PRINCIPAL INVESTIGATOR: Dickran Kazandjian, M.D.

STUDY TITLE: Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients; Clinical and Correlative Phase II Study

STUDY SITE: National Cancer Institute

Cohort: *Affected subject*

Consent Version: *04/20/2020*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see what effects, good and/or bad, the combination of carfilzomib, lenalidomide, and dexamethasone has on you and your myeloma.

Carfilzomib (Kyprolis™) is approved by the U.S. Food and Drug Administration (FDA) to be used only in certain U.S. patients with relapsed and refractory multiple myeloma that have tried

and failed other therapies. It has not been approved to be used for any other disease or condition. In this study, carfilzomib is an experimental study drug because it is not approved for use in all patients in the United States, and it is not approved by some regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country such as the European Medicines Agency and Health Canada). "Experimental" means that the drug is still being studied and that research doctors are trying to find out more about it.

Lenalidomide is a drug that alters the immune system and it may also interfere with the development of tiny blood vessels that help support tumor growth. Therefore, in theory, it may reduce or prevent the growth of cancer cells. Lenalidomide is approved by the Food and Drug Administration (FDA) for the treatment of specific types of myelodysplastic syndrome (MDS) and in combination with dexamethasone for patients with multiple myeloma (MM) who have received at least 1 prior therapy. MDS and MM are cancers of the blood. It is currently being tested in a variety of cancer conditions. In this case, it is considered experimental.

Dexamethasone is a steroid that prevents the release of substances in the body that cause inflammation. Dexamethasone is sometimes used as a direct chemotherapy agent in certain types of cancer, especially in the treatment of multiple myeloma, in which dexamethasone is given alone or in combination with other chemotherapeutic drugs.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to participate in this study because you have newly diagnosed and untreated multiple myeloma.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A minimum of 20 patients and a maximum of 50 patients.

DESCRIPTION OF RESEARCH STUDY

What will happen if you take part in this research study?

As a newly diagnosed untreated person with multiple myeloma, you will receive a total of 8 cycles of combination therapy of carfilzomib, lenalidomide, and dexamethasone. Each cycle is 28 days. After at least four cycles of therapy, if you are eligible for stem cell transplant, you will have stem cells collected and stored for an autologous (with your own cells) stem cell transplantation if and when your multiple myeloma returns. After stem cell collection, you will continue to receive additional cycles of combination therapy with carfilzomib, lenalidomide, and dexamethasone. At the end of 8 cycles, if your disease has improved or has been stable on therapy you will receive an additional 12 cycles of lenalidomide extended dosing (part 1). After receiving lenalidomide extended dosing part 1, you will have the option to receive an additional 12 cycles of lenalidomide extended dosing (part 2).

Before you begin the study

Before you begin the study, if you decide to take part, some procedures and tests will need to be performed to determine if you qualify for the study. Appointments for these tests will be made by your doctor. These tests are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. You will have:

- History and physical examination
- Blood work
- Urine laboratory tests
- 24 hour-urine sample may be required (you will be notified if this applies to you).
- A bone survey (series of x-rays of all of your bones)
- A bone marrow procedure to obtain aspirate and core biopsy is required for the diagnosis of MM and can provide important additional information. We will request that you undergo such a biopsy.
- Urine or blood Pregnancy test

You will be asked if you would like to provide extra research samples of blood, urine and bone marrow aspirate. These studies are optional and will be used to learn more about myeloma. Whenever possible, if you have given permission, these samples will be collected at the same time as when routine cancer care testing is done. You do not have to give these research samples in order to participate in this trial. You will not have to pay for the costs of collecting and analysis of these research samples. You will be asked at the end of this consent form to indicate your choice about giving research samples of blood, urine and bone marrow aspirate.

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures as part of regular cancer care.

- Physical exam
- Blood work
- Urine collection
- Bone marrow biopsy and aspirate to assess the status of your myeloma
- Register into the **REMS® program of Celgene Corporation** (see below for more information about REMS®)
- Urine or blood pregnancy tests in women of child bearing potential
- PET/CT Scans

If you agree to donate extra blood, urine and bone marrow aspirate samples, you will be asked to give the following amounts at the time points listed in the Study Chart and the samples will be used for research purposes only.

- Research blood samples (about 3 tablespoons)
- Research urine samples (about 2 ounces)
- Research bone marrow aspirate (about 2 teaspoons)
- Research FDG-PET for imaging of whole body
- Research DW-MRI (diffusion weighted whole body magnetic resonance imaging scans)

The research blood, bone marrow aspirate, and urine samples are not mandatory.

The treatment consists of three drugs (carfilzomib, lenalidomide, and dexamethasone) for the first 8 cycles. Each cycle lasts 28 days.

- Carfilzomib will be given through an IV (a tube inserted in your vein) over 30-minutes on Days 1, 2, 8, 9, 15, and 16 of the 28 day cycle.
- IV fluids will be administered with the carfilzomib treatment.
- On days 1 and 2 of cycle 1, carfilzomib will be given alone without lenalidomide or dexamethasone.
- Dexamethasone tablets or IV will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28 day cycle.
- Lenalidomide oral tablets will be given from Days 1-21 of the 28 day cycle.

After 4 cycles, if you are eligible for a transplant, you will be referred to a transplant center for collection of stem cells. After the completion of 8 cycles, if you achieve "stable disease" or better, you will continue on the extended dosing phase (part1) for cycles 9-20. During cycles 9-20, you will be given lenalidomide oral tablets days 1-21 of a 28 day cycle. If you choose to participate in part 2 of the extended dosing phase, you will be given lenalidomide on days 1-21 of a 28 day cycle for cycles 21-32 (an additional 12 cycles of treatment). If you continue without progression after 32 cycles and wish to continue or restart "maintenance dosing" at an outside facility, this may be an option after discussion with your doctor. If you do this, we may continue to follow you to see how you are doing for the study.

You will be required to take aspirin or other medication to prevent blood clots while taking lenalidomide. You will be required to take valacyclovir or acyclovir while taking carfilzomib to prevent infection by certain viruses.

Samples collected for research

The required and optional samples collected during this study may be used to help scientists understand how the study treatment works, or why they may cause side effects. These samples may also help scientists to better understand your disease, and people may respond differently to treatment.

The results of tests done in these samples are only for research. They will not be used for your medical care. They will not be used to make a diagnosis about your health. Therefore, these results will not be given to you or your study doctor.

What other tests will be done on my samples?

Your tissue (tumor and normal tissue) and blood that is collected will be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. In order to determine which parts of the DNA have mutated, we will compare the DNA

in your tumor cells to DNA from your normal cells. We will then analyze all of the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. In order to examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells) and looking in great detail at the parts of the genes that produce specific proteins. When we are examining these pieces of your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to the few research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we will keep the samples for future research.

When you are finished taking the drugs (treatment)

After you complete the treatment portion of the study, you will return to the Clinical Center for follow-up visits about 30 days after the last dose (this may be done by phone if you cannot return to clinic, this visit is to check for symptoms and toxicities only) and then every 3-6 months as long as you are participating in the study. Follow-up visits will consist of routine labs and clinic visit with history and physical exam. We may get imaging with FDG-PET about once per year to monitor your disease. If your disease comes back or worsens, we may ask you to have optional research bone marrow biopsy and/or FDG-PET.

You may have follow up visits at more frequent intervals if your doctors and the study team feel it is needed.

Study Chart

Before Starting Treatment

Completed 4 weeks prior to starting treatment unless specified	• Sign informed consent • Physical exam • Blood work (including research blood work if you choose to donate) • 24 hour urine collection (including urine research sample if you choose to donate) • Bone marrow biopsy and aspirate to assess the status of your myeloma • Register for the REMS® Program • Urine or blood pregnancy test in women of child bearing potential (performed 10-14 days prior to receiving prescription of lenalidomide) • Bone series (X-rays of all of your bones) • Research FDG-PET (if you choose to participate)

Cycle 1

Day 1	• Receive infusion of intravenous fluid and Day 1 carfilzomib
Day 2	• Optional research bone marrow on Day 2 • Receive infusion of intravenous fluid and Day 2 carfilzomib • Routine blood work and optional research blood work if you choose to donate • Routine and optional urine if you choose to donate • Begin oral lenalidomide and continue from day 2-21 • Receive oral/IV dexamethasone • Urine or blood pregnancy test in women of child bearing potential (performed within 24 hours of receiving prescription for lenalidomide)
Day 8 and 9	• Receive infusion of optional intravenous fluid and Day 8 and 9 carfilzomib • Receive oral/IV dexamethasone • Routine blood work and on Day 8: optional research blood and urine if you choose to donate

Day 15 and 16	• Receive infusion of optional intravenous fluid and Day 15 and 16 carfilzomib • Receive oral/IV dexamethasone • Routine blood work and on day 15: optional research blood and urine if you choose to donate
Day 21	• Stop lenalidomide
Day 22 and 23	• Receive oral/IV dexamethasone • Routine blood work
Day 28	• Finish cycle 1

Cycles 2-8

Day 1 and 2	• Receive infusion of optional intravenous fluid and Day 1 and 2 carfilzomib • Receive oral/IV dexamethasone • Begin oral lenalidomide and continue from day 1-21 • Day 1: Routine blood work and optional research blood if you choose to donate • Day 1: Routine and optional research urine if you choose to donate • Urine or blood pregnancy test in women of child bearing potential
Day 8 and 9	• Receive infusion of optional intravenous fluid and Day 8 and 9 carfilzomib • Receive oral/IV dexamethasone
Day 15 and 16	• Receive infusion of optional intravenous fluid and Day 15 and 16 carfilzomib • Receive oral/IV dexamethasone
Day 21	• Stop lenalidomide
Day 22 and 23	• Receive oral/IV dexamethasone
Day 28	• Finish day of each cycle
After 4 cycles	• Transplant eligible subjects will undergo evaluation at transplant center for stem cell collection
Any point that complete remission is achieved (no monoclonal protein in blood) or at the end of 8 cycles	• Optional research blood, urine and bone marrow biopsy and aspirate if you choose to donate • Optional FDG-PET will be performed on whole body imaging if you choose to participate

Cycles 9 –and beyond– Extended dosing of lenalidomide

Day 1 of every third cycle	• Routine and optional research blood work if you choose to donate • Routine and optional research urine if you choose to donate • Start lenalidomide and continue days 1-21

Day 21	• Stop lenalidomide
Day 28	• Finish day of each cycle
Any point that complete remission is achieved (no monoclonal protein in blood) or at the end of cycle 20/cycle 32 if participating in extended dosing part 2, and beyond 32 cycles	• Optional research blood, urine and bone marrow biopsy and aspirate if you choose to donate • Optional FDG-PET will be performed on whole body if you choose to participate • If at any point you stop treatment, we may also try to complete an in-person clinic visit about 30 days after stopping drug to check for symptoms and side effects • Additionally, we will continue these same optional research tests and assessments about every 3-6 months during follow-up if you continue without progression beyond 32 cycles; (except FDG-PET and DW-MRI which will be performed annually, if you are able and willing). All of the above will then be repeated if you experience progression of your disease.

BIRTH CONTROL

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females must not become pregnant while taking lenalidomide. You have been informed that the risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking lenalidomide. Lenalidomide is present at very low levels in human semen of healthy men for three days after stopping the drug according to a study. For some men, such as men with kidney problems, lenalidomide may be present in semen for more than three days. Because of the risk of birth defects, all patients taking lenalidomide must read the following statements that apply to them according to gender and menopausal status.

For these reasons, lenalidomide is provided to patients under a special distribution program called **REMS®.**

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

Pregnancy Risk – Females:

If you are a female of childbearing potential*, you will be required to have negative pregnancy tests throughout treatment: the first test within 10-14 days before lenalidomide is prescribed, the second test within 24 hours before lenalidomide is prescribed and then every 14-28 days while receiving lenalidomide treatment.

* For the purposes of this study, a female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).

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

Highly Effective Methods

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants) Tubal ligation
- Partner's vasectomy

Additional Effective Methods

- Latex condom
- Diaphragm
- Cervical Cap

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

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

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

Pregnancy Risk – Males:

Lenalidomide is detected in trace quantities in human semen according to a study. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time. For these reasons, male patients receiving lenalidomide must use a latex condom during any sexual contact with a pregnant female or with a female of childbearing potential while you are participating in this study and for at least 28 days after stopping therapy, even if you have had a successful vasectomy. You must **NEVER** donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you have stopped therapy.

All Patients:

You must **NEVER** share lenalidomide (or other study drugs) with someone else. You must **NEVER** donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study. You must receive counseling and complete phone surveys as required by the **REMS®** program.

Once it is determined that you are eligible for the study and you agree to receive treatment, you will begin therapy as described below:

- **Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.**
- **If you miss a dose of lenalidomide, take it as soon as you remember on the same day.**
- **If you miss taking your dose for the entire day, take your regular dose the next scheduled day (do NOT take double your regular dose to make up for the missed dose).**
- **If you take more than the prescribed dose of lenalidomide you should seek emergency medical care if needed and contact study staff immediately.**

Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

Any unused Revlimid® (lenalidomide) should be returned as instructed through the REMS® program.

RISKS OR DISCOMFORTS OF PARTICIPATION

What side effects or risks can I expect from being in this study?

Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

Carfilzomib

Carfilzomib (Kyprolis) is approved by the U.S. Food and Drug Administration (FDA) to be used only in certain U.S. patients with relapsed and refractory multiple myeloma that have tried and failed other therapies. It has not been approved to be used for any other disease or condition. In this study, carfilzomib is an investigational study drug because it is not approved for use in all patients in the United States, and it is not approved by some regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country such as the European Medicines Agency and Health Canada). You will be told about the known risks, which are the side effects reported previously by others who took carfilzomib. However, your 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 drug. Many of these side effects may be mild but some side effects can be serious and even fatal.

Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

If side effects occur, your health care team may give you medicines to help lessen side effects. Your doctor may have you stop taking carfilzomib or take a lower dose of carfilzomib because of the side effects, or the side effects may go away on their own even if you continue to take carfilzomib.

As of July 2019, approximately 11,000 people have received carfilzomib in research studies. Since it was approved for sale, approximately 128,,000 people have been prescribed Carfilzomib (Kyprolis) for treatment.

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

- Heart problems, including a history of chest pain (angina), 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 (dyspnea) 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 or bleeding from an injury, such as a cut that does not stop bleeding in a normal amount of time, which can indicate you have low platelets
- Blood clots in your veins
- Any other major disease for which you were hospitalized or received medication

Talk to your doctor or nurse if any of these apply to you before using carfilzomib. You may need extra tests to check that your heart, kidneys and liver are working properly.

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

- Fatigue (tiredness)
- Nausea
- Anemia (decreased red blood cell count which may lead to feeling tired)
- Shortness of breath (at rest or with exertion) which in rare cases may be life-threatening or resulting in death
- Thrombocytopenia (decreased platelet count which may lead to bleeding or bruising)
- Diarrhea
- Mild decreases in renal function which are generally reversible
- Vomiting
- Fever
- Headache
- Constipation
- Neutropenia (decreased white blood cell counts which may lead to a decreased ability to fight infection

- Swelling of hands, feet or ankles
- Cough, including cough with phlegm
- Back pain and/or joint pain
- Pain in limbs, hands or feet
- General weakness, or lack of energy or strength
- Runny nose or nasal congestion
- Respiratory tract infection
- Pneumonia (lung infection)
- Loss or decrease in appetite which may lead to weight loss
- Muscle spasms, pain, or weakness
- Numbness, tingling, or decreased sensation in hands and/or feet
- Dizziness
- Infusion reactions (see 'Conditions you need to look out for')
- Insomnia (difficulty sleeping)
- Changes to blood tests (decreased blood levels of potassium, increased blood levels of sugar and/or creatinine)
- Hypertension (high blood pressure)
- Bronchitis
- Sore throat, swelling and inflammation of the nose and throat

Common (may affect up to 1 in 10 people who receive carfilzomib):

- Stomach Pain
- Heart attack (may have a life-threatening or fatal outcome)
- Heart failure and heart problems including arrhythmias
- Low white blood cell count, which may be associated with fever
- Pulmonary hypertension
- Fluid in the lungs
- Blood clot in the lungs
- Change in voice or hoarseness
- Rash and/or itching, redness of the skin
- Flu-like symptoms such as fever, chills, or shaking that may occur at any time but are more likely to occur on the day of or the day after carfilzomib infusion.
- Chills or feeling too hot, increased sweating
- Anxiety
- Blurred or double vision
- Cataract

- Generalized pain
- Pain in the bones and muscles
- Toothache
- Aching muscles
- Abdominal pain, discomfort, or swelling
- Indigestion (upset stomach)
- Urinary tract infection
- Nosebleeds
- Dehydration
- Wheezing
- Serious infection in the blood (sepsis)
- Viral infection
- Kidney problems, including decreased ability to make urine, increased creatinine in the blood, and kidney failure which can lead to dialysis
- Liver problems including an increase in your liver enzyme in the blood
- Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, bilirubin, or c-reactive protein)
- Blood clots in the veins
- Tinnitus
- Hypotension (low blood pressure)
- Pain in throat
- Feeling unwell
- Infection and/or irritation of your stomach and bowels
- Chest pain
- Muscle weakness
- Flushing

Uncommon and rare (may affect less than 1 in 100 people who receive carfilzomib):

- Lung Problems (see 'Conditions you need to look out for'); bleeding in the lungs
- Worsening liver function up to and including liver failure
- Cholestasis, including 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
- Decreased or worsening heart function including chest pain, sudden loss of heart function, heart muscle disease which may cause shortness of breath and tiredness, reduced blood flow to the heart, and abnormal amount of fluid between the heart and the lining around the heart.

- Thrombotic microangiopathy (TMA): damage to the smallest blood vessels inside many organs, most commonly the kidneys and brain
- Allergic reaction including total body rash, hives, and difficulty breathing
- Severe infections of the blood causing low blood pressure and low blood flood to the different organs.
- Tumor lysis syndrome (TLS) (see 'Conditions you need to look out for')
- Multi-organ failure
- Bleeding in the brain
- Allergy to carfilzomib
- Stroke
- Extremely high blood pressure (see 'Conditions you need to look out for')
- Bleeding in the stomach or bowels
- Hepatitis B Virus (HBV) Reactivation: the reappearance or rise of HBV in patients who previously had the virus (see 'Conditions you need to look out for')

Very rare (may affect up to 1 in 1000 people who receive carfilzomib):

- Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS): serious disorders that involve the formation of small blood clots throughout the body that block the flow of blood to vital organs such as the brain, heart, and kidneys
- Perforation (hole or tear) in the stomach, small or large intestine.Posterior reversible encephalopathy syndrome (PRES): serious disorder of the brain which often includes symptoms of headache, confusion, seizures, visual loss, and high blood pressure (hypertension)
- Progressive Multifocal Leukoencephalopathy (PML): a fatal disease characterized by inflammation of the brain.

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 of pain in the abdomen that gets more intense with motion or touch, abdominal bloating or distention, nausea 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.

You should seek medical care immediately if you develop any of the following symptoms: severe shortness of breath, chest pain, fevers, chills, shaking with fever, vomiting, muscle weakness or cramping, seizures, fainting and/or significantly decreased urine output.

Additional side effects of carfilzomib:

- **Driving and Using Machines:** You may experience fatigue, dizziness, fainting, and/or a drop in blood pressure after 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 (Prevention of TLS):** There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your doctor's instructions regarding how much water or other fluids you should drink. Over hydration may negatively affect the heart, lungs, and kidneys.

Conditions you need to look out for:

You must look out for certain symptoms while you are taking carfilzomib to reduce the risk of problems. Carfilzomib can make some conditions worse or cause serious side effects. Carfilzomib may cause all, some, or none of the side effects listed below. There may also be unknown side effects from taking carfilzomib alone or with other drugs you may be taking. Tell your doctor or nurse as soon as possible if you get any of these:

- Chest pains, shortness of breath, or if there is swelling of your ankles and feet, which may be symptoms of heart problems
- 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, which can be signs of lung problems
- Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis
- Shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure
- Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, which can be caused by the rapid breakdown of tumor cells.
- A reaction to carfilzomib infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, facial flushing or swelling, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain
- Unusual bruising or bleeding, such as a cut that does not stop bleeding in a normal amount of time
- 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)
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be signs of liver problems, including liver failure.

- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of blood conditions known as Thrombotic Microangiopathy or TMA (including Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS).
- Headaches, confusion, seizures, blindness, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as Posterior Reversible Encephalopathy Syndrome (PRES).
- 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).
- Worsening of fatigue and yellow discoloration of the skin or eyes. These symptoms may suggest hepatitis B. Hepatitis B Reactivation is a potential side effect of Carfilzomib. Hepatitis B Reactivation refers to the sudden increase in hepatitis B virus in an individual who has inactive or resolved HBV. In patients with a history of HBV infection, taking rituximab could cause this sudden increase in HBV. If you experience HBV reactivation, we will treat your HBV and monitor you closely while on study.

Lenalidomide

Lenalidomide has been studied in healthy volunteers and in patients with cancer of the blood and other organs of the body and in patients with other diseases. As with any other experimental treatment there may be side effects or risks associated with lenalidomide, some of which are not yet known. Everyone taking part in the study will be watched carefully for any side effects.

Listed below are the side effects reported by approximately 6,600 patients who have participated in previous and ongoing clinical studies involving lenalidomide. These events were considered by the study doctors to be related to lenalidomide. Side effects may be mild to very severe. Serious is defined as side effects that; require in-patient hospitalization, cause persistent or significant disability, are life-threatening or in some cases fatal, or important medical events.

Likely (occurring in ≥ 10% of patients):

- Fatigue or feeling tired;
- Anemia or a decrease in red blood cells that can cause tiredness
- Neutropenia or a decrease in white blood cells that can make you more prone to infections
- Thrombocytopenia or a decrease in platelets which can cause you to bruise or bleed easily
- Constipation or difficulty moving your bowels
- Diarrhea or loose/frequent bowel movements
- Nausea
- Loss of appetite
- Back pain
- Joint pain

- Muscle cramps
- Swelling of the arms and legs
- Problems falling asleep or staying asleep
- Fever
- Cough
- Shortness of breath or difficulty catching your breath
- Upper respiratory infection
- Rash
- Itching and dry skin
- Lack or loss of strength
- Dizziness
- Headache
- Lymphopenia (decreased white blood cells that fight infection)

Less Likely (occurring in ≥ 1% of patients):

- Neutropenia associated with a fever
- Atrial fibrillation or irregular heartbeat
- Progression of the disease being studied
- Pneumonia or an infection of the lungs
- Sepsis or an infection of the blood
- Dehydration
- Kidney failure
- Pulmonary embolism: blood clot in or around the lungs
- Deep vein thrombosis: blood clot in a large blood vessel

Rare (occurring in < 1% of patients):

- Angioedema or an allergic skin disease characterized by patches of swelling involving the skin and/or the lining of your nose, mouth, and gastrointestinal tract
- Stevens-Johnson syndrome and toxic epidermal necrolysis: serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to detachment of the top layer of skin (could be body-wide).
- Tumor lysis syndrome: a metabolic complication that can occur during or without treatment of cancer. These complications are caused by the break-down products of dying cancer cells and include high potassium, high phosphorus, high uric acid in blood and urine, low calcium, and consequent kidney damage.
- Rhabdomyolysis: a serious condition involving destruction of skeletal muscle that can lead to kidney failure. Signs and symptoms include dark, red or cola colored urine, muscle tenderness and stiffness, aching (myalgia) or weakness.

- Occasional events such as atrial fibrillation (irregular heartbeat), myocardial infarction (heart attack), and congestive heart failure (condition where the heart becomes weak and cannot pump enough blood to the rest of the body)

Other Risks related to Lenalidomide

- Digoxin levels: Lenalidomide has been shown to increase the level of digoxin in the blood in some patients. Please tell your doctor if you are taking digoxin.
- Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE): Lenalidomide has demonstrated an increased risk of deep vein thrombosis (blood clots in larger blood vessels) and pulmonary embolism (a blood clot in or around the lungs) in some people with certain medical conditions. The study staff will ask you about any health conditions you may have that may increase your chance of developing blood clots. The risk of blood clots may also be increased when lenalidomide is combined with other drugs known to cause blood clots such as steroids, other forms of cancer drugs, hormone replacement therapy, birth control pills and erythropoietin (a drug given to help increase the red cell count). You should let your doctor know if you take birth control pills or hormone replacement therapy. You may be asked to take a blood thinner such as aspirin if your doctor feels that you are at increased risk for blood clots. If your platelet count becomes low, the blood thinners may need to be stopped temporarily. You will be instructed on the signs and symptoms of DVT and PE, including shortness of breath, chest pain or swelling of the arm and or leg, and if symptoms of DVT or PE occur you should contact your study doctor, healthcare provider or get emergency medical care promptly.
- Second Primary Malignancies (SPM): Higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving lenalidomide.

  Patients with multiple myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Your doctor will monitor for the development of second malignancies. You and your doctor should take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

Dexamethasone

Likely:

- High blood pressure
- High blood glucose
- Stomach upset,
- Burning in stomach from excess stomach acid
- Increased risk of infection
- Increased appetite

- Weight gain
- Thinning of bones
- Increase pressure in eyes
- Personality changes, e.g., irritability, euphoria, mania
- Feelings of depression
- Pulmonary tuberculosis
- Vision problems
- Acne, allergic dermatitis, dry scaly skin

Other Study Risks

Blood draws: Side effects of drawing blood include pain and bruising in the area where the blood was drawn, lightheadedness, or rarely fainting due to transient lowering of blood pressure. If you feel dizzy, you should lie down for a few minutes to avoid hurting yourself if you fall. Infection at the blood-drawing site could also occur.

Intravenous Catheter: In order to receive this treatment, you may need to have a central venous catheter. This catheter is placed under the skin of the chest wall and enters a major vein in the chest. There are several types of catheters including those which must be removed after each cycle of chemotherapy (temporary type) and those which may be kept for the duration of therapy (permanent type). These options will be discussed with you. The risks associated with placing some catheters include pain, bleeding, infection and collapsed lung. The long term risks of the catheter include infection, and clotting of your veins. If these occur, it may be necessary to remove the catheter. These risks will be explained to you in more detail at the time of insertion.

Bone marrow aspiration and biopsy: You may feel a pulling sensation and brief discomfort as the marrow is withdrawn and a pressure sensation when the needle is being inserted. The amount of marrow taken is very small and will not change your body's ability to form blood cells. Potential complications of this procedure are local bleeding, pain at the site, and infection. Both of these are very rare. Bleeding can be stopped by applying local pressure and an infection can be treated with antibiotics.

PET/CT: There is discomfort related to the PET/CT scans involved with this study. You must fast 4 to 6 hours prior to the PET/CT scan. You will be asked to drink water during this time and void prior to the injection. The PET/CT examination discomforts include the placement of an intravenous line (IV). The risks of an IV include bleeding, infection, or inflammation of the skin and vein with pain and swelling. The scan will begin approximately 1 hour after injection. During the scan, it will be necessity to remain still on your back for 30 minutes. Even though adverse side effects are not anticipated, you should tell the doctors or nurses supervising the scan of any discomfort you experience during the scans.

Radiation Exposure: This research study involves exposure to radiation from up to 2 PET/CT scans in one year (maximum 10 mCi per injection)**.** This radiation exposure is not required for your medical care and is for research purposes only. The maximum amount of radiation you will receive is 2.1 rem in one year which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in

the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material, you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

DW-MRI scan procedure: Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. The cells that make up your body contain a great deal of water. DW-MRI differ from other MRIs in that they generate images through measuring how this water moves in your body. Receiving a DWI-MRI on this study is optional.

We will obtain pictures of your whole body for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your body. You will be in the scanner about 45-60 minutes. You may be asked to lie still for up to 60 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone

having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

The DW-MRI scan does not require the use of the contrast agent, Gadolinium. Therefore, you will not be receiving Gadolinium while on this study.

PSYCHOLOGICAL OR SOCIAL RISKS ASSOCIATED WITH LOSS OF PRIVACY

Other General Issues Related to the Protocol:

The following general points are indirectly related to your participation in the research study.

1. Unanticipated medical information: During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.
2. Release of medical records. In the course of applying for certain types of insurance (e.g., medical insurance, life insurance, or disability insurance), people are often asked to sign forms that authorize insurance companies to obtain their medical records. If you sign such a release form at some point in the future, it is possible that the insurance company would present this signed release form to the Clinical Center of the National Institutes of Health. In that event, the National Institutes of Health would comply with your request to provide the insurance company with your medical record. It is possible that information contained in your medical record might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance. Your employability may also be affected.
3. Release of genetic information:

    - Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
    - While the controlled-access databases developed for this project will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.
    - Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information

potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease.

- There also may be other privacy risks that we have not foreseen.

There are state and federal laws that protect against genetic discrimination. There is also a new federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not apply to members of the United States military, to veterans obtaining health care through the Veteran's Administration or the Indian Health Service. Lastly, GINA does not forbid insurance medical underwriting based on your current health status.

Family relationships: In the course of this study, it is possible that we may learn information about relationships within the family. For example, if we collected samples from family members and compared the results within families, it is possible that we might learn that a family member is not the biological child of the parents with whom he/she lives (for example, because of adoption). We will not ordinarily provide this type of information to any member of the family or the referring physician.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental combination of carfilzomib, lenalidomide, and dexamethasone will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In any case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Celgene and/or Amgen, Inc. or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using Carfilzomib developed by Amgen, Inc, and Lenalidomide developed by Celgene Inc. through a joint study with your researchers and the company. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of Carfilzomib and/or Lenalidomide.

OPTIONAL BIOPSY

Bone marrow biopsy procedure entails having an area in the back of your hip numbed with a local anesthetic, and a large bone marrow needle inserted into the hipbone. Bone marrow aspirate is obtained, and a core biopsy is obtained. The needle is removed. The risks of the bone marrow procedure include pain, bleeding, infection of the skin or tissues, and allergy to the local anesthetic. You may have some soreness at the site for a day or so after the procedure.

The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. Even if you decide to have the biopsy you can change your mind at any time. Please think about your choice. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

You will be asked to sign a separate consent for each of the bone marrow procedures.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from Amgen Inc., the pharmaceutical company who produces Carfilzomib.
- Qualified representatives from Celgene Corporation, the pharmaceutical company who produces Lenalidomide.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect

reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dickran Kazandjian, M.D, Building 10 Room 4N115, Telephone: 240-383-6311. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.