CONSENT FOR CANCER RESEARCH

Project Title: A Phase IB/II Trial of Lenalidomide (Revlimid®), Ixazomib and Rituximab (RIXAR) as Front-line Therapy for High Risk Indolent B cell Lymphoma

Sponsor: Brian Hill, MD, PhD

Principal Investigator(s): Brian Hill, MD, PhD Cleveland Clinic
Paolo Caimi, MD University Hospitals

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic Main Campus, Cleveland Clinic Florida, Cleveland Clinic Regional Hospitals (Hillcrest, Fairview, Strongsville, and North Coast Cancer Center), and University Hospitals (UH).

One or more of the Investigators conducting this study serve as paid speakers, consultants or advisory committee members for the company that is paying for this research or a company that makes products used in this study. These financial interests are within permissible limits established by the Cleveland Clinic Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask your study doctor or call the Institutional Review Board at 216-444-2924.

What is the usual approach to my lymphoma?
Surgery and radiation are not commonly used to treat indolent B cell lymphoma. Standard care for people who have indolent B cell lymphoma that requires treatment includes rituximab, which is given in this study, in combination with intravenous chemotherapy. The chemotherapy drug most often used is bendamustine, but can also be a 4-drug combination called CHOP (Cytoxan, Adriamycin, Oncovin, prednisone).

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer. For example: comfort/palliative care

Why is this study being done?
You are being asked to participate in this research study because you have indolent B-cell non-Hodgkin lymphoma (iNHL) that has never been treated. iNHL is also sometimes called “slow growing” or “low grade” lymphoma. Types of iNHL include follicular lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma [nodal, extranodal (MALT), and splenic].

This research study uses a drug called Ixazomib in combination with Rituximab and Lenalidomide.

- Lenalidomide is approved by the Food and Drug Administration (FDA) to treat patients with multiple myeloma who have received at least one prior therapy, patients with myelodysplastic syndromes (MDS), and patients with relapsed or refractory mantle cell lymphoma who have received at least 2 prior therapies, one of which included bortezomib.
- Rituximab is approved by the FDA to treat patients with non-Hodgkin lymphoma (NHL) alone or with other chemotherapy medicines, patients with chronic lymphocytic leukemia (CLL) with fludarabine and cyclophosphamide, patients with rheumatoid arthritis (RA), and patients with granulomatosis with polyangitis (GPA) and microscopic polyangitis (MPA).
- Ixazomib is approved to treat multiple myeloma in combination with the medicines lenalidomide and dexamethasone, in people who have received at least one prior treatment for their multiple myeloma. It is considered investigational in this study because it has not been approved by the FDA to treat patients with lymphoma. Ixazomib has been evaluated as an oral single agent treatment in studies of patients with advanced solid tumors, lymphoma, relapsed/refractory multiple myeloma, and relapsed/refractory light-chain amyloidosis. Ongoing studies continue to investigate Ixazomib as a single-agent and also in combination with standard treatment.

The purpose of this study is to find out whether or not the combination of these three medications has an effect on cancer in patients with iNHL that has never been treated. The side effects (unwanted effects) of this treatment combination will also be studied. Based on previous studies, the combination of medications like Lenalidomide, Rituximab, and Ixazomib are promising regimens for therapy of iNHL. However, it is not known if the combination of these three medications is better or worse than other treatments.

About 33-42 people will take part in this research study at sites of the Case Comprehensive Cancer Center.

Millennium Pharmaceuticals, the company that makes Ixazomib, and Celgene Corporation, the company that makes Lenalidomide, are supporting this study.

One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask you study doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924 or University Hospitals Institutional Review Board at (216) 844-1529.

What are the study groups?
All patients will receive standard dosing of lenalidomide and rituximab. Ixazomib will be given at the maximally tolerated dose as determined by Phase I of the study which was 4.0 mg

This study will use treatment cycles that are 28 days long. During the first cycle you will have a

study visit once a week for 3 times. This is for Rituximab infusion on days 1, 8 and 15. You will also have an appointment for blood tests (and a pregnancy test if you are a woman who could become pregnant) on day 22.

After cycle 1, treatment with Rituxumab will be administered on day 1 of cycles 2-6, 8, 10 and 12. The first time you are treated with Rituximab, the infusion will take about 6 hours. If you do not have any reactions, the next infusion can be reduced to about 4 hours. In later cycles the infusion can be further reduced to about 2 hours.

You will take Ixazomib pills. The pills will be dispensed to you by the pharmacy. These should be taken by mouth once a week for 3 weeks, on days 1, 8 and 15 of every cycle
You will take Revlimid pills. These will be sent to your home. You should take one of these a day, every day for 3 weeks starting on day 1 of each cycle (so on days 1 through 21), and then not take them for the next 7 days (days 22 through 28).

How long will I be in this study?
You will receive treatment with Ixazomib, lenalidomide and rituximab for one year. After you finish treatment, your doctor will check your response in 2-3 months and then continue to follow up with you for up to five years.

What extra tests and procedures will I have if I take part in this study?
All of the exams, tests, and procedures you will have are part of the usual approach for your cancer.

Extra tubes of blood (about 2 teaspoons) will be drawn, at the same time other blood is drawn so there will be no extra needle sticks, at 3 times during the study: before treatment, after cycle 6 and at the end of treatment, to measure the number of different types of T cell lymphocytes in your blood. We will examine whether these T cell numbers help tell us who will respond best to the treatment. This same blood will also be tested for the number of B lymphocytes in your blood to see if this blood test can be a marker of how well the treatment has worked.

<u>Archive Tumor Tissue</u>
The biopsy taken during screening or your initial cancer diagnosis will be sent to our local laboratory to be stored and used for laboratory studies to learn more about this disease.

<u>HIV testing</u>
As part of this protocol, you will be tested for HIV (human immunodeficiency virus, which is the virus that causes the acquired immunodeficiency syndrome (AIDS). You will be notified of the results of the testing, and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with HIV, you would be ineligible to participate and you will receive additional counseling about the significance for your medical care and possible risks to other people. We are required to report all positive results to the Ohio State Board of Health. The test results will be kept confidential to the extent permissible under the law. If you do not want to be tested for HIV, then you should not agree to participate in this study.

What possible risks can I expect from taking part in this 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 which you normally do not discuss

The chemotherapy 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.
- 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 tables below show 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.

Possible side effects of lenalidomide

COMMON, SOME MAY BE SERIOUS In 100 people receiving lenalidomide, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Constipation, • Diarrhea • Tiredness • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving lenalidomide, from 4 to 20 may have:

• Nausea, vomiting • Chills, fever • Swelling of arms, legs • Infection, especially when white blood cell count is low • Weight loss, loss of appetite • Pain • Muscle spasms • Dizziness, headache • Difficulty sleeping • Cough, shortness of breath • Increased sweating • Itching, rash • Sores on the skin • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving lenalidomide, 3 or fewer may have:
• Heart attack • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to organs in the body when donor cells attack host organs which may cause dry skin, or muscle weakness • Kidney damage which may require dialysis • Cancer of bone marrow caused by chemotherapy • Damage to organs which may cause infection, bleeding, may require transfusions or changes in thinking • Increased tumor size • A new cancer resulting from treatment of earlier cancer • Stroke which may cause paralysis, weakness • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Difficulty stimulating enough stem cells in the bloodstream for future transplant

Possible side effects of rituximab:

COMMON, SOME MAY BE SERIOUS In 100 people receiving rituximab. more than 30 and up to 100 may have:
• Fever • Chills

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving rituximab, from 10 to 29 may have:

- Weakness
- Nausea
- Headache
- Cough
- Runny nose, shortness of breath, sinusitis (see cold symptoms)
- Throat irritation (see cold symptoms - pharyngitis
- Anemia (low red blood cell count, cells that carry oxygen)
- neutropenia (low white blood cell count, cells that fight infection)
- Low platelets (cells that help control bleeding)
- Rash
- Allergic reaction
- Itching
- Diarrhea
- Swelling
- Low blood pressure
- Infection
- Muscle pain

RARE, AND SERIOUS

In 100 people receiving rituximab, 9 or fewer may have:

A *serious but rare* side effect of rituximab is potential for a severe infusion reaction, typically with the first infusion (during infusion or within 30-120 minutes of infusion). You will be given medication prior to the infusion to decrease this reaction and monitored carefully during the infusion. If signs of reaction occur, the infusion is stopped. In most cases, the infusion can be restarted at a slower rate once symptoms subside.

Other rare but serious side effects:

- Patients who have had heart pain or irregular heartbeats in the past may experience this again. If these occur tell your doctor or nurse, so that they can be treated.
- Rapid destruction of cancer cells can cause disturbances in metabolism leading to kidney problems.
- If you have questions about this information ask your doctor.

Risks of Ixazomib:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Ixazomib, more than 10 and up to 100 may have:

Based on studies of IXAZOMIB it is possible to predict some of the discomforts and risks. However, it is possible that IXAZOMIB may cause risks that have not yet been observed in patients. The following risks might be seen:

- Low platelet count which may increase the chance of bleeding
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
- Feeling tired or weak
- Nausea
- Vomiting
- Diarrhea
- Numbness or tingling or pain feelings in hands and feet
-
- Constipation
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever

Other discomforts and risks reported in studies with IXAZOMIB, which may have been due to the patient's disease, IXAZOMIB, other medications, or some combination of these include:

- Not feeling like eating
- Electrolyte imbalance (blood chemical imbalance)
- Loss of water from the body (dehydration) because of vomiting and/or loose stools
- High blood creatinine and renal failure which means your kidneys are having trouble working well; Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
- Flu-like symptoms and other upper respiratory tract infections
- Lung infections including pneumonia or pneumonitis
- Chills
- Pain in the abdomen or back
- Swelling or fluid buildup in the arms or legs
- Lowered blood pressure that can commonly cause you to feel light headed, faint or pass out when you stand up
- Lowered white blood cells called lymphocytes
- Pain (muscular) in extremities

Rare but Serious Risks of Ixazomib
Some discomforts and risks that occur with lesser frequency than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience and because these events occurred while patients were receiving other drugs as well, we do not know if IXAZOMIB causes such problems. Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis,

drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and pemphigus vulgaris, have been reported in IXAZOMIB studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.

In addition, posterior reversible encephalopathy syndrome has also been reported with IXAZOMIB with lesser frequency. This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible. Transverse myelitis, also a rare condition, is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving IXAZOMIB. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether IXAZOMIB causes transverse myelitis, however, as it happened to a patient receiving IXAZOMIB, we are not able to exclude the possibility that IXAZOMIB may have contributed to transverse myelitis.

PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1 %) in patients taking Ixazomib. It is not known whether Ixazomib may contribute to the development of PML.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells, and result in blood clots in small vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders can occasionally be fatal. TMA, TTP, and HUS have been seen rarely (<0.1%) in patients treated with MLN9708.

IXAZOMIBshould not be taken if you have ever had an allergic reaction to boron or boron containing products.

The following side effects may also be a risk with IXAZOMIB because they have been reported with another proteasome inhibitor, Velcade, in patients with diseases requiring this type of treatment, or in patients who receive IXAZOMIB in combination with other drugs for cancer treatment:
• Reactivation of the herpes virus infection such as herpes zoster (shingles) that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time;
• Rapid death of cancer cells that may let large amounts of the cells into the blood that injure organs, such as kidneys (this is referred to as tumor lysis syndrome);
• Worsening of your heart function (congestive heart failure) that may require additional drugs for treatment or hospitalization;
• Disorders of your lung that could be serious enough to result in death

• Other drugs and supplements may affect the way IXAZOMIB works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Pregnancy Risk/Reproductive Health/Sexual Activity
Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Preliminary findings from a monkey study appear to indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. In addition, it is not known if the study drug Ixazomib will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study.

Lenalidomide may cause harm to an unborn baby.If you are female, you agree not to become pregnant while taking lenalidomide. For this reason, lenalidomide is provided to patients under a special distribution program called REMS.

In order to participate in this study you must register into and follow the requirements of the REMS program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate for you, and take telephone surveys regarding your compliance with the program.

Pregnancy Risk – Females
If you are a female of childbearing potential*, you will be required to have two negative pregnancy tests: the first test within 10-14 days before lenalidomide is prescribed and the second test within 24 hours before lenalidomide is prescribed.

* For the purposes of this study, a female of childbearing potential is a sexually mature female regardless of sexual orientation or whether they have undergone tubal ligation who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time during the preceding 12 consecutive months).

You will be required to use TWO reliable forms of birth control, one highly effective method and one additional effective method at the same time or practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while participating in this study; and 3) for at least 90 days after discontinuation from the study. The following are the acceptable birth control methods:

Highly Effective Methods	**Additional Effective Methods**
Intrauterine device (IUD)	Latex or non-latex condom with our without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide

Tubal ligation	Cervical cap with a spermicide
Partner's vasectomy	Sponge with a spermicide

You must not breastfeed a baby while you are participating in this study and for at least 28 days after you have been discontinued from the study.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while taking lenalidomide, at discontinuation of lenalidomide, and at days 14 and 28 following discontinuation from lenalidomide.

If you have any reason to suspect you are pregnant, you must IMMEDIATELY stop taking lenalidomide and tell your doctor.

Pregnancy Risk – Males
Lenalidomide is present at very low levels in human semen of healthy men for three days after stopping the drug according to a study. For some men, such as men with kidney problems, lenalidomide may be present in semen for more than three days. Additionally, it is not known if using Ixazomib will affect sperm.

Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period (including interruptions in treatment). Even if you are surgically sterilized (i.e., have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non-latex condom with a spermicidal agent) during the entire study drug treatment period and for 90 days after completing study drug treatment. Or you should completely avoid having heterosexual intercourse. You must NEVER donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you have stopped therapy.

All Subjects (Male or Female)
If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

What possible benefits can I expect from taking part in this study?
You will receive medical care during the study. You may not receive direct benefit from being in this study. However, taking part may help patients with lymphoma receive] better care in the future.

Can I stop taking part in this study?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:
- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?
Your involvement in this research study is voluntary and you will not be paid for your participation.

Ixazomib will be provided free of charge by Millennium and Lenalidomide will be provided free of charge by Celgene while you are participating in this study. Rituximab is a commercial drug and you, or your insurance company, will be billed. Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures. The blood work for research purposes will not be charged to you. It will be paid for by the research study.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

What happens if I am injured or hurt because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals, Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924 or University Hospitals Case Medical Center's Research Subject Rights phone line at (216) 983-4979.

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Brian Hill, MD, PhD or Paolo Caimi, MD and the research study staff at Cleveland Clinic and/or University Hospitals for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, University Hospitals Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Paolo Caimi, MD
Case Comprehensive Cancer Center
University Hospitals Case Medical Center
11100 Euclid Ave.
Cleveland, OH 44106

or

Brian Hill, MD, PhD
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic and/or University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic and/or University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) and/or University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, you can ask the Principal Investigator and/or research staff at (216)444-9451.

Emergency or after-hours contact information
If you are a University Hospitals patient, and you need to contact study staff outside normal business hours, you may contact 216-844-3951 and you will be transferred to the answering service, which can put you in contact with Paoli Caimi, MD or the oncologist (cancer doctor) on call.

If you are a Cleveland Clinic Main Campus patient, you should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

If you are a Cleveland Clinic Florida patient, please call 954-659-5000 and ask for the doctor that is on call.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924 or the University Hospitals Case Medical Center's Research Subjects Rights Phone line at 216-983-4979.

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Schedule of Events
Before you begin treatment on the study your Dr. will take a complete history and do a physical examination, and blood tests will be drawn. You will have a bone marrow aspiration and biopsy performed, unless it is already known that lymphoma is in your bone marrow. You will sign a separate consent form for this procedure. You will have a PET scan, and a CT scan of your chest, abdomen and pelvis, and a CT of the neck at the same time if there are enlarged lymph nodes can be felt in this area. If you're a woman who can become pregnant, you will have pregnancy tests as described earlier in this form.

On the day you begin treatment, called day 1 of cycle 1, you will again have a history and physical examination and some additional blood tests, and a pregnancy test if appropriate. You will then receive a rituximab infusion over approximately 6 hours.

You will be given ixazomib pills, to take one on that day. You will take another ixazomib pill for week 2 and week 3. On these days you will also have a clinic visit to have blood tests and to

receive a rituximab infusion. These infusions may be given over 4 hours if you tolerated the first rituximab infusion without a reaction.

You will have Revlimid ®, also known as lenalidomide, pills. You will take one of these each day starting on day 1 for 21 days. You will then have 7 days without taking any medication. In the first cycle, on day 22 you will also have blood tests and, if indicated, a pregnancy test. This will complete the first 28 day cycle.

For the remaining treatment cycles (2-12), you will only need to come on the first day of the cycle. On that day you will again have a history and physical examination and some additional blood tests, and a pregnancy test if appropriate.

You will then receive a rituximab infusion over 2-4 hours, except rituximab will not be given on cycles 7, 9 and 11.

You will be given ixazomib pills, to take one on that day, and another ixazomib pill 1 week and again 2 weeks later. You will have Revlimid ® pills. You will take one of these each day starting on day 1 for 21 days. You will then have 7 days without taking any medication.

Treatment is complete after the 12th cycle.

You will have a CT scan after the third and sixth cycles to see how you're lymphoma is responding to the treatment

About 2-3 months after the 12th cycle, you will be evaluated for how your disease responded to the treatment and how you tolerated the treatment. You will have a doctor visit for a history and physical examination. Blood tests will be drawn. You will have a PET scan. Bone marrow aspiration and biopsy may need to be repeated. This will be discussed at the time by your doctor. After that, you will be followed by your doctor in the standard way you would be after any treatment for your lymphoma.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____	_____	_____
Signature of Participant	Date	Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____	_____
Signature of Person Obtaining Consent	Date

_____
Printed Name of Person Obtaining Consent