT-330):

Very common side effects (≥10% of patients):
In 100 people receiving selinexor more than 10 people may have:

- Nausea

- Vomiting
- Diarrhea
- Weight loss
- Constipation
- Fatigue and asthenia – loss of energy; weakness
- Decreased appetite
- Dehydration
- Abdominal pain
- Dysgeusia – change in taste
- Shortness of breath
- Cough
- Dizziness
- Fever
- Blurred vision
- Headache
- Difficulty falling asleep
- Low platelets in the blood (thrombocytopenia), which may increase the risk of bleeding
- Decrease in red blood cells (anemia) causing fatigue
- Decrease in white blood cells (leukopenia), which may increase the risk of infection
- Decrease in neutrophils (a type of white blood cell that helps fight infections)
- Pneumonia
- Low blood sodium which may increase the risk of seizures
- Low potassium which may cause weakness, muscle cramps and spasms
- Peripheral edema – swelling in extremities due to accumulation of fluid, usually in legs
- High blood sugar which may cause fatigue, increased thirst/hunger, frequent urination, weight loss, numbness and tingling in hands/feet

Common side effects (≥1-10% of patients)
In 100 people receiving selinexor about 1 to 10 people may have:

- Rash
- Eye disorders including cataract (new or worsened), dry eye, visual impairment, seeing flashes of light
- Night sweats
- Dry mouth
- Stomatitis – a condition that causes painful swelling and sores inside the mouth
- Dyspepsia – indigestion
- Chills
- Hypotension – low blood pressure
- Hypertension

- Tachycardia – fast heart rate
- Nosebleed
- Contusion (bruise due to body injuries such as fall)
- Electrolyte disturbances including:
    - low phosphate which may cause muscle weakness and fatigue
    - low magnesium which may cause muscle twitches and cramps
    - low calcium which may cause numbness and tingling in hands/feet/face, muscle stiffness and cramps
    - high potassium which may cause muscle weakness, palpitations or irregular heartbeats and chest pain
- Low albumin (which may cause swelling especially of the hands/feet, weakness or exhaustion)
- Peripheral neuropathy – weakness, numbness, and pain from nerve damage, usually in the hands and feet
- Decrease in lymphocytes – a specific type of white blood cell that are part of your immune system
- Increase of creatinine in the blood due to a reduction in kidney function, often related to dehydration
- Elevated liver enzymes including alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
- Elevated pancreatic enzymes including high amylase and high lipase
- muscle weakness
- Febrile neutropenia - fever in the absence of a normal white blood cell response that may mean you have an infection
- Respiratory tract infection (including upper)
- Urinary tract infection
- Sepsis (including septic shock) – potentially life-threatening complication of an infection
- Pain in joints and muscles
- Malaise (a general feeling of being ill or bodily weakness)
- Muscle spasms
- Gait disturbance
- Hair loss
- Itching
- Depression
- Syncope – fainting
- Cognitive disorder
- Mental status changes including confusion

Uncommon side effects (>0.1-1% of patients)
In 1,000 people receiving selinexor about 1 to 10 people may have:

- Tumor lysis syndrome – potentially a life-threatening side effect caused by the rapid breakdown of tumor cells and may cause irregular heartbeat, kidney failure or abnormal blood test results which included elevated uric acid level, elevated serum potassium and phosphorus levels, and a decreased calcium level.
- Enterocolitis infectious (inflammation of digestive tract caused by infection)
- Gastroenteritis (stomach flu)
- Rhinovirus infection (common cold; infection of nose, ear, sinuses; very rarely leading to pneumonia or bronchitis)

Rare side effects (>0.01-0.1% of patients)
In 10,000 people receiving selinexor about 1 to 10 people may have:

- Acute cerebellar syndrome – symptoms can include a sudden loss of coordination, balance, or slurred speech

Serious adverse effects (≥3 cases reported as related by the principal investigator):

- Cardiac failure
- General physical health deterioration
- Multiple organ dysfunction syndrome
- Lung infection
- Bacteremia – bacterial infection in the blood
- Bronchitis – infection of tubes that carry air to and from lungs
- Decreased ejection fraction – reduction in amount of blood pumped out of heart
- Encephalopathy – brain disease, damage, or malfunction, which can present different symptoms that range from mild, such as some memory loss or subtle personality changes, to severe, such as dementia, seizures, or coma
- Delirium – state of acute confusion
- Acute kidney injury
- Pulmonary embolism – pulmonary embolism occurs when a clump of material, most often a blood clot, gets wedged into an artery in your lungs.
- Hypoxia – an absence of oxygen supply at tissue level

Avoid acetaminophen-containing medications such as Tylenol, Vicodin, Lortab, or Norco within 2 hours before and 2 hours after you take Selinexor. Acetaminophen may interfere with the breakdown of Selinexor in the body. Use of acetaminophen and acetaminophen-containing drugs, particularly on days of Selinexor therapy, should be minimized. If you need it for pain control, your doctor can provide you with alternative agents on selinexor dosing days.

<u>Ibrutinib</u>

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

The side effects listed below have been reported by patients who have received ibrutinib in clinical trials and from post-marketing sources.

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

- Occurrence or increase in frequency of loose or watery stools (Diarrhea)
- Muscle and bone pain (Musculoskeletal pain)
- Nausea
- Low white blood cell count (cells that help fight infection) (Neutropenia)
- Low platelet count (cells that help blood to clot) (Thrombocytopenia)
- 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

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

- Sinus infection (Sinusitis)
- Increased level of uric acid in the blood (Hyperuricemia)
- Abnormal heart rhythm (Atrial fibrillation)
- Non-melanoma skin cancer
- Blurry vision (Vision blurred)
- Low white blood cell counts with fever (Febrile neutropenia)
- Severe infection throughout the body (Sepsis)
- Redness of the skin (Erythema)
- Increase in specific white blood cell counts (Leukocytosis, Leukocytosis)

- 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 in less than 1 of every 100 (<1%) patients include:

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures. (Tumor lysis syndrome)
- Itchy rash (Urticaria)
- Inflammation of the fatty tissue underneath the skin (Panniculitis)
- Swollen face, lip, mouth, tongue or throat (Angioedema)
- High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- Liver failure (Hepatic failure)
- Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachyarrhythmia).
- Temporary or permanent decrease of brain or nerve function due to reduced blood flow to the brain (mini-stroke or stroke)

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

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

Bleeding

You may experience bruising or nosebleeds during treatment with ibrutinib. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur, sometimes resulting in death. If you take other medicines or supplements that increase your risk of bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or medicines used to prevent or treat blood clots or stroke, ibrutinib may increase this risk. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided while taking ibrutinib. Call your study doctor if you have signs or symptoms of serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.

Effects on the heart

Abnormal rapid and/or irregular heart rhythm (atrial fibrillation, atrial flutter, and/or ventricular tachyarrhythmia 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 to 3 weeks or longer after starting ibrutinib.

There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction or "SCAR", involving more than 50% of the body) or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas of the body (Stevens-Johnson syndrome). These skin rashes could be life-threatening. You should notify your study doctor immediately if you develop a rash that spreads quickly, or if you notice peeling of your skin, with or without ulcers or sores in your mouth.

Non-Melanoma Skin Cancer and Other Cancers

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and may be related to the use of ibrutinib. Other cancers have been reported such as solid tumors and blood cancers, the relationship to the use of ibrutinib is unknown. You should tell your study doctor if you develop a new cancer while in the study.

Tumor Lysis Syndrome (TLS)

Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your study doctor may do blood tests to check for TLS.

Hypertension

Hypertension is also called high blood pressure, and has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your study doctor know if you have any of the symptoms of high blood pressure which may mean that you have developed

hypertension or that your hypertension is getting worse. Your study doctor may adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Stroke

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

Liver Failure

Rare cases of liver failure have been reported in patients treated with ibrutinib. Symptoms of liver failure include yellowing of the eyes and skin (jaundice), itching of the skin, dark colored urine, gray or clay-colored stools, confusion, nausea, loss of appetite, and fatigue or diarrhea. You should tell your study doctor immediately if you have any of these symptoms which may suggest liver disease. Your study doctor may be able to diagnose and provide you required medical care.

Interstitial lung disease

Interstitial lung disease is a group of lung disorders in which the tissues become inflamed and may become damaged. Interstitial lung disease is not associated with infections (e.g., bacteria, viruses, fungi) and has been reported in patients treated with ibrutinib. You should report to your physician if you have cough, any signs of new or worsening respiratory symptoms such as shortness of breath or difficulty breathing.

Interference with other drugs

Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body processes ibrutinib. This interference could cause the amount of ibrutinib in your body to be higher or lower than expected. It is also possible that taking the study drug with your regular medications or supplements, including fish oil, Vitamin E, or other vitamins, may change how your regular medications, or your regular supplements, work. It is very important that you avoid grapefruit juice and Seville oranges and tell the study doctor about all medications, supplements, or herbal medicine like St. John's wort that you are taking during the study. You should notify your study doctor immediately about any side effects to avoid possible harm.

Drug interruption for any surgical procedures

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

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

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

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

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

<u>Reproductive effects</u>

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

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

Men: You must use a barrier method while on treatment with ibrutinib and for 1 month 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 1 month after you stop taking the study drug.

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

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

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

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

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

Additional Risks

Blood drawing risks:
There may be bruising, bleeding or inflammation at the sites where blood samples are taken. Care will be provided to avoid these complications. Infection, excess bleeding, and/or fainting also are possible, although unlikely.

Bone Marrow Biopsy risks: A small amount of bone marrow will be collected using a needle inserted into your hipbone. You may feel a mild to moderate degree of pain or discomfort during the procedure. Serious side effects of this procedure are rare. Potential risks are minor skin bleeding and skin infection at the site of the needle insertion. Other potential but rarely reported side effects after sample collection are fainting, dizziness or lightheadedness accompanied by nausea and clammy skin. You must tell your doctor if you have any reactions during or shortly after the procedure.

PET-CT Scan: PET-CT is a new method that combines two scanning techniques in one test procedure. It is often used to diagnosis cancer, measure cancer progression, and evaluate the response to treatment. During the scan, you will have to lie still on your back in the PET scanner which is a tight space. This may make you anxious.

During the PET procedure, you will be injected with a small amount of radioactive glucose. This substance is easily eliminated from the body either through radioactive decomposition or via the urine. Over 90% of the radioactive glucose will either have decomposed or left the body before you leave the clinic, because the level of radiation is very low. This test is safe for

diabetics who must control their glucose. A minor risk of the procedure is temporary soreness or redness in the arm where the IV is inserted.

For the CT Scan which is performed simultaneously, you will be exposed to a small amount of radiation and will receive an injection of contrast dye which will help your healthcare team better visualize the results of the test. The contrast injection may cause you to feel side effects such a feeling of warmth or flushing, a metallic taste in your mouth, lightheadedness, nausea, itching and/or hives. The amount of radiation you will be exposed to is very small and the risk of damage to your body is very low.

ECG (Electrocardiogram): An ECG is a test that measures the electrical activity of your heart. It involves putting sticky pads on your skin while the electrical activity of the heart is recorded. Skin irritation from the ECG electrodes or pain when removing the ECG leads is a possible risk.

Eye Examination:
Your eyes will need to be dilated for the eye exam. Dilating drops are used to dilate or enlarge the pupils of the eye to allow the eye doctor to get a better view of the inside of your eye. Dilating drops frequently blur vision for a length of time, which varies from person to person. They may also make bright lights bothersome. It is not possible for your ophthalmologist to predict how much your vision will be affected but the side effects are temporary and will eventually wear off. Driving may be difficult immediately after an examination, so it is best if you make arrangements not to drive yourself when you leave the clinic.

Reproductive risks:
Selinexor can harm an unborn or nursing baby. Therefore, women who are pregnant or nursing a child cannot participate in this study. You must confirm, to the best of your knowledge, that you are not now pregnant, and that you do not intend to become pregnant during the study.

Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

Loss of Confidentiality:
Any time information is collected there is a potential risk for loss of confidentiality. Every effort will be made to keep your personal and health information confidential; however, this cannot be guaranteed.

7. What benefits can I expect from being in the study?
There is no guarantee that this treatment will cure your cancer. Benefits you may receive from this treatment include:

- Making symptoms related to your cancer better
- Decrease in the amount of your cancer, which may mean that the treatment is helping your cancer
- Longer time until you would need a different therapy for your cancer
- Longer time you will live.

If you take part in this study, it may result in a better understanding of this treatment in other cancer patients. This understanding could benefit cancer patients like yourself in the future. However, you must understand that you may not benefit from taking part in this study.

You may also change your mind at any time during the study to stop your participation. If you do stop after you have begun the study drug, information and blood samples already collected from you may still be used for the tests described in the study but further blood samples will not be taken. Any samples provided to Karyopharm Therapeutics Inc or its vendors will not be returned and the data may still be used by Karyopharm.

You may receive other therapy for your CLL or lymphoma at any time if your doctor thinks this is best for you which will mean your participation in this study will stop.

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.

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could:

- Not participate in this study
- Get treatment or supportive care for your cancer without being in a study
- Take part in another study
- Get no treatment

Your study doctor will explain what options are available to you.

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;
- The sponsors (**OSU)** supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).
- Karyopharm Therapeutics, the drug provided

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.

By signing this form, you authorize the use and disclosure of your entire study record and any medical or other records. The purpose for the uses and disclosures you are authorizing is to conduct the study explained to you during the informed consent and research authorization process and to ensure that the information relating to that study is available to all parties who may need it for research purposes.

The NIH issues Certificates of Confidentiality for all NIH-funded studies, including this study. This Certificate provides extra protection for you and your study information, documents, or samples (blood, tissue, etc.). The Certificates are issued so that we cannot be required to disclose any identifiable information collected about you as a part of this study in a lawsuit or legal proceeding. This is a layer of protection over and above the already existing protections in place for you and your information, documents, or samples.

However, these protections do not apply in some situations. For example, we may have to release your information if a law requires us to do so, if the National Institute of Health that is funding this study requests the information, or if the FDA tells us to release this information. Please talk to your study team, or contact the Office of Responsible Research Practices at 614-688-8641, if you have questions.

Please visit the NIH website at https://humansubjects.nih.gov/coc/faqs to learn more.

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

The study agent, Selinexor, will be provided by Karyopharm Therapeutics Inc., the pharmaceutical company who manufactures the study drug and will not be billed to you or your insurance company. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. These standard of care tests/procedures include:

- physician visits

- various blood tests
- CT/PET scans
- hepatitis B and C tests
- Pregnancy test
- bone marrow biopsy and aspirate
- medication treatments given before and while you are being treated on this study

Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. In addition, you may ask that a financial counselor be made available to you to talk about the costs of this study. You are responsible for any co-pays, co-insurance, and deductibles as required by your insurance company or charges your insurance company does not pay.

11. Will I be paid for taking part in this study?
You will not be paid to take part in the study. Karyopharm Therapeutics Inc. is not providing any compensation for participating it the Study. There is a chance that some commercial value may result from the use of your data or sample(s). If that should happen, you will not be eligible to share in any profits.

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

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.

DRUG PROVIDER LIABILITY
Karyopharm Therapeutics will pay the cost for any reasonable medical expenses for the treatment of injury or illness that is proven to be caused by any manufacturing defect in the Study Drug or defects with labeling and written instructions for use of the Study Drug.

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. Your authorization to use your health information will not expire and any data or samples collected before your withdrawal will continue to be used as necessary to preserve the integrity of the study, however no additional information or samples will be

collected after you withdraw your authorization. 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. 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;
- Records about the study device; and

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;

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:

Jennifer Woyach, MD
455A Wiseman Hall
Columbus, OH 43210
Ph: 614-293-8165
24 hrs: 614-293-8000 ext. 5806

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

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

Jennifer Woyach, MD
455A Wiseman Hall
Columbus, OH 43210
Ph: 614-293-8165
24 hrs: 614-293-8000 ext. 5806

Signing the consent form

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

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

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

Investigator/Research Staff

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

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

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

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