THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

A Phase 2 Study of Ixazomib and Rituximab in Bruton Tyrosine Kinase Inhibitor Resistant Mantle Cell Lymphoma
2018-1090

Subtitle: Alliance protocol v7

Study Chair: Hun J. Lee

_____ _____
Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

This research has been reviewed and approved by the MD Anderson Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

The goal of this clinical research study is to learn if giving ixazomib in combination with rituximab can help to control mantle cell lymphoma (MCL). The safety of this drug combination will also be studied.

This is an investigational study. Rituximab is FDA approved and commercially available for the treatment of MCL. Ixazomib is not FDA approved or commercially available for the treatment of MCL. Its use in this study is investigational.

The study doctor can explain how the study drugs are designed to work.

The study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. You may not want to take part in the study due to the frequent number of study visits.

You can read a list of potential side effects below in the Possible Risks section of this consent.

You may receive up to 12 cycles of rituximab and ixazomib. You may then continue to take ixazomib by itself after Cycle 14 if your doctor thinks it is in your best interest.

Ixazomib will be provided at no cost to you while you are on study. You and/or your insurance provider will be responsible for the cost of rituximab.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard therapy. You may choose to receive other investigational therapy, if available. You may also choose to have no further treatment for your cancer. In all cases, you will receive appropriate medical care, including treatment for pain and other cancer symptoms.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have the following screening tests to help the doctor decide if you are eligible:

- You will have a physical exam.
- You will have an EKG and an echocardiogram (ECHO) to check your heart function.
- You will have a bone marrow biopsy and aspirate to check the status of the disease. To collect a bone marrow aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow is withdrawn through a large needle. Part of this sample will also be used for biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug.
- You will have a PET/CT scan to check the status of the disease.
- Blood (about 6 teaspoons) will be drawn for routine tests, to check the status of the disease, for biomarker testing, and to check for hepatitis B and C. If you can become pregnant, some of the blood will be used for a pregnancy test. To take part in this study, you must not be pregnant.
- You will have a core tumor biopsy to check the status of the disease. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Up to 24 participants will be enrolled on this study. All will take part at MD Anderson.

Study Drug Administration

Each study cycle is 28 days.

If you are found to be eligible to take part in this study, you will receive rituximab by vein over 4 to 8 hours on Days 1, 8, 15, and 22 of Cycle 1 and then Day 1 of Cycles 3 through 14.

You may be given acetaminophen (Tylenol) and diphenhydramine (Benadryl) before each dose of rituximab to help reduce the potential for side effects.

You will take ixazomib by mouth before rituximab on Days 1, 8, and 15 of each cycle.

You will no longer be able to take the study drug if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation on the study will be over after the follow-up visits.

Study Visits

On **Days 1, 8, 15 and 22 of Cycle 1**:

- You will have a physical exam (Day 1 only).
- Blood (about 4 teaspoons) will be drawn for routine tests and to see if you are having any side effects to the study drug.

On **Day 1 of each cycle**:

- You will have a physical exam.
- Blood (about 4 teaspoons) will be drawn for routine tests.
- If you can be pregnant, blood (about ½ teaspoon) will be drawn for pregnancy test.

At the **end of Cycles 4, 8, and 12**:

- If your doctor thinks it is needed, you will have a bone marrow biopsy/aspirate to check the status of the disease and for biomarker testing.
- Blood (about 4 teaspoons) will be drawn for biomarker testing.
- You will have a PET/CT scan to check the status of the disease.

After Cycle 12, you will return to the clinic for study visits **every 6 months**. At these visits:

- You will be given another 6-month supply of ixazomib doses.
- You will have imaging scans (CT or PET scans).
- A bone marrow biopsy/aspirate will be performed, depending on your disease status, diagnosis, and any laboratory evidence on follow-up that suggests more bone marrow testing is needed.

If the disease gets worse, you will have imaging scans and a bone marrow biopsy/aspirate to check the status of the disease and for biomarker testing.

End-of-Treatment Visit

Within 30 days after your last dose of study drug:

- You will have a physical exam.

- Blood (about 3 tablespoons) will be drawn for routine tests, biomarker testing, and to check the status of the disease.
- If your doctor thinks it is needed, you will have a PET/CT scan if you have not had one within the last 2 months and/or a bone marrow biopsy/aspiration to check the status of the disease.
- You will have a core tumor biopsy to check the status of the disease.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after the study drug is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Side effects will vary from person to person, and some may occur after you have stopped receiving the study drug. Tell the study staff about any side effects that you may have, even if you do not think they are related to the study drug/procedures.

Ixazomib and rituximab may each cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Ixazomib Side Effects

Common (occurring in more than 20% of patients)

• swelling (arms/legs) • fatigue • nerve damage (possible numbness, pain, and/or loss of motor function) • skin rash	• low blood levels of potassium (possible weakness and/or muscle cramps)constipation • nausea/vomiting	• diarrhea • loss of appetite • low blood cell counts (platelets/white/red) • pain (abdomen) • changes in vision

Occasional (occurring in 3-20% of patients)

• low blood pressure (possible dizziness/fainting) • dehydration • chills • fever • dizziness • headache	• difficulty sleeping • blurry vision • painful red eyes • back pain • muscle pain/weakness • joint pain • abnormal kidney test (possible kidney damage)	• kidney failure • lung infections (pneumonia) • flu-like symptoms • difficulty breathing • cough

Rare but serious (occurring in fewer than 3% of patients)

• spinal cord inflammation (possible pain, weakness, and/or loss of feeling or movement) • nerve damage (affecting movement) • posterior reversible encephalopathy syndrome (brain injury with possible headache, confusion, seizures, and/or vision loss)	• very severe blistering skin disease (with ulcers of the skin and digestive tract) • skin condition with fever and skin lesions • multiple blood clots (possible organ dysfunction and/or failure) • abnormal blood clotting in small blood vessels* • lung inflammation (possibly difficulty breathing)	• inflammation of the bile tract (possible blockage) • liver damage • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

The study drug may cause progressive multifocal leukoencephalopathy (PML). PML is brain damage that is likely to result in paralysis and/or coma, which may be permanent. PML can also lead to death.

Overdose has been reported in patients taking ixazomib. Reports of accidental overdose have been associated with risks such as nausea, lung infections (including aspiration pneumonia), multiple organ failure, and death. It is important to take only one dose of ixazomib at a time, and only at the prescribed dose and schedule.

*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, nosebleeds, and decreased urination. These disorders can occasionally be fatal. TMA, TTP, and HUS have been seen rarely (<0.1%) in patients treated with ixazomib.

<u>Rituximab Side Effects</u>

Common (occurring in more than 20% of patients)

• fever • fatigue • chills • low blood levels of phosphate (possible bone damage)	• nausea • low blood cell counts (red, white) • weakness	• nerve damage (possible numbness, pain, and/or loss of motor or sensory function) • lung inflammation (possible difficulty breathing) • infection

Rituximab may commonly cause infusion reactions such as difficulty breathing and/or tissue swelling. In some cases, life-threatening reactions such as sudden stopping of the heart and/or shock caused by heart damage may occur. It is not known how often these more serious more serious reactions may occur, however, is more common with the first infusion.

During or within the first 24 hours of the infusion you may develop fever, chills and shivering. Less frequently, some patients may experience pain at the infusion site, blisters, itching, sickness (nausea), tiredness, headache, breathing difficulties, blood pressure raised, wheezing, throat discomfort, tongue or throat swelling, itchy or runny nose, vomiting, flushing or palpitations, heart attack or low number of platelets. If you have heart disease or angina, these reactions might get worse.

Tell the person giving you the infusion immediately if you develop any of these symptoms, as the infusion may need to be slowed down or stopped. You may require additional treatment such as an antihistamine or acetaminophen. When these symptoms go away, or improve, the infusion can be continued. These reactions are less likely to happen after the second infusion. Your doctor may decide to stop your rituximab treatment if these reactions are serious.

Because rituximab is a mouse antibody that has been changed to make it similar to a human antibody, treatment with rituximab may commonly cause the body to make human antibodies to the mouse-based antibody. These antibodies are called HAMA or HACA. The potential response of your body to rituximab may lead to decreasing the effectiveness of mouse-based antibody therapies for you in the future. If you receive other drugs in the future that contain mouse proteins, you could develop an allergic reaction to those drugs.

Occasional (occurring in 3-20% of patients)

• high blood pressure • low blood pressure (possible dizziness/fainting) • chest tightness • swelling (arm/leg/ tissue)	• itching • night sweats • hives • high blood sugar (possible diabetes) • abnormal blood test • diarrhea	• abnormal liver and/or bone tests (possible liver damage) • pain (back/joint/muscle) • muscle spasms

• flushing • anxiety • headache • difficulty sleeping • dizziness • shivering • skin rash	• abdominal pain • weight gain • vomiting • upset stomach • low platelet counts • inflammation of the liver, gall bladder, and/or bile ducts	• lung damage and/or inflammation (possibly causing chest pain) • difficulty breathing (possibly due to narrowing of the airways) • cough • runny nose • nosebleed • sore throat

Rare but serious (occurring in fewer than 3% of patients)

• anemia due to destruction of red blood cells	• decreased bone marrow function and inability to make red blood cells	• high blood levels of uric acid (possible painful joints and/or kidney failure) • abnormal sensation (such as pins and needles)

Frequency Unknown

• sudden stopping of the heart • fast and/or irregular heartbeat • heart failure • heart attack • blood vessel inflammation (possible bleeding, bruising, and/or rash) • shock caused by heart damage • progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in paralysis and/or coma, which may be permanent, or death) • brain injury that may be reversible (possible	• severe painful blisters • severe skin rash • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract) • blockage and/or hole in the intestines (possibly leaking contents into the abdomen) • thick blood (possible blockage of blood flow) • condition that looks like lupus (an immune system disease) • immune system reaction (possible organ damage) • liver damage/failure • joint inflammation and swelling	• low oxygen level in the blood (possible lightheadedness) • bronchiolitis obliterans (damage of the small airways with difficulty breathing) • flu • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • worsening of Kaposi's sarcoma • tumor lysis syndrome (TLS)--breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle

headache, confusion, seizures, and/or vision loss) • lesions due to skin infection	• decreased kidney function (possible kidney failure) • inflammation inside the eye and/or of an eye nerve (possible vision problems)	cramps, kidney damage, and/or other organ damage)

Rituximab may increase your risk of serious infection. If you have signs of an infection (fever, cough, sore throat, pain while passing urine, or feeling weak/unwell), tell the doctor right away.
In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor right away. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Rituximab may also cause other viruses to reactivate. This includes cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. Rituximab may cause a serious viral brain infection called progressive multifocal leukoencephalopathy (PML). This may cause memory problems, confusion, sight loss and difficulty walking.

In some rare cases, severe skin reactions that can be life-threatening may occur. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present. Tell your doctor immediately if you experience any of these symptoms.

Talk to the study doctor before receiving any vaccines (for example, vaccines for measles, mumps, rubella, or polio). Receiving a vaccine while taking rituximab may increase the risk of serious infection or make the vaccine less effective.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **biopsies and bone marrow aspirations** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks
Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control while on study and for at least 90 days after your last dose of ixazomib if you are sexually active.

Birth Control Specifications:

Males: If you can father a child, you must use an effective barrier method of birth control while taking ixazomib and up to 90 days after your last dose of ixazomib. Effective barrier methods include a diaphragm, cervical cap, male condom, or female condom and spermicidal foam, sponges, and film. Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you can become pregnant, you must use 2 recommended methods of birth control. Highly effective methods of birth control include:

- Intrauterine device (IUD)
- Bilateral tubal occlusion ("tubes tied")
- Vasectomy of your male partner (a doctor should confirm the vasectomy was successful)
- Hormonal birth control: birth control pill (estrogen/progestin pill or progestin-only pill), skin patch, vaginal ring, or injection.

You can still become pregnant even if you use an acceptable birth control method. Some birth control pills will not work when you are taking certain drugs. Some methods, such as periodic abstinence, the withdrawal method, and some forms of hormonal birth control, are not acceptable methods of birth control to use on study. Talk with the study doctor about which methods of birth control you will use on study.

If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Takeda Alliance for this injury. You may also contact the Chair of MD Anderson’s IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of

care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. 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. You may ask that a financial counselor be made available to you to talk about the costs of this study.

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Hun J. Lee, at 713-792-2860) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, Takeda Alliance, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: Takeda Alliance.

10. In a medical emergency, you may be cared for by someone who has a financial

interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Your personal information and/or samples are being collected as part of this study. These data and/or samples may be used by researchers at MD Anderson or shared with other researchers and/or institutions for use in future research.

Before being shared for future research, every effort will be made to remove your identifying information from any data and/or samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

If you do not want your samples or data to be used for future research, tell the study doctor. You may withdraw your samples at any time by telling your study team. If you decide to withdraw your samples, they will be returned to the lab they came from or destroyed. However, the data and test results already collected from your samples will be kept and may be used.

In some cases, all of your identifying information may not be removed before your data or samples are used for future research. If this research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research

Samples collected from you as part of this study may be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment.

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 that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson
   - Takeda Alliance, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form

   Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

   The research samples collected may be stored by the sponsor for up to 20 years.

   The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, 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.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2018-1090.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION DATE
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN,
OR STUDY CHAIR)

_____
PRINTED NAME OF WITNESS TO THE VERBAL TRANSLATION