Protocol Title: A Phase II Study of once weekly Carfilzomib, Lenalidomide, Dexamethasone, and Isatuximab in Newly Diagnosed, Transplant-Eligible Multiple Myeloma

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Main Consent

INTRODUCTION AND KEY INFORMATION

All research is voluntary. It is your choice whether you take part in this research or not. If you decide to participate, please sign and date at the end of this form. We will give you a copy and you can refer to this consent form at any time.

The following is a short summary of this research study to help you decide whether you would like to be a part of this study. More detailed information is provided later in this form.

For purposes of this research, you will be referred to as a "participant."

1. Why am I being invited to take part in a research study?

You are invited to take part in in this research study, because you have newly diagnosed multiple myeloma and you are eligible for a stem cell transplant.

2. Why is this research being done?

The purpose of this research is to test the effectiveness of carfilzomib, lenalidomide, dexamethasone, and isatuximab as a treatment for your multiple myeloma.

3. Who is supporting this research?

Amgen and Sanofi, two pharmaceutical companies, are supporting this research study by providing carfilzomib and isatuximab, respectively. The sponsor of this research study is the Dana-Farber/Harvard Cancer Center.

4. What does this research study involve and how long will it last?

This research study involves an experimental drug combination as a possible treatment for your diagnosis. This research involves induction, maintenance, and follow-up.
The names of the study drugs involved in this study are:

- Carfilzomib
- Isatuximab
- Lenalidomide
- Dexamethasone

The research study procedures include screening for eligibility and study treatment including evaluations and follow up visits.

You will receive study treatment as long as you do not have unacceptable side effects and your disease does not get worse, and you will be followed for up to 2 years after you end the study treatment.

Participants should know that lenalidomide only is considered the standard of care maintenance regimen for individuals with this disease. The combination of isatuximab, carfilzomib, and lenalidomide is considered an experimental maintenance regimen. Carfilzomib and/or isatuximab are not available as standard first-line treatments at this time.

It is expected that about 50 people will take part in this research study.

Information about you and your health is personal and private. Generally, it cannot be obtained without your written permission. By signing this form, you are providing that permission and your information may be obtained and used in accordance with this informed consent and as required or allowed by law. This means that researchers may obtain information regarding your past medical history, as well as specimens and samples from previous health care providers such as hospitals and labs.

5. What are the risks to participating in this study?

There are risks to taking part in any research study. We want to make sure you know about a few key risks right now. There may also be rare, serious and potentially life-threatening side effects. More detailed information is provided in the “What are the risks or discomforts of the research study?” section.

There is a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with other approaches for your cancer. There may be additional or unknown risks from taking the study drugs together.

Some of the most common side effects that the study doctors know about are:

- Carfilzomib: low blood cell counts (white, red, platelets, neutrophils), fatigue, low white blood cell count, swelling of arms/legs, high blood pressure, upper respiratory infection
- Isatuximab: infusion-related reactions (nasal congestion, throat irritation, cough, shortness of breath, chills, vomiting), upper respiratory infection, low blood cell counts (white, red, platelets, neutrophils), fatigue, diarrhea

6. Will being in this study benefit me in any way?
We do not know if taking part in this study will benefit you. This study may help researchers learn information that could help people in the future.

7. What are my options?
Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including lenalidomide, bortezomib, and dexamethasone.
- Receive the same drugs, but not as part of a research study.
- Decide not to participate in this research study
- Participate in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions at any time.

A. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational drug combination to learn whether the drug combination works in treating a specific disease. “Investigational” means that the drug combination is being studied.

The U.S. Food and Drug Administration (FDA) has approved carfilzomib or isatuximab as a treatment for relapsed/refractory multiple myeloma. The FDA has also approved lenalidomide and dexamethasone as a treatment option for your disease. However, the FDA has not approved the combination of isatuximab, carfilzomib, lenalidomide, and dexamethasone as an approved regimen. The combination is considered to be investigational for the treatment of individuals with newly diagnosed multiple myeloma.

Carfilzomib is a type of inhibitor that works by inhibiting (blocking) your multiple myeloma cells from breaking down proteins within the cells. This is believed to cause a buildup of proteins within the multiple myeloma cells, which may lead to cell death.

Isatuximab is a type of drug called a monoclonal antibody. In common language, an antibody is a protein produced in the blood to fight diseases by attacking and killing harmful foreign organisms such as bacteria and viruses. In some diseases like cancer, the antibody will protect the participant by attaching itself to a target molecule inside the body, which is also a protein. Isatuximab will attach itself to a protein called CD38 located on the surface of immune cells and some cancer cells in your body and can induce the killing of those cells.

Lenalidomide is an oral anti-cancer therapy that has many ways of attacking tumor cells including activating the immune system against the tumor, and increasing tumor cell death, and decreasing tumor blood vessel growth.

Dexamethasone is a corticosteroid (a type of steroid) that kills cancer cells.

In this research study, we are studying how well this combination of drugs might work in treating people with your diagnosis.

B. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies. At screening, your demographic information will also be collected. At future visits, you will be asked about any changes to your health or medications or any new symptoms you may be experiencing.
- **A physical exam,** including height (at screening) and weight measurements. This will be done to check and track your health.
- **Your vital signs will be measured,** including your temperature, respiratory rate, heart rate, and blood pressure
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An electrocardiogram (ECG),** which measures the electrical activity of your heart
- **A Pulmonary Function Test** for patients with certain medical histories. Your doctor will let you know if this is needed. These are a group of tests that measure how well your lungs are working. These tests will require you to blow into a device called a Spirometer. It will test the amount of air and the speed you breathe out.
- **Radiological imaging:**
  - You will have whole-body **skeletal survey** done to examine the health of your bones. This will be done by a series of plain x-rays of the bones in your body
  - You will be examined to see if you have extramedullary plasmacytomas (soft tissue or nonbone-based myeloma tumors) by **MRI** or by physical exam.
  - **DXA Scan:** Density scanning, also called dual-energy x-ray absorptiometry (DXA), is an enhanced form of x-ray technology that is used to measure bone loss and body composition. The DXA machine will send a thin, invisible beam of low-dose x-rays through your body

that will measure the amount of muscle and fat in your body.This scan is used to assess your body composition, including what amount of your body is fat or lean mass.

- **Bone marrow biopsy and/or aspiration.** This is where some of the bone marrow tissue and fluid are removed using a needle for analysis. At some future visits, you may just have a biopsy or aspiration. At screening, you will have both.
- **Blood tests, totaling up to 2 tablespoons**
  - To confirm your blood type and to analyze the antibodies in your blood
  - To test the health of your various body systems via standard laboratory tests
  - To look for proteins and antibodies in your blood associated with multiple myeloma
  - To check your pregnancy status if you are a woman of childbearing potential
- **Urine test**
  - To check the health of your various body systems via standard laboratory tests
  - To look for certain proteins in your urine that are associated with multiple myeloma

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Parts of This Study:
The study treatment portion of this study is comprised of an induction phase and a maintenance phase.

Induction Phase:
During induction, all participants will receive the same study drugs (carfilzomib, isatuximab, lenalidomide, and dexamethasone) for up to 8 cycles. Each cycle is 28 days in length. All participants will perform stem cell collection after 4 cycles of therapy.

Based on the recommendation of your doctor, you may or may not proceed to an autologous stem cell transplant (SCT) as part of your induction therapy. An autologous SCT is an additional treatment for multiple myeloma that can be done as part of your initial treatment or can be deferred to a subsequent line of

therapy. The decision about whether to do the SCT (upfront) after 4 cycles of induction therapy or at a later time (deferred) will be a decision that you will make with your doctor during your induction therapy.

For participants undergoing upfront SCT:
You will receive 4 cycles of treatment followed by stem cell collection, high-dose chemotherapy, and autologous SCT followed by 2 additional cycles of therapy (called consolidation) and then maintenance.

For participants deferring SCT following collection:
You will receive 4 cycles of treatment followed by stem cell collection followed by 4 additional cycles of therapy and then maintenance.

Maintenance Phase:
During maintenance for standard -risk features, you will receive study treatment with lenalidomide. This will continue as long as you do not have unacceptable side effects and your disease does not get worse.

During maintenance for high -risk features, you will receive study treatment with isatuximab, carfilzomib and lenalidomide for up to two years after induction as long as you do not have unacceptable side effects and your disease does not get worse. After completing two years of maintenance, you will continue treatment with carfilzomib and lenalidomide but isatuximab will be discontinued.

Study Treatment Overview:

- Each study cycle lasts 28 days.
- **Study Drugs:**
  - **Carfilzomib** You will be given Carfilzomib on days 1, 8, and 15 of each induction cycle into your vein (by intravenous infusion). If you receive carfilzomib during the maintenance period, you will have infusions on day 1 and 15 only during each cycle.
  - **Isatuximab** You will be given isatuximab once every week during Cycles 1 and 2, every 2 weeks during Cycles 3-6, and every 4 weeks after that during induction.. It will be given into your vein (by intravenous infusion). The time it takes for the infusion will depend on your dose and how well you tolerate the infusion, but it should be between about 2 and 7 hours. If you receive isatuximab during the maintenance period, you will have the infusion on day 1 only of each 28-day cycle.

- **Lenalidomide** You will be taking lenalidomide once a day on days 1-21 of each cycle during induction and maintenance..
- **Dexamethasone** You will be taking dexamethasone the day of and the day after all doses of carfilzomib (Days 1, 2, 8, 9, 15, and 16) and the days of isatuximab infusions (Days 22 and 23 of Cycles 1 and 2), as applicable during induction and maintenance.
  - On some days before isatuximab infusions, dexamethasone may be given to you in the clinic as an oral medication or as an infusion over about 10 minutes. On those days, you will not take the dexamethasone pills at home. Your study team will confirm when those days occur.

- **Pre-medications:** You may be pre-medicated with drugs to reduce the chance of having a sensitivity reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor.

If you take part in this research study you will be given a drug diary. You will be asked to document information in the drug diary about the study treatment you are being asked to take.

<u>Study Visit</u>: Upfront SCT Participants

All participants will undergo 4 cycles of the study treatment, called Induction, and then have stem cells collected an SCT. Then, participants will have the SCT shortly after the collection, followed by 2 more cycles of study treatment in a period called consolidation, and then enter a maintenance period of the study treatment.

These visits may involve any of the procedures described in the screening section above, as well as the following:

- **Carfilzomib** for 4 cycles, then for 2 additional cycles after SCT.
- **Isatuximab** for 4 cycles, then for then for 2 additional cycles after SCT.
- **Lenalidomide** for 4 cycles, then for then for 2 additional cycles after SCT.
- **Dexamethasone** for 4 cycles, then for then for 2 additional cycles after SCT.
- **Quality of Life Assessments:** You will be asked to complete some questionnaires that are used to collect information about how your day to day life is going in relation to your disease and the study treatment.

Study Visit: Deferred SCT

Participants in this group will undergo a 4 cycle induction phase, then have stem cells collected for a SCT. They will then have 4 more cycles of the study treatment, called induction. Then they will have 4 more cycles of therapy and enter a maintenance period of the study treatment.

These visits may involve any of the procedures described in the screening section above, as well as the following:

- **Carfilzomib** for 4 cycles, prior to stem cell collection then for 4 additional cycles.
- **Isatuximab** for 4 cycles, prior to stem cell collection then for 4 additional cycles.
- **Lenalidomide** for 4 cycles, prior to stem cell collection then for 4 additional cycles.
- **Dexamethasone** for 4 cycles, prior to stem cell collection then for 4 additional cycles.
- **Quality of Life Assessments:** You will be asked to complete some questionnaires that are used to collect information about how your day to day life is going in relation to your disease and the study treatment.

Study Visit: Maintenance Phase

The purpose of the maintenance phase is to maintain disease control and to prevent or delay your myeloma's return Once in the maintenance period, you may receive lenalidomide only or the combination of isatuximab, carfilzomib, and lenalidomide. The treatment that you will receive for maintenance will be based on the biological features (or cytogenetics) of your myeloma determined from your bone marrow biopsy at the time of diagnosis. There are certain biological features of multiple myeloma that are used to classify multiple myeloma as either standard-risk or high-risk. High-risk means that your myeloma may be at a higher risk of recurring or progressing through treatment. Your doctor will use these pre-defined biological features (or cytogenetics) to determine if your multiple myeloma is standard-risk or high-risk. Patients with standard-risk cytogenetics will receive standard of care lenalidomide maintenance. Patients with high-risk features will receive isatuximab, carfilzomib and lenalidomide for maintenance. Patients receiving isatuximab for maintenance will receive it for up to two years (24 cycles) and then discontinue.

The procedures you may undergo are listed in the sections above and indicated in the research study plan below.

Research Study Plan:

Upfront SCT Participants: Treatment Period

	Screening	Induction Cycles 1-4	Consolidation Cycles 5-6
		Visits on Day 1, 8, 15, 22	Visits on Days 1, 8, and 15
Medical History	X	X	X
Physical Exam	X	X	X
Vital Signs	X	X	X
Performance Status	X	X	X
ECG	X		
Pulmonary Function Test	X		
Skeletal Survey	X		
Extramedullary Plasmacytoma Assessment	X		
Bone Marrow Biopsy and/or Aspiration	X		At the end of consolidation
Blood Tests	X	X	X
Urine Test	X	X	If your doctor thinks it is needed: Day 1
Carfilzomib		Days 1, 8, and 15	Days 1, 8, and 15
Isatuximab		Cycles 1 and 2 once per week, Cycles 3 and 4 every other week	Every other week
Lenalidomide		Days 1-21	Days 1-21
Dexamethasone		Days 1, 2, 8, 9, 15, and 16. Cycles 1 and 2, also Days 22 and 23	Days 1, 2, 8, 9, 15, and 16.
DXA Scan	X		At the end of cycle 6
Quality of Life Assessments		X	X

Deferred SCT Participants: Treatment Period

	Screening	Induction Cycles 1-4	Induction Cycles 5-8
		Visits on Day 1, 8, 15, 22	Visits on Days 1, 8, and 15
Medical History	X	X	X
Physical Exam	X	X	X
Vital Signs	X	X	X
Performance Status	X	X	X
ECG	X		
Pulmonary Function Test	X		
Skeletal Survey	X		
Extramedullary Plasmacytoma Assessment	X		
Bone Marrow Biopsy and/or Aspiration	X	At the end of Cycle 4	At the end of induction
Blood Tests	X	X	X
Urine Test	X	X	If your doctor thinks it is needed: Day 1
Carfilzomib		Days 1, 8, and 15	Days 1, 8, and 15
Isatuximab		Cycles 1 and 2 once per week, Cycles 3 and 4 every other week	Cycles 5 and 6 every other week, Cycles 7 and 8 once every 4 weeks
Lenalidomide		Days 1-21	Days 1-21
Dexamethasone		Days 1, 2, 8, 9, 15, and 16. Cycles 1 and 2, also Days 22 and 23	Days 1, 2, 8, 9, 15, and 16.
DXA Scan	X		At the end of cycle 8
Quality of Life Assessments		X	X

All Participants: Maintenance and Beyond

	Maintenance Cycles 9 and beyond	End of Treatment	Follow-up
	Visits either Days 1 and 15, or once during every 28-day cycle		
Medical History	X	X	X
Physical Exam	X	X	X
Vital Signs	X	X	X
Performance Status	X	X	X
Bone Marrow Biopsy and/or Aspiration	After Cycle 24 or if disease progresses.		
Blood Tests	X	X	X
Urine Test	If your doctor thinks it is needed: Day 1	X	If your doctor thinks it is needed
Carfilzomib	If your doctor thinks it is needed: Days 1 and 15		
Isatuximab	If your doctor thinks it is needed: Day 1		
Lenalidomide	Days 1-21		
Dexamethasone	If your doctor thinks it is needed: Day 1		
Quality of Life Assessments	X	X	

Planned Follow-up:

We would like to keep track of your medical condition. We would like to do this by having you come into the clinic every three months for the first two years until confirmation of disease progression, you start a new treatment for your cancer, withdrawal of consent, or you are lost to follow-up. If you experience disease progression or you start a new treatment for your cancer, we may contact you via telephone for a period of 5 years from when you enrolled onto this study.

Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

C. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study treatment that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Carfilzomib:

- **Cases of progressive multifocal leukoencephalopathy (PML, which is a rare and severe viral infection of the brain, which can cause brain damage, memory loss, trouble thinking, muscle weakness, blindness and death), have been reported in patients treated with carfilzomib who have had prior or concurrent immunosuppressive therapy.**

Very Common (More than a 10% chance that this will happen)

- Low red blood cell count (anemia), which may cause tiredness and fatigue. May require a blood transfusion.
- Low platelet count (thrombocytopenia) which can increase your risk of bleeding such as nosebleeds, bruising, stroke, and/or digestive system bleeding. You may need a platelet transfusion.
- Low white blood cell count including lymphocytes (lymphopenia) and neutrophils (neutropenia), which may increase your risk of getting an infection or getting a more severe infection
- Decreased appetite
- Shortness of breath
- Cough with or without phlegm
- Diarrhea
- Nausea
- Constipation
- Vomiting
- Tiredness (fatigue)
- Fever
- Swelling of the hands, feet, or ankles
- General weakness or loss of energy
- Nasopharyngitis, which may cause pain in your sinuses, nasal congestion, nasal drip, sneezing, fatigue, and throat irritation
- Pneumonia (infection of the lungs). Symptoms of infection may include fever, pain, and/or difficulty breathing
- Bronchitis, which may cause fever, soreness in your chest, feeling tired all the time, wheezing, and chills

- Decreased appetite
- Back pain
- Bone and muscle pain
- Muscle spasms
- Headache
- Dizziness
- Difficulty sleeping (insomnia)
- Changes in blood tests (decreased blood levels of potassium, increased blood levels of sugar and/or creatinine) which may result in the need for additional medications or supplements to correct the levels
- High blood pressure

Common (Between a 1-10% chance that this will happen)

- Fever associated with low white blood cell count
- Heart failure and heart problems including rapid, strong, or irregular heartbeat
- Heart attack
- Blood clot in vein
- Fluid in the lungs
- Nose bleed
- Change in voice or hoarseness
- Pain in throat or mouth
- Wheezing
- Pulmonary hypertension which may cause shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells
- Blurred vision
- Cataract (cloudiness of the lens of your eye)
- Toothache
- Chills
- Feeling unwell
- Infusion reactions such as pain, swelling, irritation, or discomfort where you received the injection into your vein
- Liver problems including an increase in your liver enzymes in the blood. This may mean that your liver is not functioning properly and can cause fatigue, and jaundice (yellowing of the skin and eyes).

Although this is usually mild and reversible, this can be serious or life threatening.
- Sore throat
- Runny nose or nasal congestion
- Urinary tract infection, which may cause frequent or painful urination
- Inflammation of the nose and throat
- Infection in the blood
- Viral infection
- Infection and/or irritation of your stomach and bowels
- Dehydration
- Chest pain
- Muscle weakness
- Abnormal sensation such as tingling or decreased sensation in arms and/or legs
- Anxiety
- Kidney problems, including decreased ability to make urine, and kidney failure needing dialysis
- Rash
- Itchy skin
- Redness of the skin (flushing)
- Increased sweating
- Changes to blood tests (for example decreased blood levels of sodium, magnesium, protein, calcium, or phosphate, increased blood levels of calcium, uric acid, potassium) that may result in the need for additional medications or supplements to raise or lower the blood levels accordingly)
- Low blood pressure
- Ringing in the ears
- Infection of the blood causing low blood pressure and low blood flow to the different organs

Uncommon (Between a 0.1-1% chance that this will happen)
- Sudden loss or stoppage of the heart function
- Heart failure or reduction in the ability of your heart to contract
- Reduced blood flow to the heart
- Abnormal amount of fluid between the heart and the lining around the heart which may cause a life-threatening condition where the heart is

unable to pump correctly due to the external pressure. This may require medical intervention to drain the fluid and remove the pressure.
- Lung problems such as difficulty breathing, including shortness of breath at rest or with activity or a cough, rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough
- Bleeding in the lungs
- Bleeding in the stomach and bowels, which may cause black stool, red vomit, cramps in the abdomen, dizziness, or shortness of breath
- Multi-organ failure due to infection
- Liver failure, which can cause fatigue and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious, or life threatening and may require hospitalization and surgery.
- 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
- Tumor lysis syndrome which is caused by the rapid breakdown of tumor cells. This may cause irregular heartbeat, kidney failure or abnormal blood test results.
- Bleeding in the brain, which may cause a severe headache, seizures, weakness in arms or legs, nausea, or vomiting
- Allergy to carfilzomib
- Stroke
- Bleeding
- Extremely high blood pressure which may cause severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety
- Thrombotic microangiopathy which may cause bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure
- Infectious diarrhea (Clostridium difficile colitis)
- Hepatitis B virus reactivation
- Inflammation of the pancreas (Inflammation of the pancreas causing pain in the upper abdomen. This could become sever and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening).
- Intestinal obstruction (Blockage of the intestine of bowel which can cause nausea, vomiting, and abdominal pain. It may be serious or life-threatening and may require hospitalization and surgery).
- Lack of blood flow to the eyes which may potentially lead to vision loss

Rare (Less than a 0.1% chance that this will happen)

- Thrombotic thrombocytopenia purpura which may cause bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure
- Hemolytic uremic syndrome which may cause bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure
- Swelling and irritation of the lining around the heart, which may cause chest pain
- Hole in the stomach, small intestine, or large bowel, which may cause abdominal pain, nausea, vomiting, and swelling of the abdomen
- Posterior reversible encephalopathy syndrome which may cause headaches, confusion, seizures, blindness, and high blood pressure.
- Viral infection of the eye (cytomegalovirus chorioretinitis)
- Swelling of the vocal cords

Risks Associated with Isatuximab:

Likely (Greater than a 10% chance that this will happen)

- Infusion-related reaction
    - Isatuximab may cause infusion reactions, which typically occur within 24 hours of the infusion, and most commonly during the first infusion, but can occur during any infusion. Although usually mild-to-moderate and reversible with treatment, infusion reactions can also be severe or even life threatening. Most frequently, symptoms include chills, shortness of breath, nausea, chest discomfort, flushing, headache, and cough. More serious difficulty breathing, lowered blood pressure or severely increased blood pressure. You may be given medications before each infusion to prevent these symptoms.
- Fatigue (tiredness)
- Nausea
- Low number of red blood cells (anemia) that can causes tiredness and shortness of breath. May require a blood transfusion
- Cough
- Upper respiratory infection, cough, fever, throat ache, runny nose
- Diarrhea
- Back pain

- Difficulty breathing
- Headache
- Constipation
- Chest discomfort
- Peripheral edema – swelling in the arms and legs
- Vomiting
- Fever
- Decreased appetite
- Chills

Frequent (Between a 5-10% chance that this will happen)

- Insomnia
- Flushing
- Low platelet count (thrombocytopenia)
- Pneumonia
- Dizziness
- Nasal congestion
- Abdominal pain
- Nose bleeds
- Wheezing
- Bronchitis
- Hypercalcemia (increased level of calcium in blood which can cause altered mental status, weakness, and/or kidney damage)
- Muscle and bone pain
- Weight loss
- Blood creatinine increased (creatinine is a substance normally eliminated by the kidneys into the urine. This may mean that your kidneys are not functioning properly.)
- Hypertension (high blood pressure).
- Hypokalemia (decreased level of potassium in blood which can cause an abnormal heart rate. This could cause an irregular heartbeat, which can be serious and life threatening)
- Pain
- Urinary tract infection
- Acute kidney injury
- Lack of energy
- Distortion of taste

- Sore throat
- Peripheral sensory neuropathy (damage to the sensory nerves in your hands and feet. This can cause numbness, tingling or burning sensations.)
- Runny nose

Occasional (Between a 1-10% chance that this will happen)

- Anti-drug antibodies - Your body may develop antibodies (proteins your body makes when exposed to foreign substances) against isatuximab. This has been reported in less than 5% of patients treated with isatuximab. It is possible that this may cause illness or decrease the ability of isatuximab to cause your disease to respond to the treatment.

The following may occur at any time following the administration of monoclonal antibodies, including isatuximab:

- Cytokine release syndrome (flu-like symptoms and/or shortness of breath caused by the release of proteins from cells during the infusion which can be life threatening and may be reversible with symptoms such as nausea, headache, rapid heartbeat, shortness of breath, kidney damage, and rash)
- There is a rare, but serious, risk of tumor lysis syndrome. Tumor lysis syndrome (TLS) is caused by the sudden, rapid death of cancer cells in response to treatment. When cancer cells die they may spill their inner (intracellular) contents, which accumulate faster than they can be eliminated. This debris from the cancer cells can change the balance of the chemistry of the body, which can be dangerous. Symptoms of tumor lysis syndrome include severe nausea and vomiting, shortness of breath, an irregular heartbeat, kidney failure, urine abnormalities, severe fatigue and/or joint pain

Because the drugs **dexamethasone** and **lenalidomide** are standard of care options for your disease, the risks related to those drugs are not listed in this consent form. That is because they are not specific to the research happening in this study. Your study doctor will share the risks of those drugs with you in the clinic.

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Risks Associated with Bone Marrow Biopsies:
For this procedure, a numbing drug is injected into the skin over one of your hipbones. A needle is then inserted into the hipbones and a small piece of bone is removed. The risks may include:

- Moderate pain and discomfort
- Bleeding at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site
- Rarely, nerve injury at the biopsy site

Risks Associated with Bone Marrow Aspiration:
For this procedure, a numbing drug is injected into the skin over the same hipbone. A needle is then inserted into the hipbone and a sample of bone marrow fluid is removed. Risks of this procedure are small, but may include:

- Pain from the needle sticks
- Pain from aspirating the bone marrow with a syringe
- Bleeding
- Infection
- Local nerve damage

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans, PET/CT scans, and DXA scans utilizing radioactivity may be used to evaluate your disease.

In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the MRI. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus.

While participating in this research study for 30 days after the last dose of lenalidomide or carfilzomib, and for 4 months after the last dose of isatuximab for women or for 4 weeks after the last dose of lenalidomide, and for 90 days of the last dose of carfilzomib, and for 4 months after the last dose of isatuximab for men, you should not:

- become pregnant
- nurse a baby
- father a baby

Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. If your partner becomes pregnant while you are on the study, it may be critical to share information regarding your participation in this research study with that person. Your research doctor should also be told if this happens.

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. 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.

In order to participate in this study you must register into and follow the requirements of the REVLIMID REMS® program of Celgene Corporation. You will be registered in the REVLIMID REMS® program. Prior to signing and dating this consent form, there is important information for you to know about the pregnancy risk precautions for this study, that a female of childbearing potential must use two effective birth control methods (for example birth control pills, condoms) beginning 28 days before starting study treatment, throughout the entire duration of study treatment, if there is a dose interruption, and 28 days after the end of study treatment with lenalidomide.

When taking lenalidomide, the study drug is present in semen of healthy men at very low levels for three days after stopping the study drug. For subjects who may not be able to get rid of the study drug, such as people with kidney problems, lenalidomide may be present for more than three days. To be safe, all male subjects should use condoms when engaging in sexual intercourse while taking lenalidomide, when temporarily stopping lenalidomide, and for 28 days after permanently stopping lenalidomide study treatment if their partner is either pregnant or able to have children.

Before you consent to participating in this study, your study doctor will discuss with you the full requirements of the pregnancy precautions.

You have been informed of the risk of birth defects. If you are female, you agree not to become pregnant while taking lenalidomide. For this reason, lenalidomide is provided to subjects under a special distribution program

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

The questionnaires used in this study may be upsetting. If you find the questionnaires upsetting, you may speak with the research doctor or ask to be referred for additional emotional support.

D. WHAT WILL HAPPEN IF I AM REMOVED FROM THE STUDY OR DECIDE TO END MY PARTICIPATION IN THE RESEARCH?

You may be taken off the research study for any reason including:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to end the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

You can also choose to stop participating in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study treatment.

It is important to note that although you may withdraw from study participation, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from study records. Additionally, the research doctor may consult public records after you have withdrawn from the study.

E. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

F. WHAT ARE YOUR COSTS?

Taking part in this research study may lead to added costs to you or your insurance company. This may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your disease. You may:

- Have more travel costs
- Need to take more time off work
- Have other additional personal costs

You will not be charged for Carfilzomib or Isatuximab

You or your insurance company will be charged for portions of your care during this research study that are considered standard care, including lenalidomide and dexamethasone. Standard of care is the care that you would receive regardless of whether you were enrolled in the study or not. You may be responsible for co-payments, co-insurance, premiums and deductibles that are typical for your insurance coverage. This includes the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests, done for research only, are supplied at no charge.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Beth Israel Deaconess Medical Center: (617) 667-5661
- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485
- Dana-Farber Cancer Institute: (617) 632-3455
- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov
or 1-800-4-CANCER (1-800-422-6237)

G. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments may be billed to you or your insurance company. You will be responsible for deductibles, co-payments and co-insurance. There are no plans to pay you or give you other compensation for the injury.

You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in this research. If possible, you should give them a copy of this consent form.

H. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital
- Noopur Raje, MD: (617) 724-4000

Dana-Farber Cancer Institute
- Clifton Mo, MD: (617) 582-7969

Beth Israel Deaconess Medical Center
- Jacalyn Rosenblatt, MD: (617) 667-9920

24-hour contact: Please contact your hospital and ask that your doctor be paged:
- Massachusetts General Hospital at 617-724-4000
- Dana Farber Cancer Institute at 617-632-3000
- Beth-Israel Deaconess Medical Center at 617-667-7000

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt

under pressure to enroll in this research study or to continue to participate in this research study.

I. RETURN OF RESEARCH RESULTS

Tests done on samples in this research study, with your identifiable information, will give results that have meaning for your health care. One of your doctors will share the clinically relevant research test results with you. If you do not wish to receive the results from these research tests, please notify your study doctor.

J. CLINICALTRIALS.GOV (CT.GOV)

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.

K. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. Any personal identifiers will be removed, before they are shared, so that the information or samples cannot be linked back to you.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your identifiable information or samples in future research.

Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research, if the samples and specimens are identified. There is a risk that you might be reidentified in the future as genetic research progresses

L. CONFIDENTIALITY

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a research database.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

Your de-identified specimens or genetic data may also be placed into one or more publicly-accessible scientific databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research.

There is a risk that deidentified research data that is shared with outside collaborators may be reidentified. When deidentified data and specimens are shared with outside collaborators agreements limit what the outside collaborators can do with the information to help prevent reidentification.

M. FINANCIAL DISCLOSURES

It is possible that certain researchers on this study may have earned money from, or own some publicly-traded stock in, the company that makes or is developing the study drugs. The amount of money that a researcher may earn and still take part in research is limited by the Harvard Medical School Faculty of Medicine Policy on Conflicts of Interest and Commitment. If you have further questions, please speak with a member of the study team or contact the Dana-Farber Cancer Institute Office of Research Integrity at 617-432-4557 or researchintegrity@dfci.harvard.edu.

N. GENETIC RESEARCH

This research will not involve genomic or germline testing.

O. PRIVACY OF PROTECTED HEALTH INFORMATION (HIPAA AUTHORIZATION)

The Health Insurance Portability and Accountability Act (HIPAA) is a federal law that requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The pharmaceutical companies supporting this study, its subcontractors, representatives, business partners, and its agent(s): Amgen and Sanofi
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

P. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant
or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

☐ *As someone who understands both English and the language used by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.*

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate