Official Title: LCI-HEM-MYE-CRD-004 (MMRC-073 CARJAK): Phase I/II Study of Carfilzomib, Ruxolitinib, and Low Dose Dexamethasone for Carfilzomib-Refractory Multiple Myeloma
NCT03773107
IRB-Approved Date: 11/22/2022

ATRIUM HEALTH
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Sponsor / Study Title:	**Levine Cancer Institute / Phase I/II Study of Carfilzomib, Ruxolitinib and Low-Dose Dexamethasone for Carfilzomib-Refractory Multiple Myeloma**
Protocol Number:	**LCI-HEM-MYE-CRD-004**
Principal Investigator:	**Shebli Atrash, MD, MS**
Telephone:	[redacted] **(24 Hours)** **(24 Hours)**
Address:	**Levine Cancer Institute - Carolinas Medical Center** [redacted]

This form is for use in a research study that may involve subjects who may or may not have the capacity to consent to take part in the study. Accordingly, when the subject cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the subject rather than the person (legally authorized representative) who is signing and dating this form for the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the subject regains the capacity to consent, informed consent will be obtained from the subject and the subject offered the ability to leave the study if desired.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may also discuss your decision with your friends and family. You have also been told that you have the option not to participate.

INTRODUCTION TO THE RESEARCH STUDY

You are being asked to participate in this research study conducted by Dr. Atrash and his associates (the investigators) at Levine Cancer Institute (LCI) and Atrium Health testing carfilzomib, ruxolitinib and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma (RRMM). You are being asked to take part in this study because you have RRMM for which you have received more than two prior therapies.

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This study is being carried out under the sponsorship of Levine Cancer Institute (LCI). Amgen and Incyte are the companies supplying drug and/or funding that will be used in this study.

Ruxolitinib is a kinase inhibitor (drug that blocks enzymes fueling cancer growth) that is Food and Drug Administration (FDA) approved for myelofibrosis (disorder that disrupts normal blood cell production) and polycythemia vera (production of too many red blood cells) but is investigational (not FDA approved) in multiple myeloma. Carfilzomib is a protease inhibitor (drug that stops cancer cells from growing) and is FDA approved for multiple myeloma. Dexamethasone is a corticosteroid that prevents the release of substances in the body that cause inflammation and is FDA approved.

Taking part in this study is entirely voluntary.

PURPOSE OF THE RESEARCH STUDY

The purpose of this study is to determine if treatment with carfilzomib, ruxolitinib and low-dose dexamethasone improves progression free survival (disease doesn't worsen) in patients with RRMM.

INFORMATION ABOUT THE STUDY

This study is being done because, despite major advances in therapy, multiple myeloma is still considered an incurable cancer. The majority of patients relapse (disease returns) with progressively shorter times between each following relapse. There is a need to identify patients at high risk of disease relapse and develop new treatments that extend survival. The first part (Phase I) of this study will determine the most tolerated dose of ruxolitinib in combination with carfilzomib/dexamethasone and the second part (Phase II) will determine the safety and efficacy of the study treatment (carfilzomib/dexamethasone with or without ruxolitinib) along with evaluation of progression free survival (the length of time during and after treatment of disease that a patient lives with the disease but it does not get worse) and overall survival. Correlative tests (measure relationship between processes in the body and their effect on disease) using bone marrow (soft tissue inside bone) and blood will also be done to evaluate connections between cell abnormalities, changes in biology (structure), and response to treatment.

You will be one of up to 48 subjects participating in this study. Your participation is expected to last approximately 5 years.

WHAT WILL HAPPEN DURING THE STUDY

To participate in this study, you or your legally authorized representative will need to review, sign and date this consent from and provide authorization for the release of your medical records for research purposes. By doing so, you are giving us permission to determine if you are eligible to participate in this study. To determine if you are eligible (screening), the following procedures/tests

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will be done. If you have had some of the tests or procedures below recently, they may not need to be repeated at screening:

Before you begin the study (Baseline):

- Medical and disease history
- Physical exam
- Vital signs (body temperature, breathing rate, pulse, blood pressure)
- ECOG performance status (assesses daily living abilities)
- Pregnancy tests (blood and urine) for females of childbearing potential
- Electrocardiogram (ECG) – a measure of the heart's electrical activity
- ECHO (echocardiogram – heart test done using sound waves), MUGA (multigated acquisition scan - checks the pumping action of the heart) or cardiac MRI (magnetic resonance imaging of the heart – pictures made using strong magnets and a computer)
- Check for concomitant medications (all ongoing medications and those taken within 14 days prior to first dose)
- Bone marrow biopsy/aspirate (sample) for disease evaluation and correlative studies
- Blood draw for disease evaluation and to check blood count, blood chemistries, blood clotting ability and for correlative studies. Blood will also be tested for HIV and hepatitis (liver disease).
- Urine sample collected over a 24-hour period
- PET/CT (positron emission tomography/computed tomography – special types of x-rays) scan or MRI (magnetic resonance imaging – pictures made using strong magnets and a computer) if your physician feels it is necessary to evaluate your disease
- Bone skeletal survey (various x-rays of all the bones in the body)

During the study:

All study treatment will be given on an outpatient basis. If you are having unfavorable side effects, the study treatment may be stopped for a while, or the dose of the study drug may be reduced. Your study doctor will also discuss with you whether it is in your best interest to continue the treatment with the study drugs. You will continue treatment until your disease progresses (once you have started ruxolitinib) or treatment is stopped for any reason. You will receive additional antiviral medications while receiving study treatment to prevent reactivation of VZV (varicella zoster virus).

<u>Phase I</u>

If you are participating in the Phase I portion of this study, you will be placed in one of three groups in order to determine the maximum tolerated dose (MTD) of the study drug ruxolitinib. This procedure is known as dose escalation. Each cycle lasts 28 days. Prior to each carfilzomib dose, you will receive additional antiviral medications, to prevent reactivation of VZV (varicella zoster virus

[shingles]). Note: If you are 75 years of age or older and/or diabetic, you may receive 20 mg of dexamethasone instead of 40 mg (see below).

- If you are in group one, you will receive 56 mg/m^2 carfilzomib through an IV (intravenous – through a vein) over 30 minutes on Days 1, 2, 8, 9, 15 and 16 of all cycles. You will receive 40 mg dexamethasone orally (by mouth) on Days 1, 8, and 15 of all cycles and 5 mg ruxolitinib orally with or without food twice daily for 28 days.
- If you are in group two, you will receive 56 mg/ m^2 of carfilzomib through an IV over 30 minutes on Days 1, 2, 8, 9, 15 and 16 of all cycles. You will receive 40 mg dexamethasone orally on Days 1, 8 and 15 of all cycles and 10 mg ruxolitinib orally with or without food twice daily for 28 days.
- If you are in group three, you will receive 56 mg/ m^2 carfilzomib through an IV over 30 minutes on Days 1, 2, 8, 9, 15 and 16 of all cycles. You will receive 40 mg dexamethasone orally on Days 1, 8 and 15 of all cycles and 15 mg ruxolitinib orally with or without food twice daily for 28 days.

The following tests and/or procedures will be done when you come to the clinic for treatment:

- Physical exam (Day 1 of each cycle)
- Vital signs (prior to each infusion of carfilzomib)
- ECOG performance status (Day 1 of each cycle)
- Blood draw to check blood cell counts, blood chemistries, blood clotting abilities, cardiac biomarkers (evaluates heart function), and disease response (Day 1 of each cycle). Blood draw to check cell counts prior to each carfilzomib as infusion as well as Day 22 and blood chemistries on Days 1, 8, 15 and 22 of each cycle.
- ECHO, MUGA or cardiac MRI (Day 1 of every 2 cycles)
- Bone marrow aspirate for research purposes (Cycle 1 between Day 20-27 of ruxolitinib treatment and at disease relapse or progression after ruxolitinib has been started) and additionally if clinically indicated
- Blood draw for research purposes (Day 8 and between Day 20-27 of Cycle 1 of ruxolitinib treatment and at disease relapse or progression after ruxolitinib has been started)
- Urine collection sample for disease evaluation (Day 1 of all cycles until disease progression)

The phase I portion of the study is expected to be no longer than 12 months.

Phase II

If you are participating in the phase II portion of the study:

If you previously received carfilzomib at a dose greater than or equal to 56 mg/m^2, you will begin 28-day treatment cycles with carfilzomib (IV)/dexamethasone (by mouth)/ruxolitinib (by mouth) regimen until your disease progresses. Ruxolitinib will be given at the MTD level established in Phase 1 – either 5, 10 or 15 mg twice daily. If you previously received carfilzomib less than 56

mg/m^2, you will begin a 28-day treatment cycle (Cycle 1) with 56 mg/m^2 carfilzomib through an IV over 30 minutes on Days 1, 2, 8, 9, 15 and 16. You will also receive 40 mg dexamethasone orally (by mouth) PO on Days 1, 8, and 15. If you are 75 years of age or older and/or diabetic, you may receive 20 mg of dexamethasone instead of 40 mg.

If your disease responds well to the carfilzomib/dexamethasone treatment after Cycle 1, you will continue on 28-day cycles of carfilzomib/dexamethasone as described above until disease progression, you decide you no longer wish to receive study treatment, or your study doctor decides it is in your best interest to stop study treatment. If your disease progresses on the carfilzomib/dexamethasone, you will be given the option to have ruxolitinib (at the MTD level established in Phase I- either 5, 10, or 15 mg taken orally twice a day) added to the carfilzomib/dexamethasone treatment regimen. If you choose to add ruxolitinib to the carfilzomib/dexamethasone, you will continue this regimen until disease progression, you decide you no longer wish to receive study treatment, or your study doctor decides it is in your best interest to stop study treatment.

If your disease does not respond well to the treatment after Cycle 1, you will then have ruxolitinib (at the MTD level established in Phase 1 – either 5, 10 or 15 mg PO twice daily) added to the carfilzomib/dexamethasone treatment regimen and will continue this treatment regimen until disease progression or your study doctor decides it is in your best interest to stop study treatment.

The following tests and/or procedures will be done when you come to the clinic for treatment:

- Physical exam (Day 1 of each cycle)
- Vital signs
- ECOG performance status (Day 1 of each cycle)
- Blood draw to check blood cell counts, blood chemistries, blood clotting abilities, cardiac biomarkers (evaluates heart function), and disease response (Day 1 of each cycle). Blood draw to check cell counts prior to each carfilzomib as infusion as well as Day 22 and blood chemistries on Days 1, 8, 15 and 22 of each cycle.
- ECHO, MUGA or cardiac MRI (Day 1 of every 2 cycles)
- Bone marrow aspirate for research purposes (Cycle 1 between Day 20-27 of ruxolitinib treatment and at disease relapse or progression after ruxolitinib has been started) and additionally if clinically indicated
- Blood draw for research purposes (Day 8 and between Day 20-27 of Cycle 1 of ruxolitinib treatment and at disease relapse or progression after ruxolitinib has been started)
- Urine collection sample for disease evaluation (Day 1 of all cycles until disease progression)

The following tests may be done at any time while you are receiving study treatment (either Phase I or Phase II) only if clinically indicated as determined by your study doctor:

- Bone skeletal survey
- Bone marrow biopsy/aspirate (sample) for disease evaluation
- PET/CT scan or MRI
- Bone marrow aspirate for disease evaluation
- Urine collection sample to check disease response

The phase II portion of the study is expected to be no longer than 24 months.

After you complete the intervention (either Phase I or Phase II):

An end of treatment visit will be done when you stop study treatment for any reason. During this visit, the following procedures and tests will be done:

- Physical exam
- Vital signs
- ECOG performance status
- Pregnancy test (urine or blood) for females of childbearing potential
- ECHO, MUGA or cardiac MRI
- Blood draw to check blood cell counts, blood chemistries and disease response
- Urine collection sample to check disease response (if clinically indicated)
- Bone skeletal survey (if clinically indicated)
- Bone marrow biopsy/aspirate for disease evaluation (if clinically indicated)

Throughout the study:

The following test will be done while you are receiving study treatment (Cycle 1 Day 20 – Day 27) or during follow-up if your disease relapses (returns) or has progressed (gotten worse) after you have begun treatment with ruxolitinib:

- Bone marrow biopsy/aspirate for correlative studies

Follow-up:

If you received ruxolitinib in the study and you stop study treatment for any reason other than disease progression, you should continue to have monthly disease assessments at your study doctor's discretion done until your disease worsens or you start another cancer therapy. You will be followed for at least 3 years from the day you started ruxolitinib and possibly longer until Levine Cancer Institute determines follow-up is no longer required. You will be contacted by phone once every 3 months if you are not seen in the clinic. You will be notified when follow-up is no longer required.

If you do not receive ruxolitinib on the study, you will be followed for side effects for at least 30 days after your last dose of study treatment. After this safety monitoring period has ended, your participation on the study will be complete.

YOUR ROLE IN THE STUDY

Taking part in a research study can be an inconvenience to your daily life. Please consider the study time commitments and responsibilities as a research subject when you are deciding to take part. Your responsibilities as a study subject include the following:

- Tell the truth about your medical history and current conditions.
- Tell the study doctor if you have been in a research study in the last 30 days or are in another research study now.
- Tell the study doctor about any problems you have during the study.
- Take the study drug as directed by the study doctor and study staff.
- Do not share the study drug with anyone else. Keep the study drug out of the reach of children and persons of limited capacity to read or understand.
- The study doctor or study staff will talk to you about any food or medicines that you should not take while in this study.
- Use care when driving or using machinery while you are taking the study drug.

RISKS OF THE STUDY

You may have side effects while you are on this study. Everyone taking part in the study will be carefully watched for side effects. However, side effects may occur that are not yet known.

Side effects can be mild or very serious. Your healthcare team may give you medicines to lessen side effects. Many side effects go away after you stop taking the study drugs. In some cases, side effects can be serious in that they can be long lasting, may never go away, may result in hospitalization, or may result in death.

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

Carfilzomib Side Effects:

You will be told about the known risks, which are the side effects reported previously by others who took carfilzomib. However, your study doctors do not know all the side effects that you may experience. As with all investigational drugs, all risks may not have been identified at this time. There may be serious unexpected or unforeseen risks while taking carfilzomib, including death. It is known that nearly everyone who takes carfilzomib will have some side effects while on the study drug. Many of these side effects may be mild but some side effects can be serious and even fatal.

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Before you take carfilzomib, your study doctor needs to know if you have any:

- Heart problems, including a history or chest pain, heart attack, heart failure, high blood pressure, irregular heartbeat, or if you have ever taken a medicine for your heart
- Lung problems, including a history of shortness of breath at rest or with activity
- Kidney problems, including kidney failure or if you have ever received dialysis
- Liver problems, including a history of hepatitis; particularly previous hepatitis B virus infection, fatty liver, or if you have ever been told your liver is not working properly
- Unusual bleeding, including easy bruising, bleeding from an injury, such as a cut that does not stop bleeding in a normal amount of time, or internal bleeding, which can indicate you have low platelets
- Blood clots in your veins
- Any other major disease for which you were hospitalized or received medication

Please notify your study doctor as soon as possible if you experience blurred or double vision, vision loss, difficulty speaking, weakness in an arm or a leg, a change in the way you walk, problems with your balance, persistent numbness, decreased sensation or loss of sensation, decreased alertness, memory loss or confusion which may be symptoms of a central nervous system infection known as Progressive Multifocal Leukoencephalopathy (PML).

Very Common (may affect more than 1 in 10 people):

- Low red blood cell count, which may cause tiredness
- Low platelets, which may cause easy bruising or prolonged bleeding
- Low white blood cell count, which may decrease your ability to fight infection
- Shortness of breath
- Cough, cough with phlegm
- Diarrhea
- Queasy/feeling like you need to throw up (nausea)
- Constipation
- Vomiting
- Tiredness (fatigue)
- Fever
- Swelling of the hands, feet or ankles
- General weakness
- Respiratory tract infection
- Lung infection (pneumonia)
- Infection of the tubes of the lungs (bronchitis)
- Inflammation of the nose and throat

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- Decreased appetite
- Back pain, joint pain, pain in limbs, hands or feet
- Muscle spasms
- Headache
- Dizziness
- Numbness
- Insomnia (difficulty sleeping)
- Changes to blood tests (decreased blood levels of potassium, increased blood levels of creatinine)
- High blood pressure (hypertension)

Less Common (may affect up to 1 in 10 people):

- Fever associated with low white blood cell count
- Heart failure, and heart problems including rapid, strong or irregular heartbeat. The risk of developing heart failure when receiving carfilzomib is higher if you are 75 years of age or older. This risk is also higher if you are Asian
- Heart attack
- Blood clot in the lungs
- Fluid in the lungs
- Nosebleed
- Change in voice or hoarseness
- Pain in throat
- Wheezing
- Pulmonary hypertension, symptoms include shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells
- Blurred vision
- Cataract (clouding of the lens of the eye)
- Stomach pain
- Indigestion
- Toothache
- Chills, pain, feeling unwell
- Infusion site reactions such as pain, swelling, irritation or discomfort where you received the study drug injection into your vein
- Liver problems including an abnormal increase in your liver enzymes in the blood
- Runny nose or nasal congestion
- Urinary tract infection
- Flu-like symptoms (influenza)
- Serious infection in the blood (sepsis)

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- Viral infection
- Infection and/or irritation of your stomach and bowels
- Lung infection
- Dehydration (lack of fluids)
- Bone and muscle pain
- Chest pain
- Muscle weakness
- Aching muscles
- Abnormal sensation such as tingling or decreased sensation in arms and/or legs
- Anxiety
- Kidney problems, including decreased ability to make urine, increased creatinine in the blood, and kidney failure needing dialysis
- Rash, itchy skin, redness of the skin
- Increased sweating
- Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of sugars, calcium, uric acid, potassium bilirubin, or c-reactive protein)
- Low blood pressure (hypotension)
- Leg pain (which could be a symptom of blood clots in the deep veins of the leg), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)
- Flushing (skin or face become red and hot)
- Ringing in the ears
- A reaction to carfilzomib infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, facial red, hot skin or swelling, swelling of the throat, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain.

Uncommon (may affect up to 1 in 100 people):

- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombotic Microangiopathy (including Thrombotic Thrombocytopenic Purpura [TTP])
- Sudden loss of heart function
- Reduced blood flow to the heart
- Abnormal amount of fluid between the heart and the lining around the heart
- Heart muscle disease which may cause shortness of breath and tiredness
- Swelling and irritation of the lining around the heart
- Lung problems, symptoms include difficulty breathing, including shortness of breath (dyspnea) at rest or with activity or a cough, rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough.

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- Bleeding in the lungs
- Bleeding in the stomach and bowels
- Blockage of the intestines
- Inflammation of the pancreas gland
- Multi organ failure
- Yellowing of your skin and eyes, stomach pain or swelling, queasy/feeling like you need to throw up or vomiting, which could be signs of liver problems, including liver failure. If you have previously had hepatitis B virus infection, study treatment with carfilzomib may cause hepatitis B virus infection to become active again
- Liver failure
- Itchy skin, yellow skin, very dark urine and very pale stools which may be caused by a blockage in the flow of bile from the liver (cholestasis)
- Severe infection of the blood causing low blood pressure and low blood flow to the different organs
- Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, a condition that can occur after treatment of a fast-growing cancer. As tumor cells die, they break apart and release their contents into the blood. This causes a change in certain chemicals in the blood, which may cause damage to organs, including the kidneys, heart, and liver
- Bleeding in the brain
- Headaches, confusion, seizures, blindness, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as Posterior Reversible Encephalopathy Syndrome (PRES)
- Allergy to carfilzomib
- Stroke
- Bleeding
- Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, queasy/feeling like you need to throw up and vomiting, or severe anxiety, can be signs for a condition known as hypertensive crisis

<u>Rare</u> (may affect up to 1 in 1000 people):

- Hemolytic uremic syndrome (HUS) (condition that can occur when small blood vessels in your kidneys become damaged and inflamed which can cause clots to form resulting in kidney failure, which could be life-threatening)
- Swelling and irritation of the lining around the heart
- Swelling of the throat
- Hole in the stomach, small intestine, or large bowel
- Infection of the back of the eye (cytomegalovirus)

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Other risks include fainting, bleeding, swelling, or (rarely) infection. If carfilzomib should accidentally be injected under your skin during administration, a local skin reaction may occur (for example, redness, swelling, tenderness, stiffness).

The following side effects have been seen in people who received carfilzomib. It is unknown if they were caused by carfilzomib, you may or may not experience these side effects:

- Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML).
- Tenderness or pain in the abdomen that gets more intense with motion or touch, abdominal bloating or distention, queasy/feeling like you need to throw up and vomiting, diarrhea, constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs.

Driving and Using Machines
You may experience tiredness, dizziness, fainting, and/or a drop in blood pressure after study treatment with carfilzomib. This may impair your ability to drive or operate machinery. If you have these symptoms, you should not drive a car or operate machinery.

Hydration Risks
There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your study doctor's instructions regarding how much water or other fluids you should drink. Over hydration can cause side effect to your heart, lungs, and kidneys.

Dexamethasone Side Effects:

Likely (occurring in greater than or equal to 30% of subjects):

- Difficulty sleeping
- Fatigue (feeling tired)

Less Likely (occurring in 10%-29% of subjects):

- Low red blood cells or platelets
- Blurred vision
- Constipation or diarrhea
- Upset stomach, heartburn, or ulcer
- Fever
- Swelling of the arms or legs
- Upper respiratory tract infection
- Weight gain
- High blood sugar
- High blood pressure

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- Increased appetite
- Muscle cramps
- Bone pain or back
- Joint pain
- Muscle weakness or muscle aches
- Headache
- Dizziness
- Tingling in the hands or feet
- Mood changes (depression, or abnormal feelings of well-being and excitement)
- Skin changes leading to thinning and easy bruising
- Gradual changes to bones that may increase their risk of breaking

Infrequent but Serious (occurred in less than 10% of subjects):

- Low white blood cell counts
- Vomiting
- Abdominal pain
- Pneumonia
- Low blood potassium
- Pain in the arms or legs
- Tremor
- Altered taste sensation
- Numbness in the hands or feet
- Bronchitis
- Inflammation of the nose or throat
- Gradual development of cataracts
- If used for a prolonged period of time, steroids can suppress the function of the normal glands that make steroids (adrenal glands) leading to the need for continued replacement with steroid medication
- Glaucoma, which means having high pressure within the eyeball possibly leading to blindness. May require medical intervention to prevent visual impairment.
- Pancreatitis, which is an inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.

Ruxolitinib Side Effects:

The risks (possible side effects) of taking ruxolitinib are not yet fully known and may vary depending on the diseases or conditions you are being treated for. Many side effects go away after ruxolitinib is stopped, but in rare cases any of the described side effects may be serious, long lasting, and/or

permanent, and may even cause death. If you experience any of the side effects listed below or have any other problems, you should immediately tell the study staff or the study doctor. If you feel that these symptoms or side effects are life threatening, seek medical assistance immediately.

Ruxolitinib may cause low blood cell counts (white blood cells, red blood cells and platelets). If your white blood cell count becomes low while you take ruxolitinib, this means you may have an increased chance of getting an infection, including urinary tract infections and viral infections. You will be checked for any signs of infection before starting ruxolitinib. Any serious infections should be treated before you begin taking ruxolitinib. Your study doctor will check you carefully for signs of infection while you are being treated.

You also may become anemic (low red blood cell count) while you take the drug, and that may cause you to feel fatigued or short of breath. If your platelet count becomes low while you take the drug, it may lead to bleeding and/or bruising.

In some people taking ruxolitinib, the decreases in blood cell counts have been severe. In most cases, low blood cell counts can be reversed by stopping the drug temporarily or reducing the dose; you will be checked often for this side effect while taking the medication. If your blood cell counts do not recover quickly, your drug dose may be stopped for a longer duration to allow the blood cell counts to recover.

The most frequently reported side effects in subjects with MF (myelofibrosis) and/ or PV (polycythemia vera) who have been treated with ruxolitinib are:

<u>Very Common</u> (at least 10% of subjects)

- Anemia (low red blood cells)
- Thrombocytopenia (low platelets)
- Bruising
- Bleeding
- Thrombosis (blood clot)
- Neutropenia (low white blood cells)
- Infections
- Viral Infections
- Tiredness
- Diarrhea
- Swelling
- Rash
- Dizziness
- Headache

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- Shortness of Breath
- Muscle Spasms

Common (more than 1% but less than 10% of subjects)

- Queasy/feeling like you need to throw up
- Weight gain
- Flatulence (gas)
- Constipation
- Pneumonia (infection of the lungs)
- Raised ALT and AST (blood proteins that may indicate mild liver damage)
- Hypercholesterolemia (increased cholesterol)
- Hypertriglyceridemia (increased triglycerides)
- Herpes Zoster (shingles)
- Urinary tract infections
- Hypertension (high blood pressure)

Rare but Serious (less than or equal to 1% of subjects)

- Tuberculosis has occurred in a small number of subjects (less than 1%) with MF who were treated with ruxolitinib, but it is not known whether this was due to MF, ruxolitinib, or other factors that are known to increase the risk of tuberculosis (such as diabetes, bronchitis, asthma, smoking, emphysema, or steroid use). Tell the study doctor if you have been treated for TB in the past or have ever had a positive skin test for TB. Additionally, you should tell the study doctor immediately if you have any of the following symptoms while taking ruxolitinib: chronic cough with spit that has blood in it, fever, night sweats, and weight loss.
- A rare disease called progressive multifocal leukoencephalopathy (PML) has been reported during ruxolitinib treatment. PML comes from a viral infection that causes brain damage and can be fatal. It is unknown whether this was due to ruxolitinib treatment since PML has occurred in subjects with blood cancers, including MF, who were not treated with ruxolitinib. Tell the study doctor immediately if you have any of the following symptoms or if anyone close to you notices that you have any of these symptoms: confusion or problems thinking, loss of balance or problems walking, clumsiness, difficulty speaking, decreased strength or weakness on one side of your body, and blurred and/or loss of vision.
- Non-melanoma skin cancers, including basal cell, squamous cell, and a rare and aggressive type of skin cancer called Merkel Cell Carcinoma have been reported in subjects who took ruxolitinib. It is unknown whether this was due to ruxolitinib treatment, as many of these subjects had been either diagnosed with non-melanoma skin cancer in the past or had previously been treated with hydroxyurea which is associated with multiple types of skin cancers. Periodic skin examination is recommended for subjects who are at increased risk of skin cancer.

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- Pancytopenia is a condition when a subject has low counts of all three types of blood cells: red blood cells, white blood cells, and platelets. It has occurred in a small proportion of subjects (less than 0.5%) who were treated with ruxolitinib.

The effect of ruxolitinib on viral replication in subjects with chronic hepatitis B virus is unknown. You should tell the study doctor if you have chronic viral hepatitis or had viral hepatitis in the past.

Treatment with ruxolitinib was associated with increases in blood lipids including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides.

In some subjects who stopped taking ruxolitinib, symptoms of their MF or PV returned rapidly (also called "withdrawal effect"). Do not stop taking ruxolitinib without talking to your study doctor.

Other Risks:

Bone Marrow Biopsy Risks: you may experience pain and/or discomfort at the site of the needle insertion. The amount of pain and/or discomfort will depend on your pain tolerance, which differs from person to person. Some people describe a sharp pain in the bone where the needle is inserted. Other patients describe it as a long, hard punch or kick. This pain and/or discomfort only lasts a few seconds during the actual procedure. Tenderness over the area may last for a few days. Bleeding from the site or infection may occur but is rare.

You will be asked to sign a separate procedure consent prior to undergoing a bone marrow biopsy, and any other risks associated with these procedures will be discussed with you by your study doctor and/or clinic staff. You will be monitored carefully during these procedures by specially trained medical staff.

Blood Draw/IV Insertion Risks: You may have pain or bruising at the site where the blood is drawn or IV is inserted. You may feel faint. An infection at the site of the blood draw or IV insertion is possible. If you feel faint, you should immediately lie down to avoid falling.

Radiological Exams (PET/ CT scans and x-rays) Risks: PET/CT scans and standard x-rays use x-ray radiation. Radiation has the potential to cause cancer or harm an unborn child. The amount of radiation you will receive during a CT scan is very low and most doctors agree that the benefits outweigh the risks. Some CT scans and PET scans will require you take a "contrast solution" either by mouth, through the rectum or by injection into a vein. You may experience discomfort from lying still in an enclosed space for a prolonged period of time.

Although rare, the contrast solution used in PET/CT scans may cause an allergic reaction such as nausea, vomiting, itching, skin rash, or in very rare instances swelling of the throat and difficulty breathing. If you feel any of these symptoms of an allergic reaction you must tell the clinical staff immediately so that you can be treated quickly.

Echocardiogram or MUGA Scan Risks: An echocardiogram (heart ultrasound) does not typically cause any discomfort. A gel will be applied to your chest area, and then a wand-like instrument is used to detect sound waves. There is a very low risk of complications. The MUGA scan uses a drug [radioactive isotope (technetium)] that is given with an injection. The needle puncture for injecting of the isotope before the exam could be painful and could cause bleeding at the site of the injection, inflammation (redness and swelling of the vein) and/or bruising. You will be exposed to a small amount of radiation during the exam.

MRI Risks: During MRI scanning, you may feel some heat and hear banging noises. Some patients experience a "closed-in" sensation or claustrophobia while inside the MRI machine, and this can be uncomfortable for some individuals. Some MRI scans need preparation beforehand; if there are special preparations you will be told about them prior to the day of your scan. You may have an injection of a type of dye just before the scan to help define certain organs more clearly. The injection may make you sick to your stomach or have pain, warmth, swelling, bruising, a small blood clot or infection at the injection site. Rarely, you may get a rash or other signs of allergy from the injection. If you have a history of kidney problems, you must inform the technologist or physician as you may not be able to receive an injection during the MRI exam. You will also need to inform staff if you have any metal implanted in your body. For example, some hip replacements, hearing aids, pacemakers, bullets, or jewelry that cannot be removed and the staff needs to know beforehand because you may not have an MRI as the scan uses very powerful magnets.

ECG (Electrocardiogram) Risks: An ECG traces the electrical activity of the heart. You may have mild irritation, slight redness, or itching at the sites on your skin where the recording patches are placed.

Allergic Reaction Risks: As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat, or eyes
- A fast pulse
- Sweating

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms, or any other side effects, during the study.

Reproductive Risks:

Women Who Can Get Pregnant or Are Breastfeeding

You may not take part in this study if you are breastfeeding, are pregnant, think that you may be pregnant, or are trying to get pregnant. If you are pregnant or breastfeeding, there may be risks to you and the baby that are not known at this time. Women who can get pregnant will be tested for pregnancy during this study. You will be asked to take a urine pregnancy test within 3 days prior to the first study drug administration.

You must avoid getting pregnant in order to take part in this research study. You should not have sexual intercourse or you should use a method of birth control that is acceptable to you, the study doctor, and the sponsor. Women of childbearing potential must agree to use two highly effective birth control (contraception) methods during the study and for 6 months after your last dose of study drug. Your study doctor will talk with you about the best way to prevent pregnancy while receiving the study treatment.

It is important for you to tell the study doctor at once if you get pregnant or think that you might be pregnant while you in the research study. If this happens, the study doctor will discuss with you what you should do. If you get pregnant, you will be asked to stop taking part in the study. You may also be asked questions about your pregnancy and the baby.

Men

The effect of the study drug on sperm is unknown. Male subjects must not donate sperm during and for at least 90 days after study treatment.

You should not have sexual intercourse or you should use a method of birth control that is acceptable to you, the study doctor, and the sponsor. If you think that you have gotten a woman pregnant, you must tell the study doctor at once. If your partner gets pregnant during the study, you may be asked questions about the pregnancy and the baby.

Sexually active males must agree to use two forms of highly effective birth control (contraception) methods throughout the study and for 90 days after your last dose of study drug. Your study doctor will talk with you about the best way to prevent pregnancy while receiving the study treatment. If your partner gets pregnant during the study or for 90 days after your last dose of study drug, you may be asked questions about the pregnancy and the baby.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

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ALTERNATIVES TO BEING IN THE STUDY

You do not need to take part in this research study. You may choose not to participate in this study and receive routine care treatment as recommended by your study doctor, such as other chemotherapy or targeted therapies. Your study doctor can discuss the alternatives and the risks and benefits of these alternatives with you.

POTENTIAL BENEFITS OF BEING IN THE STUDY

The benefits of treatment with carfilzomib, ruxolitinib, and low-dose dexamethasone are not fully known. You may or may not receive any benefit from being in the study. It is possible that you may get better, stay the same, or get worse. If you take part in this study, other people with RRMM may be helped.

COSTS OF BEING IN THE STUDY

If you choose to take part in the study, you and/or your health plan/insurance will need to pay for all your routine care procedures. You and/or your insurance company will not be responsible for paying for any procedures done solely for research purposes that would not have been done if you were not participating in the study. The study drugs carfilzomib and ruxolitinib will be covered by the study.

You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage You can print a copy of the "Clinical Trials and Insurance Coverage" information from this web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

YOUR PAYMENT FOR BEING IN THE STUDY

You will not be paid for being in this study.

STUDY STAFF PAYMENT/FINANCIAL DISCLOSURE

None of the doctors asking you to participate in this study has received or will receive money or other benefits for personal use from the companies (Amgen and Incyte) that developed some of the drugs used in this study.

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COMPENSATION FOR INJURY

In the event that you are injured as a result of your participation in this study, we will provide or arrange for treatment as necessary. This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner. You may be responsible for deductibles, co-payments, and co-insurance. There are no plans to pay or give you other compensation for the injury. You do not waive any legal rights by signing this consent form.

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

For insurance or other payment reporting purposes, we may need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because we may have to check to see if you receive Medicare and if you do, report the payment we make to Medicare.

In no way does signing this consent form waive your legal rights nor does it relieve the investigators, Sponsor or involved institutions from their legal and professional responsibilities.

CONFIDENTIALITY

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a patient. Your record for this study may, however, be reviewed and/or photocopied by Levine Cancer Institute, by Atrium Health, or by representatives of the Food and Drug Administration or other government agencies. To that extent, confidentiality is not absolute.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

Your samples may be used to determine the sequence of some or all of your genes (DNA – traits passed in families). However, this study is not intended to identify disease causing mutations that can affect the health of close family members (such as your parents, siblings, or children). You will not receive any results from any analyses performed on blood and/or bone marrow collected for research purposes.

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AUTHORIZATION TO USE AND DISCLOSE YOUR PROTECTED HEALTH INFORMATION

If you wish to participate in this research study, you

_____

Printed Name of Research Subject

must sign this Authorization. By signing this Authorization, you give all healthcare providers, including Atrium Health, permission to use or disclose (release) your protected health information, both past and present, for the research study described here:

LCI-HEM-MYE-CRD-004: Phase I/II Study of Carfilzomib, Ruxolitinib and Low-Dose Dexamethasone for Carfilzomib-Refractory Multiple Myeloma

The protected health information that we may use or disclose (release) for this research may include all information in your medical record, such as results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition.

The health information listed above may be used by and/or disclosed (released) to*:*

- Study investigator and research staff
- Study sponsor and/or its associated companies, including Amgen and Incyte
- Regulatory or other governmental authorities of the United States or other countries based on this study
- Other persons or agents authorized by the study sponsor
- Atrium Health employees
- Other persons or agencies as required by law or allowed by federal regulations
- Advarra Institutional Review Board (Advarra IRB) or Data Safety and Monitoring Boards.

Atrium Health is required by law to protect your protected health information. By signing this Authorization, you authorize Atrium Health to use and/or disclose (release) your protected health information for this research study. Those persons who receive your protected health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your protected health information with others without your permission, if permitted by laws governing them. Your protected health information may then no longer be protected by the Privacy Rule.

Please note that you do not have to sign this Authorization, but if you do not, you may not receive research-related treatment through this study. However, Atrium Health may not condition (withhold or refuse) your other Atrium Health providers treating you on whether you sign this Authorization. You may change your mind and withdraw (take back) this Authorization at any time, except to the

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extent that Atrium Health or the Sponsor has already used or disclosed your protected health information based on this Authorization. To withdraw this Authorization, you must write to the Study Doctor at the address listed on the first page of this form.

No publication or public presentation about the research described above will reveal your identity without another Authorization from you. If all protected health information that does or can identify you is removed, the remaining information will no longer be subject to this Authorization or federal rules (such as the Privacy Rule) and may be used or disclosed for other purposes.

When the research for which the use or disclosure is made involves treatment and is conducted by Atrium Health: To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete.

At the conclusion of the research study and at your request, you generally will have access to your protected health information. Access to your protected health information in a medical record is described in the Notice of Privacy Practices provided to you by Atrium Health.

When conducting research, the data and results may be used or disclosed for further treatment outcomes research or to research a secondary result. This Authorization will remain in effect after the end of the current study, and any future related secondary study unless it is revoked by you in writing as described above.

_____

Signature of Research Subject or Research Subject's Legally Authorized Representative

_____

Printed name of Research Subject or Research Subject's Legally Authorized Representative

_____

Date

WHOM TO CONTACT ABOUT THIS STUDY

During this study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

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An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  [redacted]
- or call **collect**: [redacted]
- or by **email**: [redacted]

Please reference the following number when contacting the Study Subject Adviser: Pro00031040.

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.

BEING A STUDY VOLUNTEER AND WITHDRAWING FROM THE STUDY

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Atrium Health. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Atrium Health.

- You may always say no. You do not have to take part in the study.
- If you start a study, you may stop at any time. You do not need to give a reason.
- If you do not want to be in a study or you stop the study at a later time, you will not be penalized or lose any benefits.
- If you stop, you should tell the study staff and follow the instructions they may give you.

Your part in the research may stop at any time for any reason, such as:

- The sponsor or the study doctor decides to stop the study.
- The sponsor or the study doctor decides to stop your part in the study for your safety.
- You need additional medicine.
- You do not follow the study rules.
- You have a new injury or illness.
- You decide to stop.

You may be asked to stop the study even if you do not want to stop.

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If you stop taking part in this study, any specimens which may have already been collected and processed will remain de-identified and part of the study. Any specimens which may have been collected but have not yet been processed may be destroyed upon your written request. No specimens will be returned to you.

NEW INFORMATION ABOUT THE STUDY

You will be told about any new information found during the study that may affect whether you want to continue to take part.

STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____ _____
Signature of Research Subject Date Time

_____
Printed Name of Research Subject

_____ ____/____/____ _____
Signature of Legally Authorized Representative (if applicable) Date Time

_____
Printed Name of Legally Authorized Representative (if applicable)

STATEMENT OF IMPARTIAL WITNESS (AS APPLICABLE)

I have witnessed the accurate reading of this consent form to the potential research subject, and the subject had the opportunity to ask questions. I confirm that the research subject has freely provided his/her consent to participate in this study.

_____ ____/____/____ _____
Signature of Impartial Witness Date Time

_____
Printed Name of Impartial Witness

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STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject or the subject's legally authorized representative the nature and purpose of the above study. There has been an opportunity for the subject or the subject's legally authorized representative to ask questions about this research study. I have been available to answer any questions that the subject or the subject's legally authorized representative has about this study.

_____ ____/____/____ _____

Signature of Person Explaining Consent Date Time

_____

Printed Name of Person Explaining Consent

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