NCI Community Oncology Research Program – Kansas City (NCORP-KC)

Randomized Phase III Trial of Bortezomib, LENalidomide and Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide and Dexamethasone (CRd) Followed by Limited or Indefinite DURation Lenalidomide MaintenANCE in Patients with Newly Diagnosed Symptomatic Multiple Myeloma (ENDURANCE)

Version Date: May 31, 2018
NCI Update Date: May 9, 2017

Informed Consent

This is a clinical trial, a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation.

You are being asked to take part in this study because you have a type of cancer called multiple myeloma that requires treatment.

Why is this study being done?

The treatment of myeloma has significantly changed as a result of several drugs being introduced for its treatment such as bortezomib, carfilzomib and lenalidomide. All these drugs used with dexamethasone or in combinations that contain more than one of these drugs allow greater control of the disease process. However, we still do not fully understand the best way to combine these drugs and how long the treatment process needs to be continued in order to provide the maximum benefit to the patients. The treatment combinations that are being compared in this study are both effective, but they have different side effects, which can impact whether patients tolerate the treatment for a prolonged time.

This study has two parts, the first part is related to the initial treatment of your myeloma (also called induction) and a second part is related to continued long term control of the myeloma (also called maintenance). The purpose of the first part of the study is to compare the effects, good and/or bad, of a combination of carfilzomib, lenalidomide and dexamethasone with another combination of bortezomib, lenalidomide and dexamethasone, on you and your cancer to find out which is better. In this study, you will get either the combination that contains carfilzomib or that containing bortezomib. You will not get both. Following the initial treatment of your myeloma (induction), the second part of the study will examine if it is better to continue lenalidomide until the myeloma comes back or limit it for a defined period of 2 years. In this study, your lenalidomide will be either stopped after 2 years or you will stay on it until the myeloma relapses.

Both lenalidomide and carfilzomib have been approved by the FDA (Food and Drug Administration) for treatment of multiple myeloma that has relapsed after other therapies, but are considered investigational for treatment of newly diagnosed myeloma. Bortezomib has been approved for treatment of both newly diagnosed myeloma as well as myeloma that has relapsed after other treatments.

How many people will take part in the study?

About 1080 people will take part in this study.

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

The first step is to ensure that you can enroll onto the study, by checking the necessary criteria as required by the study. To be eligible to participate, you must not have received prior treatment for your myeloma except for a short (4 weeks or less) period of treatment. Once it is determined that you are eligible to participate, and all the test results are acceptable, you will start the treatment. While you are on the treatment, examinations and tests will be done on a regular basis to ensure that the treatment is working and to examine the possible side effects related to treatment. Once you complete the treatment, your physician will continue to see you on a regular basis in order to follow the course of the myeloma. The steps involved in each of the phases are detailed below.

Before you begin the study

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures 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 doctor.

- A general exam will be done to ensure your overall health.
- Blood will be taken (approximately 2 teaspoons) to test your general health and well-being. These tests will check your blood counts, liver and kidney functions, and confirm diagnosis.
- Electrocardiogram (a non-invasive, painless measurement of your heart beat using electricity, also known as an ECG or EKG).
- You will have a biopsy to obtain a sample of your bone marrow.
- You will be asked to provide urine samples.
- You will have a bone survey, which is a series of x-rays looking at the entire body.

- If you are a female who could become pregnant, you will need to have two pregnancy tests, one will be 10-14 days before treatment, and the other will be no more than 24 hours before the start of treatment.
- You will be asked to complete quality of life questionnaires to assess your current overall well-being before receiving treatment.

During the study

You will receive bortezomib, lenalidomide and dexamethasone at multiple time points every 3 weeks if you are in Arm A and carfilzomib, lenalidomide and dexamethasone at multiple time points every 4 weeks if you are in Arm B. Following this, every patient will get lenalidomide daily for 3 out of every 4 weeks for 96 weeks (roughly 2 years in Arm C or until myeloma comes back in Arm D). Each cycle is numbered in order.

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. They are part of regular cancer care.

- A general exam will be done to ensure your overall health.
- Blood will be taken (approximately 2 teaspoons) to test your general health and well being, including blood counts, and liver and kidney function tests. This will be completed on day 1 of each cycle.
- An ultrasound of your legs may be done if you have any pain or swelling.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- You will be asked to provide blood and urine tests.
- If you are a woman of childbearing potential, you will also be required to have a blood or urine pregnancy test for the first 4 weeks of treatment as well as every month (if regular or no menstruation) or every 2 weeks (if irregular menstruation) while on treatment.

You will not need to be hospitalized to take part in this study unless you experience a serious side effect.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Bone marrow tests will be performed to see if there are very small numbers of myeloma cells still present and if they look different than from the beginning.
- You will be asked to complete quality of life questionnaires to understand the impact of the disease and side effects associated with treatment on your daily living and overall well-being.
- If you are on Arm A an additional bone marrow biopsy needs to be done at the end of Cycle 4, 12 and 24 or when your myeloma worsens (whichever

comes first). If you are on Arm B an additional bone marrow biopsy needs to be done at the end of Cycle 3, 9 and 24 or when your myeloma worsens (whichever comes first). An additional bone marrow biopsy will also be performed if your doctor thinks the myeloma has gone away completely and needs confirmation or at your doctor's discretion.

- If you are on Arm A a metastatic bone survey needs to be done at the end of Cycle 12 and then repeated every 12 cycles during treatment or observation. If you are on Arm B a metastatic bone survey needs to be done at the end of Cycle 9 and then repeated every 12 cycles during treatment or observation.

Medication Calendar: Your doctor will provide you with a patient diary. You will mark in the patient diary the date, time, and exact number of lenalidomide capsules and dexamethasone tablets taken and any comments you might have regarding side effects. The diary will be reviewed during visits to your doctor's office or clinic.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group (called "arms"). Randomization is important because it is the only way we can scientifically determine which of the treatments is better.

Procedures

Group 1 ("Arm A"): If you are assigned to Arm A, you will receive 12 cycles (1 cycle = 21 days) of treatment. On days 1, 4, 8, 11 of cycles 1-8 and days 1 and 8 of cycles 9-12, you will receive bortezomib by injection under the skin or intravenously, along with dexamethasone tablets given the day of and the day after bortezomib. In addition, you will take lenalidomide capsules daily for the first two weeks of the cycle.

You will take 325 mg of enteric-coated aspirin by mouth every day of each cycle of treatment. This is to prevent a side effect (blood clotting, which could be serious) associated with the drug lenalidomide. Your doctor may choose to use other drugs to prevent clotting instead of enteric-coated aspirin if he feels you are at high risk for blood clots. You will also be placed on one or more antibiotics to prevent specific types of infections while on treatment.

Group 2 ("Arm B"): If you are assigned to Arm B, you will receive 9 cycles (1 cycle = 28 days) of treatment. On days 1, 2, 8, 9, 15, 16 of each cycle you will receive carfilzomib intravenously, along with dexamethasone tablets given once a week. In addition, you will take lenalidomide capsules daily for the first three

weeks of the cycle.

You will take 325 mg of enteric-coated aspirin by mouth every day of each cycle of treatment. This is to prevent a side effect (blood clotting, which could be serious) associated with the drug lenalidomide. Your doctor may choose to use other drugs to prevent clotting instead of enteric-coated aspirin if he feels you are at high risk for blood clots. You will also be placed on one or more antibiotics to prevent specific types of infections while on treatment.

At the end of the first part of the treatment (induction), if your myeloma has not gotten worse, you will be "randomized" again into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

Group 1 ("Arm C"): If you are in Arm C, you will continue to receive lenalidomide capsules at a lower dose for 24 cycles, taken once daily by mouth for the first 3 weeks out of every 4-week cycle. After 24 cycles, you will not take any more lenalidomide but will continue to be watched on a regular basis with the required blood tests to see how the myeloma is behaving.

Group 2 ("Arm D"): If you are in Arm D, you will continue to receive lenalidomide capsules at a lower dose until the myeloma comes back, taken once daily by mouth for the first 3 weeks out of every 4-week cycle. You will continue to be watched on a regular basis with the required blood tests to see how the myeloma is behaving.

NOTE:

- 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 **RevAssist®** program.
- 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 RevAssist® program.

When I am finished taking drugs

- A general exam will be done to ensure your overall health.
- Tubes (approximately 2 teaspoons) of your blood will be taken to test your general health and well being, including blood counts and liver and kidney function tests.
- You will have a bone survey, which is a series of x-rays looking at the entire body.
- You will have a biopsy to obtain a sample of your bone marrow.
- If you are a woman of childbearing potential, you will have a blood or urine pregnancy test after the last lenalidomide pills have been taken and again 4 weeks (if regular or no menstruation) or 2 weeks (if irregular menstruation) after the last lenalidomide pills have been taken.

Laboratory Research Studies

This study includes laboratory assessments that will analyze small samples of bone marrow. The bone marrow will be collected from bone using a needle, with the risk of a small amount of bleeding at the biopsy site. The bone marrow samples will be collected at the time biopsies are performed as part of your routine clinical care. A portion of each sample will be utilized for research purposes and will not affect your care. No additional procedures will be done to obtain the bone marrow. Bone marrow samples (less than one (1) teaspoon per time point) will be collected after induction cycles three (3) and nine (9) for Arm B patients and after induction cycles four (4) and twelve (12) for Arm A patients, after maintenance cycles 24 and 36, and at the time of confirmation of complete response.

The samples will be sent to a laboratory, where tests will be performed. Researchers will perform these tests in order to understand the changes in the myeloma cancer cells that predicts for efficacy of the drugs used to treat myeloma. These studies will also help us assess if very small amounts of cancer cells are still present after treatment and how that might affect the long term results.

Quality of Life

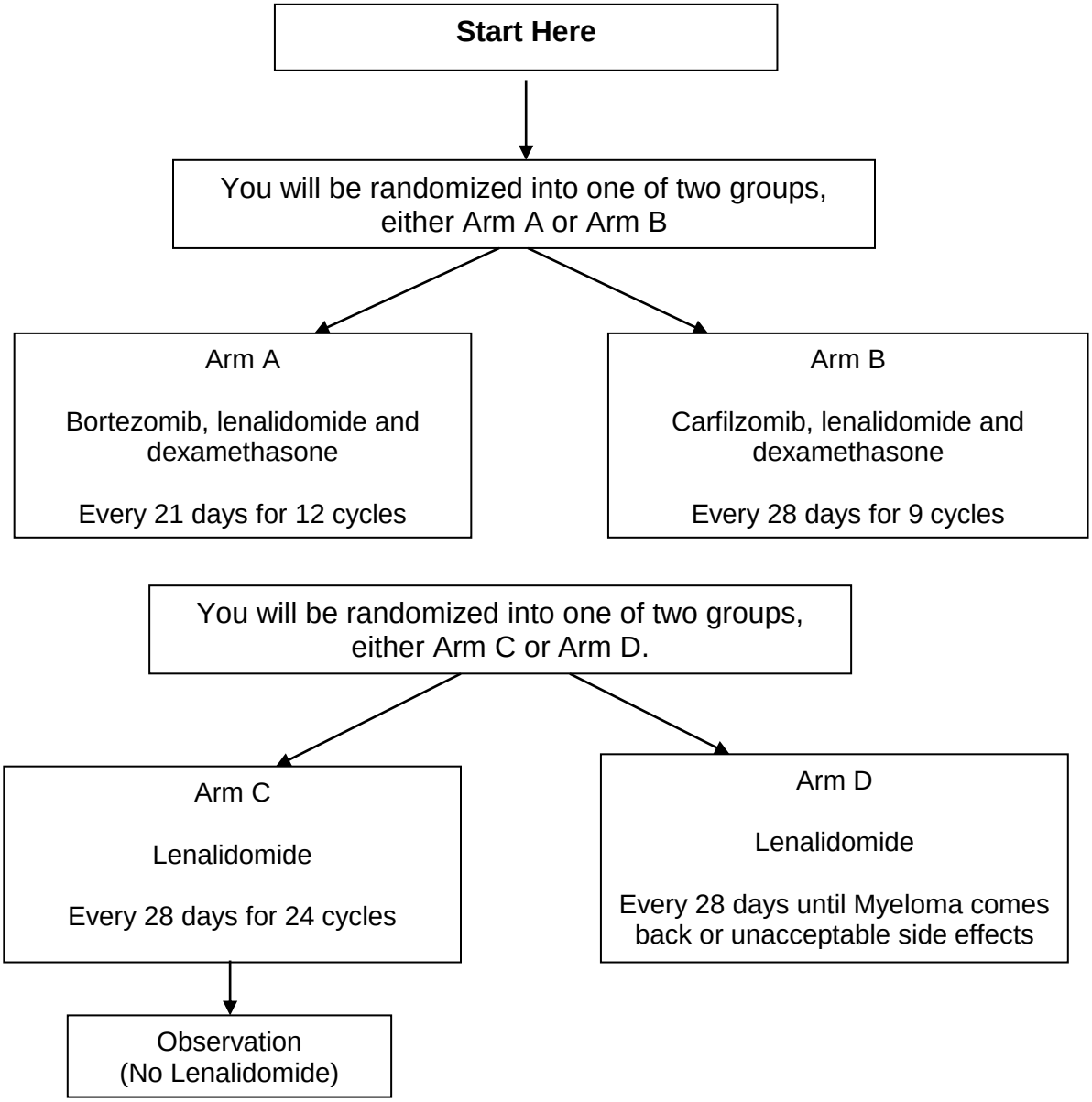
Patients on all arms will be asked to complete questionnaires to assess well-being during and after the study. This includes how you were affected by side effects associated with treatments you will receive. There are 39 questions in all. We expect it will take about 30 minutes to answer these questions. You will be asked to complete quality of life questionnaires before treatment is received. During induction, there will be 4 assessments for each arm as follows: Arm A at the end of cycles 1, 4 (month 2.8), 8 (month 5.5) and 12 (month 8.3 induction end); and, Arm B at the end of cycles 1, 3 (month 2.8), 6 (month 5.5) and 9 (month 8.3 induction end). If your disease gets worse or you discontinue treatment early for another reason before induction is completed, you will be asked to answer the questions at that time. During maintenance, there will be 7 quality of life assessments for each arm as follows: Arm C at the end of cycles 6, 12 and 24 of therapy and at the end of the following observation months 28, 33, 44 and 55 after starting on maintenance; and, Arm D at the end of cycles 6, 12, 24, 30, 36, 48 and 60 of maintenance therapy. Again, if your disease gets worse or you decide to discontinue treatment early for another reason before maintenance therapy is completed, you will be asked to answer the questions at that time.

Study chart

You will receive bortezomib, lenalidomide and dexamethasone at multiple time points every 3 weeks if you are in Arm A and carfilzomib, lenalidomide and dexamethasone at multiple time points every 4 weeks if you are in Arm B. Following this, every patient will get lenalidomide daily for 3 out of every 4 weeks for 96 weeks (roughly 2 years in Arm C or until myeloma comes back in Arm D). Each cycle is numbered in order.

STUDY PLAN

The diagram below gives an overview of what happens in the study in terms of the different treatments used. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

You will be in the study until one of the following happens:

- Your disease gets worse
- You no longer want to continue with treatment
- You begin another treatment
- You experience serious side-effects

After you have finished your designated regimen, your doctor will ask you to visit the office for follow-up exams for at least 15 years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the doctor if you are thinking about stopping so any risks from the drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.

- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Possible side effects of bortezomib:

COMMON, SOME MAY BE SERIOUS In 100 people receiving bortezomib (Velcade), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, nausea, vomiting • Tiredness, fever • Infection • Bruising, bleeding • Loss of appetite • Muscle weakness • Numbness, tingling or pain of the arms and legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bortezomib (Velcade), from 4 to 20 may have:
• Pain • Heartburn • Bleeding from multiple sites • Internal bleeding which may cause black tarry stool or blood in vomit • Chills • Swelling of arms, legs • Weight loss • Dehydration • Muscle spasms • Dizziness, headache

- Feeling of "pins and needles" in arms and legs
- Worry
- Difficulty sleeping
- Cough, shortness of breath, sore throat
- Rash
- Low blood pressure which may cause feeling faint

RARE, AND SERIOUS
In 100 people receiving bortezomib (Velcade), 3 or fewer may have:

- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- A tear or hole in internal organs that may require surgery which may cause difficulty swallowing
- Liver damage which may cause yellowing of eyes and skin, swelling
- Kidney damage which may require dialysis
- Damage to organs (brain, lungs, blood vessel in lungs, others) which may cause changes in thinking, or shortness of breath
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)

Possible side effects of carfilzomib:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving carfilzomib, more than 20 and up to 100 may have:

- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Feeling sick to your stomach (Nausea)
- Feeling tired (Fatigue)
- Fever
- Headache
- Vomiting
- Loose stools (Diarrhea)
- Cough or shortness of breath (Dyspnea)
- Difficulty passing stools (Constipation)
- A low number of a type of white blood cells, which are the infection fighting cells, which could put you at risk for infection (Lymphopenia)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding) (Thrombocytopenia)
- Back pain

- Upper respiratory tract infection
- Swelling of the arms or legs (Edema)

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving carfilzomib, from 4 to 20 may have:

- Chills
- Loss of appetite, not feeling hungry (Anorexia) which may lead to weight loss
- Changes in blood chemistries, including liver function tests, and electrolyte alterations
- A low number of a type of white blood cells, which are the infection fighting cells, which could put you at risk for infection (Neutropenia, Leukopenia)
- Sensation of lightheadedness or vertigo (Dizziness)
- Inflammation of the liver (mild, reversible changes in liver function tests)
- Rash and/or itching
- 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
- Difficulty sleeping (Insomnia)
- Anxiety
- Confusion or changes in mental state
- Blurred or double vision
- Numbness, tingling, or decreased sensation in hands and/or feet
- Generalized pain
- Pain in the bones or joint pain
- Muscle spasm, pain, or weakness
- General weakness, or lack of energy or strength
- Abdominal pain, discomfort, or swelling
- Increase or decrease in blood pressure
- Pneumonia or other lower respiratory tract infections
- Urinary tract infection
- Nosebleeds
- Dehydration

RARE, AND SERIOUS
In 100 people receiving carfilzomib, 3 or fewer may have:

- Infusion reactions (which can occur during or shortly after carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, tightness in chest, and low blood pressure
- Tumor lysis syndrome (a complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream, called uric acid, phosphorus, potassium, creatinine, and calcium). Severe tumor lysis can result in kidney failure and may harm muscle or nerve function.
- Kidney failure which can lead to dialysis
- Worsening liver function up to and including liver failure
- Decreased or worsening heart function including abnormal heart rhythm, heart attack and heart failure
- Myelodysplastic syndromes (MDS)/Acute Myeloid Leukemia (AML) which is a disorder that develops when the cells in the bone marrow (the soft inner part of the bones, where new blood cells are made) do not work properly and have problems making new blood cells. A person with MDS may experience no symptoms or may experience fatigue, infection, easy bruising or bleeding. MDS can turn into a cancer of bone marrow cells called acute myeloid leukemia (AML).
- Posterior reversible encephalopathy syndrome (PRES) which is a rare condition that causes swelling of the brain and affects how it functions. A person with PRES may experience headaches, confusion, loss or decreased level of consciousness, blurred vision or blindness, seizures, and possible death. If caught early and treated, PRES may be reversed.
- Hypertensive emergencies, which is a rare condition associated with sudden increase in blood pressure. This can lead to heart failure and strokes if not controlled adequately.
- Pulmonary hypertension, which is a condition associated with increase in pressure in the blood vessels of the lungs that can lead to symptoms of shortness of breath and heart failure. If uncontrolled, it can become irreversible.
- Other pulmonary complications such as interstitial fibrosis (scarring within lungs), acute respiratory distress syndrome (sudden worsening of lung function leading to shortness of breath and inability of the lung to transfer enough oxygen to the blood) or acute respiratory failure (failure of lung function) have been seen rarely.
- Gastrointestinal Perforation is a condition resulting from damage to the lining of the bowel and can lead to leakage of intestinal contents and risk of infection. It can cause abdominal pain and can be life threatening. With early diagnosis and effective treatment, this is unlikely to cause permanent

damage.

- Pericardial Effusion is a condition where fluid can accumulate between the heart wall and the lining around it. It can lead to chest pain, decreased blood pressure, heart failure and shortness of breath. The symptoms are reversible with adequate treatment
- Pericarditis is a condition resulting from inflammation of the outer lining of the heart and can lead to pain, and drop in blood pressure

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

Carfilzomib may impair ability to operate a car, other motorized vehicle, or machinery because of tiredness, dizziness, changes in blood pressure, or fainting.

Possible side effects of dexamethasone:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving dexamethasone, more than 20 and up to 100 may have:

- Stomach and throat ulcers or worsening of any ulcers you had before treatment
- Heartburn (belly pain)
- Swelling and pain of the pancreas
- Increased appetite
- Weight gain around the stomach
- Puffiness (especially in the face and ankles)
- Buildup of fluids and a rise in blood pressure
- A possible rise in your blood sugar
- Changes in the blood levels of potassium.
- Muscle weakness
- Hot flashes and menstrual changes
- Depression
- Trouble sleeping
- Changes in personality (irritability)
- Increased risk of infection
- Nausea and vomiting
- Skin changes (acne, stretch marks, slow healing and hair growth)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, from 4 to 20 may have:
• Itching • Dizziness • Headaches • Mood swings • Cataracts (film over eye lens), glaucoma (increased eye pressure) and bone thinning (all with long term use)

RARE, AND SERIOUS In 100 people receiving dexamethasone, 3 or fewer may have:
• Allergic reactions • Seizures

Possible side effects of lenalidomide: Version 2.7, March 14, 2018

COMMON, SOME MAY BE SERIOUS In 100 people receiving lenalidomide (CC-5013), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea • Tiredness • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving lenalidomide (CC-5013), from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Dizziness, fainting • Blurred vision • Cloudiness of the eye, visual disturbances • Pain • Dry mouth, skin • Heartburn, nausea, vomiting • Chills, fever • Swelling of the body • Fall • Weight loss, loss of appetite • Dehydration • Muscle weakness • Headache

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving lenalidomide (CC-5013), from 4 to 20 may have:

- Abnormal unpleasant sensation, body movement
- Change in taste
- Numbness, tingling or pain of the arms and legs
- Feeling of "pins and needles" in arms and legs
- Depression
- Difficulty sleeping
- Change in mood
- Cough, shortness of breath
- Nose bleed
- Increased sweating
- Itching, rash
- Sores on the skin
- High blood pressure which may cause headaches, dizziness, blurred vision
- Low blood pressure
- Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS
In 100 people receiving lenalidomide (CC-5013), 3 or fewer may have:

- Abnormal heartbeat
- Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness
- Liver damage which may cause yellowing of eyes and skin, swelling
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Damage to organs in the body when donor cells attack host organs
- Kidney damage which may require dialysis
- Damage to muscle which may cause muscle pain, dark red urine
- Cancer of bone marrow caused by chemotherapy
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Increased tumor size
- A new cancer unrelated to an earlier cancer
- A new cancer resulting from treatment of earlier cancer
- Stroke which may cause paralysis, weakness
- Damage to the lungs which may cause shortness of breath
- Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

- Difficulty stimulating enough stem cells in the bloodstream for future transplant

Occasional adverse 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) have been reported with the use of lenalidomide from clinical studies and post-marketing.

Deep Vein Thrombosis and Pulmonary Embolism

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

Second new cancers

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

Other Risk

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

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

Pregnancy:

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Preliminary findings from a monkey study appear to 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. For this reason, lenalidomide is provided to patients under a special distribution program called RevAssist.

In order to participate in this study you must also register into and follow the requirements of the RevAssist 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.

FOR FEMALES WHO *ARE ABLE* TO BECOME PREGNANT*

*Any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who

meets the following criteria: 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.

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that my unborn baby may have birth defects and can even die, if I am pregnant or become pregnant while I am taking lenalidomide.

_____: I understand that I must NOT take lenalidomide if I am pregnant, breast-feeding a baby or able to get pregnant and not using 2 reliable methods of birth control.

_____: If I am having sexual relations with a man, my uterus and/or both ovaries have not been removed, I have had at least one menstrual period in the past 24 months and/or my menses stopped due to treatment of my disease, I understand that I am able to become pregnant. I must use one highly effective method of birth control plus one additional effective method of birth control (contraception) at the SAME TIME.

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	Cervical Cap

_____: These birth control methods must be used during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide therapy; 2) while participating in the study; during interruptions in therapy and 3) for at least 28 days after lenalidomide has been stopped. I must use these methods unless I completely abstain from heterosexual sexual contact. If a hormone (birth control pill, injection, patch or implant) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

_____: I know I must have a pregnancy test done by my doctor within 10 – 14 days and again within 24 hours prior to starting lenalidomide therapy, even if I have not had my menses due to treatment of my disease or had as little as one menstrual period in the past 24 months. If I have regular or no menstrual cycles, I will then have pregnancy tests every week for the first 28 days, then every 28 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy and then 28 days after I have stopped taking lenalidomide. If I have irregular menstrual cycles, I will have pregnancy tests every week for the first 28 days, then every 14 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy, and then 14 days and 28 days after I have stopped taking lenalidomide.

_____: I know I must immediately stop taking lenalidomide and inform my doctor, if I become pregnant while taking the drug, if I miss my menstrual period or have unusual menstrual bleeding, if I stop using 2 reliable forms of birth control, or if I think for any reason that I may be pregnant. I must talk to my doctor before changing any birth control methods.

_____: I am not now pregnant, nor will I try to become pregnant for at least 28 days after I have completely finished taking lenalidomide.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are pregnant or able to have children.

_____: I agree any unused drug supply will be returned per the instructions provided by RevAssist.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide. Study patients who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30

days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

_____: I agree to use contraception or abstinence for 30 days after last dose of carfilzomib.

FOR ALL MALES

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide.

_____: I have been told by my doctor that I must NEVER have unprotected sexual contact with a female who can become pregnant. Because lenalidomide is present in small quantities in semen, my doctor has explained that I must completely abstain from sexual contact with females who are pregnant or able to become pregnant, or I must use a latex condom every time I engage in any sexual contact with females who are pregnant or may become pregnant. I must do this while I am taking lenalidomide and for 28 days after I stop taking lenalidomide, even if I have had a successful vasectomy.

_____: I know I must inform my doctor if I have unprotected sexual contact with a female who is pregnant or can become pregnant or if I think, for ANY REASON, that my sexual partner may be pregnant. Female partners of male patients taking lenalidomide should be advised to call their own physician immediately if they get pregnant.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are able to have children.

_____: I agree any unused drug supply will be returned per the instructions provided by RevAssist.

_____: I know that I cannot donate blood, sperm or semen while taking lenalidomide and for 28 days after stopping lenalidomide.

_____: I agree to use condoms for 90 days after discontinuation of carfilzomib.

FOR FEMALES THAT ARE *NOT* ABLE TO BECOME PREGNANT

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide.

_____: I certify that I am not now pregnant, nor am I of child bearing potential as I have been in a natural menopause for at least 24 months (been through the change in

life without even 1 menstrual period for the past 24 months); or I had my uterus removed (hysterectomy) or had both my ovaries removed (bilateral oophorectomy).

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are pregnant or able to have children.

_____: I agree any unused drug supply will be returned per the instructions provided by RevAssist.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

FOR ALL PATIENTS

You will be counseled at least every 28 days during lenalidomide treatment and again one

last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the treatments used in the study will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these drugs as a treatment for myeloma. This information could help future cancer patients.

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

You do not have to be in this study to receive treatment for your condition.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Getting treatment or care for your cancer with same or other drugs which work in myeloma
- Having a blood stem cell transplant
- Taking part in another study
- Getting no treatment

- 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, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

The ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG-ACRIN may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your doctor and ECOG-ACRIN may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- ECOG-ACRIN Cancer Research Group (ECOG-ACRIN)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories, banks and/or reviewers

- Cancer Trials Support Unit (CTSU), a service provided by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- The Multiple Myeloma Research Foundation (MMRF) [if you participate in the genomic sequencing laboratory research study] through CoMMpass.

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.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Onyx Corporation will supply the carfilzomib at no charge while you take part in this study. Onyx does not cover the cost of getting carfilzomib ready and giving it to you, so you or your insurance company may have to pay for this.

Celgene Patient Support: Celgene has a Celgene Patient Support (CPS) team that is focused on providing assistance accessing lenalidomide to patients who are insured, uninsured and/or underinsured. CPS can work with patients, caregivers, and/or physicians' offices who opt in for support. Please discuss with your doctor if you would like to use this support team.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at:

http://www.cancer.gov/clinicaltrials/learningabout/payingfor

You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your doctor, _____ *[investigator's name(s)]***, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at** _____ *[telephone number]***.**

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment.

The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your doctor about any questions or concerns you have about this study. Contact your doctor _____ *[name(s)]* **at** _____ *[telephone number].*

For questions about your rights while taking part in this study, call the Central Institutional Review Board (a group of people who review the research to protect your rights) at 888-657-3711.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About providing samples (specimens) for research

Please read this form and ask about anything that is not clear to you. This is part of the process for research. This is to inform you of the possible risks, benefits, and limits of giving your samples for research.

You are being asked to give some of your samples (called specimens) and related information to be used for research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for research is up to you. No matter what you decide, it will not affect your medical care.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of samples requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your samples will be used only for the projects in which you agree to participate.

What are samples and where are they stored?

A sample is any material taken from your body such as tissue, blood, urine and other fluids.

If you agree, your samples will be sent to laboratories to be used in research or will be stored for research in a Cooperative Group bank supported by the National Cancer Institute. A Cooperative Group bank contains samples and information. Your samples are kept along with those from other people in this bank. Researchers then ask for samples from the bank to study them.

What information will be collected?

When your samples are sent from the institution treating you to a research laboratory or Cooperative Group bank, some personal identifying information (such as your initials) will be sent with the samples. Any personal identifying information sent with the samples is <u>not</u> given to other researchers. The personal identifying information is used only by the laboratory or bank to identify your samples. Your privacy will be protected to the fullest extent possible. This will be

discussed later in the section “How will information related to my samples be protected?”

Other information that might be used for research includes:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments

What will happen to my samples if I agree to give them for research?

If you agree to provide samples for the planned laboratory research studies, your samples will be sent to researchers who will study them to find answers to specific questions. These researchers may receive some personal identifying information but it will be used only to identify your samples.

If you agree to let your samples be kept for future research (research not yet defined), your samples will be stored in a Cooperative Group bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. This information will not be put into your health record. Results may be used for future research.

You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Some of the coded research information may be sent to a central database. The information will continue to be made available for approved research. Your name or contact information will not be put in the database.

What kind of research will be done with my samples?

Many types of research use normal or diseased (cancerous) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called **genetic research**.

Your samples may be looked at:

- To see if a trait is passed down in families from one generation to the next (**inherited**). This type of research may help to explain why some cancers run

in families or why some people have side effects from treatment while others do not. This is often studied through blood cells and DNA (**genes**).

- To learn about changes in the body that happen after you were born (**non-inherited**). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

Will it help me if I give my samples for research?

Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

What are the risks of giving my samples for research?

- There can be side effects when samples for research are collected. Side effects from the collection of the samples for research, if this occurs, are described in the projects below.
- There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives.

  Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.
- Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

The chance that your information could be misused is very small. We have many protections in place to lower this risk. See the next section, “How will the information related to your samples be protected?” Your privacy will be protected to the fullest extent possible.

Some states have laws to protect against genetic discrimination [*list appropriate state information if your state has such laws]*. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

How will information related to my samples be protected?

We have many ways to protect the information related to your samples:

1. Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the ECOG-ACRIN Cancer Research Group can match you to the code on your samples and related information.

2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include password protected access to databases and restricted access to freezers or rooms that contain samples.
3. Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.
4. Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.
5. ECOG-ACRIN also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the Cooperative Group bank or database.

   What this means is that ECOG-ACRIN cannot be forced to disclose your identity to any third party. It is possible that for some legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.

Making your choice

The choice to take part is up to you. You may choose not to let us store and use your samples. If you decide not to let us store and use your samples, it will not affect your care and you may still participate in the main part of this clinical trial. You may also take part in other research studies.

To learn more, ask the study staff for the booklet called “Providing Your Tissue for Research: What You Need to Know" and it can be found at https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P067. The web version of the information is located at: http://www.cancer.gov/clinicaltrials/learningabout/providingtissue. You may want to read the section “Why do people do research with tissue?” If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff and let them know that you do not want your samples used for research [*Insert contact number]*. Then, any samples that remain in the bank will no longer be used. Samples that have already been given to or used by researchers cannot be returned or destroyed.

Thank you for considering whether to allow your samples to be banked for future research. Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. **If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at *[IRB's phone number].***

Laboratory Research Studies

This study includes one or more laboratory tests that will analyze small samples of bone marrow and blood. The bone marrow will be collected from bone using a needle, with the risk of a small amount of bleeding at the biopsy site. The bone marrow samples will be collected at the time biopsies are performed as part of your routine clinical care. A portion of each sample will be utilized for research purposes and will not affect your care. No additional procedures will be done to obtain the bone marrow. Bone marrow samples (less than one (1) teaspoon per time point) will be collected at pre-registration (before you begin treatment). Blood will be collected from your vein using a needle according to standard procedures for routine blood sampling. In most cases, the blood will be collected at the time you are going through your routine blood draws. There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Blood samples (approximately two (2) teaspoons per time point) will be collected at pre-registration (before you begin treatment), after induction cycles three (3) and nine (9) for Arm B patients and after induction cycles four (4) and twelve (12) for Arm A patients, after maintenance cycles 24 and 36, at the time of confirmation of complete response, and if your cancer gets worse.

The samples will be sent to a laboratory, where tests will be performed. Researchers will perform these tests in order to understand the changes in the myeloma cancer cells that predicts for efficacy of the drugs used to treat myeloma. These studies will also help us assess if very small amounts of cancer cells are still present after treatment and how that might affect the long term results.

Please read the questions below and circle “Yes” or “No”.

I agree to participate in the laboratory research studies that are being done as part of this clinical trial.

Yes No

Genomics Study

If you agree to participate in this study additional laboratory tests will be performed that will analyze small samples of bone marrow and blood.

The bone marrow will be collected from bone using a needle, with the risk of a small amount of bleeding at the biopsy site. The bone marrow samples will be collected at the time biopsies are performed as part of your routine clinical care. A portion of each sample will be utilized for research purposes and will not affect your care. No additional procedures will be done to obtain the bone marrow. Bone marrow samples (one (1) teaspoon per time point) will be collected at pre-registration (before you begin treatment), at the time of suspected complete response, and if your cancer gets worse.

The blood will be collected from your vein using a needle according to standard procedures for routine blood sampling. In most cases, the blood samples will be collected at the time you are going through your routine blood draws. There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Blood samples (two (2) teaspoons per time point) will be collected at pre-registration (before you begin treatment), at the time of suspected complete response, and if your cancer gets worse.

The samples will be sent to a laboratory, where tests will be performed. The tests are for research purposes only.

For the most part, you will never know about the results from this study that uses your samples. Study results will not impact your specific care or appear in your medical record unless researchers decide that a test result may be useful for health care purposes. If such research leads to results that may be helpful for your healthcare, the researcher may contact your study doctor. Your study doctor may then contact you and give you general information on the potential risks, benefits, and costs of choosing to learn the test results. No test results from these studies will be put into your medical record unless you choose to learn the results of the studies.

Studies in recent years have highlighted the importance of various genetic changes that happen in the myeloma cells as the disease progresses. In particular, these genetic changes can lead to resistance to various treatments used for myeloma. Understanding the types of changes, how often and how soon these changes happen in the myeloma cells with different therapies will allow us to design the future treatments for myeloma. These studies, especially in the setting of the study you are participating in, will be highly informative and invaluable in the quest for improved treatments for myeloma. Specifically, the myeloma cells will be analyzed to identify mutations that are present at the time of diagnosis and how new mutations evolve during treatment of myeloma. In addition, the expression of various genes that play an important role in the myeloma biology will be studied and how they change with treatment will be observed.

Researchers will use the results of these studies and other clinical tests to identify subgroups of patients who may have certain genetic changes and clinical signs and symptoms of the disease. This will help researchers understand what causes multiple myeloma to occur, and how best to treat it. The ultimate goal is to develop better drugs against multiple myeloma and to improve patient care.

Please read the question below and circle “Yes” or “No”.

I agree to participate in the genomic sequencing laboratory research study.

Yes No

Tobacco Use Assessment Substudy

If you agree to participate in this study you will be asked to do an online survey regarding your tobacco use. Regardless if you have used tobacco or not, the information you provide is important to us. You will complete the survey online at 3 different timepoints (before the study treatment, 3 months after starting treatment, and 6 months after starting treatment). Each survey should take you about 6 minutes to complete. To participate, you will be asked for your email address so we can send you a link to the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO).

Up to 1500 patients will be enrolled in this study.

Please read the question below and circle “Yes” or “No”.

I agree to participate in the Tobacco Use Assessment Substudy.

Yes No

Using samples (specimens) for future research

We would like to keep some of your samples for future research. This means any samples left over after the completion of the laboratory research studies will be stored.

We would like to collect additional bone marrow aspirate (approximately three (3) teaspoons per time point) and slides (five (5) per time point) for banking for future research at pre-registration (before you begin treatment), after cycles three (3) and nine (9) for Arm B patients and after cycles four (4) and twelve (12) for Arm A patients, and after cycles 24 and 36, at the time of confirmation of complete response, and if your cancer gets worse or excessive toxicity for Arm D. The bone marrow samples will be collected as part of your routine clinical care. No additional procedures will be done to obtain the bone marrow.

We would also like to collect blood (approximately two (2) teaspoons per time point) for banking for future research at pre-registration (before you begin treatment), after cycles three (3) and nine (9) for Arm B patients and after cycles four (4) and twelve (12) for Arm A patients, after cycles 24 and 36, and if your cancer gets worse.

Blood will be collected from your vein using a needle according to standard procedures for routine blood sampling. In most cases, the blood will be collected at the time you are going through your routine blood draws. There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed.

Although most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer’s disease.

As indicated above, the samples will only be given to researchers approved by scientific reviewers appointed by the NCI Clinical Trials Network. Any research done on the samples must also be reviewed by the researcher's Institutional Review Board.

Please read the questions below carefully and circle “Yes” or “No”.

I agree to provide additional specimens for research.

Yes No

My coded samples and related coded information may be kept for use in research to learn about, prevent, find or treat cancer. This may also include research on inherited traits (genes passed on in families).

Yes No

My coded samples and related coded information may be kept for use in research to learn about, prevent, find or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).

Yes No

Permission to contact you in the future

We request your permission to contact you in the future about taking part in more research studies. If you agree and we decide to contact you in the future, we will first contact your doctor or someone at your hospital. They will tell you why we would like to contact you and, if you agree, they will send us your contact information. We will not attempt any direct contact without obtaining this second permission from you.

Someone from my hospital or the ECOG-ACRIN Cancer Research Group may contact me in the future to ask me to take part in more research.

Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/

For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your doctor.

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. this may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all 33 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Participant's signature_____

Date of signature_____

Person obtaining consent_____

Signature of person obtaining consent_____

Date of signature_____