MC148A / 16-004179

Phase I/II Trial of Ibrutinib, Dexamethasone, and Lenalidomide as Initial Therapy for Transplant Ineligible Multiple Myeloma Patients

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Document Date: 03/10/2022

MAYO CLINIC

Name and Clinic Number

Approval Date: **March 10, 2022**
Not to be used after: **November 1, 2022**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC148A: Phase I/II Trial of Ibrutinib, Dexamethasone, and Lenalidomide as Initial Therapy for Transplant Ineligible Multiple Myeloma Patients

IRB#: 16-004179

Principal Investigator: Sikander Ailawadhi, M.D. and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

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CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigator: Sikander Ailawadhi, M.D. **Study Team Contact:** Michele Maharaj, RN	**Phone:** (904) 953-2607 **Phone:** (904) 953-6136 **Institution Name and Address:** Mayo Clinic 4500 San Pablo Rd Jacksonville, FL 32256	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate **(The RSA is independent of the Study Team)**	**Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study
Patient Account Services	**Toll-Free:** (844) 217-9591	▪ Billing or insurance related to this research study

Other Information:

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.

1. Why are you being asked to take part in this research study?

You are being asked to take part in this study because you have been diagnosed with a type of blood cancer called Multiple Myeloma that requires treatment.

2. Why is this research study being done?

In this study, you will be treated with a drug called ibrutinib (Imbruvica®), in addition to the standard regimen of dexamethasone, and lenalidomide. It is thought that ibrutinib will block the activity of a protein that is found in multiple myeloma cells. Lenalidomide is an immunomodulatory drug (altering the immune effects on the tumor cell). This study is being done to find out the effects (good and bad) of treating myeloma with the combination of ibrutinib, lenalidomide, and dexamethasone.

All the drugs are FDA approved, however, their use in this research study is considered investigational for Multiple Myeloma.

3. Information you should know

Who is Funding the Study?

Pharmacyclics LLC, an AbbVie Company, is funding the study and providing study drug. Pharmacyclics LLC will pay Mayo Clinic to cover the costs related to running the study.

4. How long will you be in this research study?

You will receive treatment with ibrutinib, dexamethasone, and lenalidomide for about 2 years. After this, if your study doctor thinks it is in your best interest, you may continue to receive the dexamethasone and lenalidomide. You will be in the study as long as your multiple myeloma is responding to the treatment and you are not having side effects that cannot be managed.

5. What will happen to you while you are in this research study?

If you agree to be in the study, you will first sign this this form, called an Informed Consent form, then you will be asked to participate in the following:

Screening (before you start the first cycle of study treatment)

- Complete medical history, physical exam including: weight, vitals and height, and an assessment of your ability to carry out daily activities.
- Routine blood and urine tests
- Skeletal survey
- Bone marrow aspirate and biopsy
- Electrocardiogram (ECG)
- PET scan
- Pregnancy test for women of child bearing potential
- Research blood tests
- Complete a Quality of Life Questionnaire

As part of your clinical care, you will automatically be enrolled in the REVLIMID REMS™ program in order to receive the lenalidomide. Before you can be enrolled in this program, you must read and agree to all the instructions of the program.

Every 14 days (during the first 2 cycles)

- Physical exam including: weight, vitals and height
- Routine blood tests

Day 1 of Every Cycle, before treatment

- Complete medical history, physical exam including: weight, vitals, and an assessment of your ability to carry out daily activities.
- Routine blood and urine tests
- Pregnancy test for women of child bearing potential
- Research blood tests
- Complete a Quality of Life Questionnaire

During the Study

- Skeletal survey will be done only if clinically indicated by your study doctor
- Electrocardiogram (ECG) will be done only if clinically indicated by your study doctor

- PET scan will be done only if clinically indicated by your study doctor.
- Bone marrow aspirate and biopsy will be done at the end of Cycle 1, and if your disease gets worse

At the end of treatment

- Complete medical history, physical exam including: weight, vitals, and an assessment of your ability to carry out daily activities.
- Routine blood and urine tests
- Skeletal survey
- Research blood tests
- Complete a Patient Medication Diary
- Complete a Quality of Life Questionnaire

If you agree to take part in the study, you also agree to take all study medications as directed by the study staff. You will need to return to the study doctor's office to receive the study medications.

Many prescription and over-the-counter medicines and supplements can affect how ibrutinib works. We will review your medication list with you before you start the study and at every visit. Please talk to the study team before starting any new medications or supplements.

Ibrutinib

Ibrutinib is a capsule that should be taken every day, at approximately the same time every day. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole with water, and be taken either with or without food.

You should not eat Seville oranges or drink grapefruit juice while taking the ibrutinib.

What if I miss a dose of Ibrutinib? If you miss a dose, it should not be made up. If you vomit after taking a dose, you should not take another dose but please record this information in your medication diary.

Lenalidomide

Lenalidomide is a capsule and should be taken at about the same time each day. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.

What if I miss a dose of lenalidomide? If less than 12 hours has passed since missing a dose, you can take the dose. If more than 12 hours has passed since missing a dose at the normal time, you should not take the dose, but take the next dose at the normal time on the following day. If you miss a dose let your study doctor know.

Dexamethasone
Dexamethasone is a tablet. You will take the dexamethasone on Days 1, 8, 15, and 22 of every cycle. The tablets should be taken about the same time each day. The tablets should not be broken or chewed. The tablets should be swallowed whole with water.

What if I miss a dose of dexamethasone? If you forget a dose, take it as soon as you remember it. However, if more than 12 hours have passed since missing a dose at the normal time skip the missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

6. What are the possible risks or discomforts from being in this research study?

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)
- Fever (Pyrexia)
- Rash
- Nausea
- Low white blood cell count (cells that help fight infection) (Neutropenia)
- Low platelet count (cells that help blood to clot) (Thrombocytopenia)
- Bleeding (Hemorrhage)

Side effects that have been seen in at least 1 of every 10 (≥ 10%) patients include:

- Common Cold (Upper Respiratory Tract Infection)
- Sores in the mouth (Stomatitis)

- Constipation
- Swelling of the hands or feet (Oedema Peripheral)
- Joint aches (Arthralgia)
- Vomiting
- Skin infection
- Pneumonia
- Headache
- Muscle spasms
- High blood pressure (Hypertension)
- 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:

- Blurry vision (Vision blurred)
- Increased level of uric acid in the blood (Hyperuricemia)
- Abnormal heart rhythm (Atrial fibrillation)
- Low white blood cell counts with fever (Febrile neutropenia)
- Skin redness (Erythema)
- Severe infection throughout the body (Sepsis)
- Sinus Infection (Sinusitis)
- Breaking of the nails (Onychoclasis)
- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Increase in specific white blood cell count (Leukocytosis, Lymphocytosis)
- Increased level of "creatinine" in the blood (blood creatinine increased)
- Non-melanoma skin cancer
- Heart failure (Cardiac failure)
- Indigestion (Dyspepsia)

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 White Blood Cell 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)
- Tender or painful bumps or ulcers on the skin, sometimes with a fever (Neutrophilic dermatosis)
- Bleeding in the eye (Eye hemorrhage)

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 non-steroidal anti-inflammatory drugs (NSAIDs) or medicines used to prevent or treat blood clots or stroke, ibrutinib may increase this risk further. On this study you will also be getting lenalidomide, which can increase the risk of blood clots. To minimize this risk your doctor will prescribe you low-dose aspirin or an equivalent medication. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib without the knowledge of your doctor. 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 and heart failure, including some fatal events, which could sometimes be sudden, have been reported in patients treated with ibrutinib, especially when they also have heart conditions, increased blood pressure or have diabetes, infections, or had abnormal heartbeat

in the past. Tell your study doctor immediately if you have any symptoms of heart problems such as feeling as if your heartbeat is fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, swollen legs, or you faint.

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, also called high blood pressure, has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your study doctor know if you have any of the symptoms of high blood pressure which may mean that you have developed hypertension or that your hypertension is getting worse. Your study doctor may adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Stroke

Cases of stroke, with and without changes in heartbeat rhythm and/or hypertension have been reported with the use of ibrutinib. Some of these cases have led to death. Seek immediate medical attention if you notice or someone notices in you, any of the following: 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, and/or sudden severe headache with no known cause. These may be signs and symptoms of a 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 a cough, or any signs of a new or worsening respiratory symptom such as shortness of breath or difficulty breathing.

Interference with other drugs/food
Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body processes 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.

Ibrutinib in combination with intensive chemoimmunotherapy treatments
When ibrutinib is given in combination with certain intensive chemoimmunotherapy treatments, older patients may experience more side effects, which may limit their ability to receive the full course of treatment. If you are 65 years of age or older, your study doctor may recommend a lower dose of ibrutinib, discontinuing ibrutinib, and/or more frequent follow-up visits and tests.

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.

Reproductive effects

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

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

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

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

Be aware that you can still become pregnant even if you use 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.

Lenalidomide

Likely risks of lenalidomide *(events occurring greater than 20% of the time)*
Side effects considered serious are **bolded.*

- **Neutropenia** or a decrease in white blood cells that can make you more prone to infections
- **Thrombocytopenia** or a decrease in platelets which can cause you to bruise or bleed easily and/or may require platelet transfusion
- Constipation or difficulty moving your bowels
- Diarrhea or loose/frequent bowel movements
- Infections involving various organs

Less likely risks of lenalidomide *(events occurring less than or equal to 20% of the time)*
- **Anemia** or a decrease in red blood cells that can cause tiredness which may require red blood cell transfusion
- Nausea
- Loss of appetite
- **Back pain**
- Peripheral neuropathy
- Joint pain
- Muscle cramps
- Swelling of the arms and legs

- Problems falling asleep or staying asleep
- **Fever**
- Cough
- **Shortness of breath** or difficulty catching your breath
- Upper respiratory infection
- Rash
- Itching and dry skin
- Lack or loss of strength
- Dizziness
- Headache
- Abnormal thyroid function or inflammation of thyroid gland
- Abdominal pain and or distension
- Gastrointestinal bleeding
- Bowel obstruction
- Abnormalities of liver tests
- Allergic reaction to drug
- Abnormalities of mineral levels in blood
- Heartburn
- Muscle pain

Serious side effects occurring in 1% or more of patients and not listed in bold above

- Neutropenia associated with a fever
- Pulmonary embolism or blood clot in or around the lungs
- Deep vein thrombosis or blood clots in a larger blood vessel
- Atrial fibrillation or irregular heartbeat
- Progression of the disease being studied including multiple myeloma
- Pneumonia or an infection of the lungs
- Sepsis or an infection of the blood
- Dehydration
- Kidney failure which can cause increases or decreases in the amounts of chemicals in your blood which can cause irregular heart beats, muscle twitching, seizures, and/or death
- Myocardial infarction (heart attack)
- Stroke (bleeding in the brain or clotting)

Rare cases of the following events have been reported:

- Angioedema- an allergic skin disease characterized by patches of swelling involving the skin and/or the lining of your nose, mouth, and gastrointestinal tract.
- Anaphylaxis- serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness.

- Stevens-Johnson syndrome and toxic epidermal necrolysis- serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to detachment of the top layer of skin (could be body-wide). Medical journals have reported patients with allergic skin reaction with thalidomide who also developed the same type of reaction with lenalidomide.
- Drug reaction with eosinophilia and systemic symptoms (DRESS) may present with a cutaneous reaction; eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis.
- Tumor lysis syndrome- metabolic complication that can occur during or without treatment of cancer. These complications are caused by the break-down products of dying cancer cells and include hyperkalemia (high potassium), hyperphosphatemia (high phosphorus), hyperuricemia and hyperuricosuria (high uric acid in blood and urine), hypocalcemia (low calcium), and consequent acute uric acid nephropathy and acute renal failure (kidney damage).
- Tumor Flare reaction- a condition that involves any of the following increase in the size of the cancerous lymph nodes, rash and slight fever.
- Rhabdomyolysis- a serious condition involving the destruction of skeletal muscle that can lead to kidney failure. Signs and symptoms include dark, red, or cola colored urine and muscle tenderness, stiffness, aching (myalgia) or weakness.
- Increase in blood levels of lipase due to inflammation of pancreas gland.
- Abnormalities of blood clotting.
- Bone marrow failure.
- Decrease in lymphocytes (type of white blood cells).
- Enlarged spleen.
- Abnormal heart rhythms.
- Congestive heart failure (condition where the heart becomes weak and cannot pump enough blood to the rest of the body).
- Decreased function of adrenal gland.
- Decreased hearing.
- Vision abnormalities.
- Clotting in blood vessels of intestines.
- Seizures.
- Graft-versus-host disease (when transplanted donor tissue attacks the tissues of the recipient's body) - (graft vs. host disease).

Also Reported on Lenalidomide Trials But with the Relationship to Lenalidomide Still Undetermined:

- Tissue swelling - (angioedema)
- Rhabdomyolysis is a breakdown of muscle fibers. It occurs when muscle cells die and release cell contents into the blood stream. It can cause muscle pain and a number of health problems, including damage to the kidneys. If severe, this could be life threatening. - (rhabdomyolysis)

These events have the potential to be fatal.

Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking study drug. In some cases, side effects can be serious, long lasting or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Hematological Toxicity
Lenalidomide is associated with significant neutropenia (decrease in white blood cells that help fight infection) and thrombocytopenia (decrease in platelets that help with blood clotting). You will have your blood counts checked frequently when starting treatment with lenalidomide.

Deep Vein Thrombosis and Pulmonary Embolism
Lenalidomide has demonstrated an increased risk of deep vein thrombosis (DVT, blood clot in a larger blood vessel) and pulmonary embolism (PE, a blood clot in or around the lungs) in some people with certain medical conditions. The study staff will ask you about any risk factors you may have. [If you have a history of blood clots your doctor will prescribe either heparin or coumadin for the first four months of the study treatment. The doctor may continue to prescribe the medication or aspirin for the remainder of your course of study treatment. All other patients will receive (at the discretion of the treating physician) either oral low–dose aspirin or another treatment to prevent blood clotting during study participation.] Patients unable or unwilling to undergo treatment for prevention of blood clots will not be eligible to participate in this study. You will be instructed on the signs and symptoms of DVT and PE and if symptoms occur you should contact your study doctor promptly.

Second new cancers
According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

Other Risks
If any physician other than the study doctor prescribes medication for you for another condition or you are taking any over-the-counter medications or vitamins, you must inform the study staff. This is important because the interaction of some medications may cause serious side effects.

Lenalidomide has been shown to increase the level of digoxin in the blood in some patients; please tell your doctor if you are taking digoxin.

Your condition may not get better or may become worse while you are in this study.

Risks Associated with Lenalidomide and Pregnancy
Lenalidomide is related to thalidomide. Thalidomide is a known to cause severe life-threatening human birth defects. Findings from a monkey study 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 any unborn baby. Females must not become pregnant while taking lenalidomide. You have been informed that the risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking lenalidomide.

Lenalidomide is detected in trace quantities in human semen according to a study. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time. For these reasons male patients receiving lenalidomide must use a latex condom while taking lenalidomide, when temporarily stopping lenalidomide, and for 28 days after permanently stopping lenalidomide treatment during any sexual contact with a pregnant female or a female of child bearing potential even if you have undergone a successful vasectomy.

Why do I have to prevent becoming pregnant (if I am of childbearing potential)?
There is no information on the effect of the study treatment on embryos, fetuses and nursing infants, but it has to be expected from its mode of action that there are considerable risks. Lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. For this reason, females with childbearing potential (this means that your uterus has not been

removed or it has been less than two year since you had your last period) have to enroll in the Revlimid REMS™ Program and must agree to follow the pregnancy guidelines according to the Revlimid REMS™ Program. Your study doctor will explain how to register to the Revlimid REMS™ Program. You must agree to take a pregnancy test within 10-14 days and again within 24 hours prior to receiving an initial prescription for lenalidomide even if continuous abstinence is the chosen method of birth control. Once treatment has started pregnancy test will occur weekly during the first treatment cycle (4 weeks) and at least every 4 weeks thereafter. You **must not** become pregnant during this study. If you are a female of childbearing potential, you must use 2 separate forms of effective birth control during this study.

Acceptable methods of birth control during your time in this study include:

- Consistent use of a double-barrier method (diaphragm with spermicide, condom with spermicide),
- Approved hormonal contraceptives, such as birth control pills (with 2 hormones), patches, injections, vaginal ring, or implants
- An intrauterine device (IUD)
- Abstinence (no sex).

This is required for the duration of study and at least 4 weeks before first dose of Lenalidomide and Ibrutinib following the last dose of Lenalidomide and study drug (Ibrutinib).

Males taking Lenalidomide and Dexamethasone must agree to use a latex or synthetic condom during sexual contact with a pregnant female or a female who can become pregnant even if you have had a successful vasectomy. This is required for the duration of study and at least 4 weeks following the last dose of Lenalidomide and 3 months after stopping study drug (Ibrutinib).

Male subjects must agree to not donate semen or sperm while taking and 28 days after the last dose of Lenalidomide and 3 months after stopping study drug (Ibrutinib).

Patients should not donate blood during treatment therapy or for 28 days following discontinuation of Lenalidomide.

Dexamethasone

Likely risks of dexamethasone (events occurring greater than 20% of the time)

- Stomach and throat ulcers or worsening of any ulcers you had before treatment
- Swelling and pain of the pancreas
- Weight gain around the stomach
- Puffiness (especially in the face)
- Buildup of fluids and a rise in blood pressure

- Possible rise in your blood sugar
- Changes in the blood levels of potassium
- Infection
- Peripheral Neuropathy

Less likely risks of dexamethasone (events occurring less than or equal to 20% of the time)

- Muscle weakness
- Brittle bones
- Menstrual changes
- Itching, and other allergic reactions, some severe

Rare but serious risks of dexamethasone (events occurring less than 2-3% of time)

- Mood swings
- Depression
- Trouble sleeping
- Changes in personality
- Seizures
- Dizziness
- Patients who are more likely to get heart disease may have heart failure
- Drug reaction with eosinophilia and systemic symptoms (DRESS) may present with a cutaneous reaction; eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis.

As with any medication, allergic reactions are a possibility.

Bone Marrow Aspiration

Bone marrow aspiration is done to find the reason for many blood disorders, and it may be used to find out if cancer or infection has spread to the bone marrow, or if the cancer cells are increased or decreased. The skin is cleansed, and a local anesthetic, such as lidocaine, is injected to numb the area. An aspirate needle is inserted through the skin until it touches the bone. Then, with a twisting motion, the needle is advanced through the bony cortex (the hard outer layer of the bone) and into the marrow cavity. Once the needle is in the marrow cavity, a syringe is attached and used to aspirate ("suck out") liquid bone marrow. It is common for soreness to be present for 2-3 days after the procedure and in rare cases, pain, redness, fever, bleeding or swelling can arise.

7. Are there reasons you might leave this research study early?

Taking part in this research study is your decision. You may decide to stop at any time. You should tell your study doctor if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the researchers, the company supplying drug and funding, or Mayo may stop you from taking part in this study at any time:

- if it is in your best interest,
- if you do not follow the study rules,
- if the study is stopped

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

8. What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

9. What are the possible benefits from being in this research study?

This study may not make your health better. If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other people with multiple myeloma in the future.

10. What alternative do you have if you choose not to participate in this research study?

You do not have to be in this study to receive treatment for your condition. Your other choices may include other chemotherapy. You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

11. What tests or procedures will you need to pay for if you take part in this research study?

You will not need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Bone marrow Biopsy/Aspiration after completion of Cycle 1 prior to Cycle 2 – (only if enrolled in the Phase II portion of the study)
- Ibrutinib and dispensing
- Research Blood Tests

However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular medical care.

- Dexamethasone, Lenalidomide and Dispensing
- Routine Labs, Exams, and Urine Testing
- ECG
- Bone Marrow testing at all time points except (after one month of starting in the Phase II portion of the study – and only in enrolled in Phase II)

However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular medical care.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

12. Will you be paid for taking part in this research study?

You will not be paid for taking part in this study.

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

13. What will happen to your samples?

We would like to keep your sample for future research. You can still take part in this current study even if you don't want your sample used for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Other researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.
Please read the following statements and mark your choices:

1. I permit my sample to be stored and used in future research of Multiple Myeloma at Mayo Clinic:

☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my sample to be stored and used in future research at Mayo Clinic to learn about, prevent, or treat any other health problems:

☐ Yes ☐ No Please initial here: _____Date: _____

3. I permit Mayo Clinic to give my sample to researchers at other institutions:

☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your samples will be used in the future, we cannot promise that samples can be retrieved and destroyed.

14. How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study.

Your coded information will be sent to the sponsor, Pharmacyclics LLC, its affiliates, and its collaborators, who may study the data collected from your medical records or from analysis of your tissue, blood, or other specimens collected from you.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study.
- Pharmacyclics LLC, an AbbVie Company, its affiliates, and its collaborators (Janssen Biotech, Inc.)

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research.
- Other Mayo Clinic physicians involved in your clinical care.
- Researchers involved in this study at other institutions.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- Pharmacyclics and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts forever, unless you cancel it.

MAYO CLINIC

Name and Clinic Number

Approval Date: **March 10, 2022**
Not to be used after: **November 1, 2022**

ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permission to take part in this research.

	/ /	: AM/PM
Printed Name	Date	Time

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

	/ /	: AM/PM
Printed Name	Date	Time

Signature