CONSENT FOR CANCER RESEARCH

Project Title: A phase I/II trial of very low to low-doses of continuous azacitidine in combination with standard doses of lenalidomide and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma

Principal Investigator: *FREDERIC REU, MD 216-636-0200*

Sub-investigator: *Ehsan Malek, M.D. 216 844-3951*
Study Coordinator: Sherry Fada 216-445-6235

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (CaseCCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC) and University Hospitals (UH).

1. Introduction

You are being invited to take part in a research study, also known as a clinical study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and others if you wish.

Please ask questions if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. This copy of the information sheet is yours to keep.

Before agreeing to participate in this study, it is important that the following explanation of the research study be read and understood. This form describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes alternative procedures available and the right to withdraw from the study at any time. It is important to understand that no guarantee or assurance can be made as to the results. It is also understood that refusal to participate in this study will not influence your rights to receive standard treatment or other therapies.

You have been asked to participate in the research study under the direction and medical supervision of Dr. Frederic J. Reu, located at the Cleveland Clinic Taussig Cancer Institute. Dr. Ehsan Malek oversees study activities at University Hospitals Seidman Cancer Center. Other professionals working with Dr. Reu and Dr. Malek as study staff may assist or act for them.

Conflict of Interest Disclosure
One or more of the Investigators conducting this study serve as paid speakers, consultants to advisory committee members for the company that is paying for this research or a company that

makes products used in this study. These financial interests are within permissible limits established by the Cleveland Clinic Conflict of Interest Policy. If you have any questions, please ask your study doctor or call the Institutional Review Board at (216) 444-2924.

2. Purpose

You have been asked to participate in this research study because you have multiple myeloma that has relapsed after previous treatment or did nor respond to the last treatment. Current therapy for your disease includes lenalidomide (Revlimid ®), thalidomide (Thalomid ®), dexamethasone (e.g. Decadron ®), prednisone, bortezomib (Velcade ®), chemotherapeutic agents like cyclophosphamide (Cytoxan ®) or liposomal doxorubicin (Doxil ®) alone or in various combinations.

The purpose of this research is to evaluate the use of azacitidine in combination with lenalidomide and dexamethasone for six 28-day cycles followed by maintenance with lenalidomide alone. This study will also seek to find an appropriate dose of azacitidine (one that is not too toxic) given once or twice a week in combination with lenalidomide and dexamethasone.

Azacitidine can reactivate genes that cancer cells have shut down to grow better and live longer. It is approved by the Food and Drug Administration (FDA) for the treatment of myelodysplastic syndrome, a cancer of the blood. Laboratory and animal studies suggest that, by reactivating genes, azacitidine can overcome resistance of various cancers, including myeloma, to other therapies. Lenalidomide is a drug that is felt to exert anti-cancer effects by altering the immune system and the production of myeloma supporting molecules in the bone marrow, and by interfering with the development of tiny blood vessels that help support tumor growth. Lenalidomide is approved by the 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. A study of azacitidine and lenalidomide in combination in patients with MDS has shown promising efficacy and good tolerability but the combination has not been tested in myeloma yet, making this initial study necessary.

This study will enroll up to 40 patients, who will be monitored for toxicity and efficacy.

Duration

As long as your myeloma responds you may stay on study. Monitoring for toxicity and efficacy will be weekly during the first four weeks, then monthly for an additional eleven months, then every other month.

3. Study Procedures

You will be asked to take lenalidomide every day on Days 1-21 of each 28-day cycle of therapy and dexamethasone once a week starting on Day 1 of each 28-day cycle (day 1, 8, 15, 22). You will find more information on how to take lenalidomide and dexamethasone on page 12 to 13 under “all patients”. You will be given azacitidine by subcutaneous (under the skin) injection

once or twice a week starting on Day 1 of each 28-day cycle. The dose of azacitidine and the number of times per week that you receive azacitidine will be determined by how many patients have been treated on the study before you start, and by the side effects seen in the patients treated before you. The first six 28 day cycles consist of combination therapy with azacitidine (Vidaza ®), lenalidomide (Revlimid ®), and dexamethasone, followed by maintenance with lenalidomide (Revlimid ®) alone until your myeloma stops responding. If your physician feels your myeloma would not be sufficiently controlled with lenalidomide (Revlimid ®) alone you may be offered to continue azacitidine (Vidaza ®) and/or dexamethasone beyond six 28 day cycles. Also, if your myeloma progresses while on maintenance therapy with lenalidomide (Revlimid ®), with or without dexamethasone, you may be offered to restart azacitidine (Vidaza ®) and if not already on it, dexamethasone too, if your physician thinks this may again control your myeloma. During the first 4 weeks you will have to come to the Cleveland Clinic and/or University Hospitals Case Medical Center weekly for toxicity evaluation including history, physical, and blood tests. Also, in order to determine if the study is appropriate for your participation and to obtain a new baseline status of your myeloma and of your organs that could possibly be affected by side effects, some tests must be done and you must meet certain criteria.

These tests will include standard tests and research related tests.

- Complete Physical Examination (measuring your heart rate, blood pressure, temperature, height, weight, and body surface area, inquire about prescription, over-the-counter medication, vitamins, nutritional supplements, natural and herbal products)
- Serum Chemistry (to check your general body functions)
- Complete Blood Count (CBC) (to check your blood count)
- Bone marrow biopsy and aspirate (to determine percent plasma cell involvement)
- Skeletal survey (to detect any fractures or tumors of the bone; the standard set of X-rays includes X-rays of the skull, entire spine, pelvis, ribs, and legs)
- Electrocardiogram (to check your heart function)
- For females of childbearing potential a pregnancy blood test
- Thyroid function blood test
- Myeloma blood and urine tests (from a 24hour urine collection)

Research related tests:

- Blood sample (three tablespoons) obtained during the routine blood draw
- Bone marrow sample (8 teaspoons)

The charts below shows what will happen to you during the first cycle and future treatment cycles. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Cycle One:

Day	**What you do**
Screening- Anytime within 7 days of starting study	• Get physical examination, routine blood tests, Thyroid function blood test, Myeloma blood and urine tests (from a 24hour urine collection), Electrocardiogram, bone marrow biopsy/aspirate, skeletal survey, and pregnancy tests for females of childbearing potential 10 to 14 days before and again within 24 hours before lenalidomide is prescribed for you.
Day 1 (if screening assessments were done within 7 days of Day 1, they do not need to be repeated at Study Day 1)	• Get physical examination and routine blood tests • Bone marrow biopsy/aspirate • Thyroid function blood test • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every week for the first 28 days • Research blood sample
Day 8	• Get physical examination and routine blood tests • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every week for the first 28 days • Research blood sample
Day 15	• Get physical examination and routine blood tests • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every week for the first 28 days • Research blood sample
Day 22	• Get physical examination and routine blood tests • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every week for the first 28 days • Research blood sample

Cycle 2:

Day	What you do
Day 1	• Get physical examination and routine blood tests • Bone marrow sample • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every 28 days if you have regular or no menstrual cycles or every 14 days if you have irregular menstrual cycles • Research blood sample

Cycles 3-6:

Day	What you do
Day 1	• Get physical examination and routine blood tests • Thyroid function test (every 16 weeks) • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every 28 days if you have regular or no menstrual cycles or every 14 days if you have irregular menstrual cycles • Research blood sample

Maintenance Cycles 1-6: (every 2 months thereafter)

Day	What you do
Day 1	• Get physical examination and routine blood tests • Thyroid function test (every 16 weeks) • Myeloma blood and urine tests • Pregnancy test for females of childbearing potential every 28 days if you have regular or no menstrual cycles or every 14 days if you have irregular menstrual cycles

Research samples:

A bone marrow aspiration will be performed after the first cycle to investigate how well the current administration schedule of azacitidine reactivates anti-cancer genes in the myeloma cells. Research blood draws will be done during routine blood draws to answer two additional questions: 1) Can genes shut down specifically in myeloma be identified in the blood with sensitive methods as well? 2) Is the gene reactivating effect of azacitidine already maximal after one cycle or does it increase over six cycles?

Discontinuation Procedures:
Standard tests:

- Complete Physical Examination (measuring your heart rate, blood pressure, temperature, height, weight, and body surface area, inquire about prescription, over-the-counter medication, vitamins, nutritional supplements, natural and herbal products)

- Serum Chemistry (to check your general body functions)
- Complete Blood Count (CBC) (to check your blood count)
- For females of childbearing potential a pregnancy blood test when lenalidomide is stopped and again 28 days after lenalidomide was stopped. If you have irregular menstrual cycles, you will also have a pregnancy blood test 14 days after lenalidomide was stopped.
- Thyroid function blood test
- Myeloma blood and urine tests (from a 24hour urine collection)

Long-term Follow Up:

All participants will be followed by telephone contact for disease progression and overall survival every 3 months after study discontinuation for up to 3 years from entry.

4. Risks

There is always a risk involved in taking any drugs, but you will be carefully monitored for any problems and you are encouraged to report anything that is bothering you. There may be risks or side effects of the study drugs that are unknown or cannot be predicted at this time. You should not hesitate to report anything that upsets you or may be troubling you to your Study Doctor, even if you do not think it is connected to taking the study drugs. If you have any questions you should contact Dr. Frederic Reu at 216-636-0200 or Dr. Ehsan Malek at 216-844-3951.

Everything possible will be done to prevent or reduce any discomfort or risk. You understand that there may be risks and discomforts that are unknown. You may experience all, some or none of these side effects listed. You will be asked to contact your study doctor for any problems or questions that arise at any time during your treatment, so that measures can be started to prevent or decrease serious problems. If, during the course of treatment, your doctor becomes aware of additional toxic or therapeutic effects, your doctor will discuss them with you.

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. Side effects may be mild to severe. Side effects listed below are grouped as follows: side effects of any grade that occurred in 10% or more of patients and serious side effects that occurred in 1% or more of patients. 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.

Side Effects of any grade occurring in 10% or more of patients

Side effects considered serious are **bolded.*

- Fatigue or feeling tired;
- Lack or loss of strength;
- Problems falling asleep or staying asleep;
- **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;
- **Fever**;
- Cough;
- **Shortness of breath** or difficulty catching your breath;
- Upper respiratory infection**;**
- Rash;
- Itching and dry skin;
- Dizziness;
- Headache.

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

- Fever with neutropenia which is a decrease in white blood cells that help fight infections;
- Pulmonary embolism or blood clot in or around the lungs;
- Deep vein thrombosis or blood clots in larger blood vessels;
- Atrial fibrillation or irregular heartbeat;
- Pneumonia or an infection of the lungs;
- Sepsis or an infection of the blood;
- Dehydration or loss of water from the body, organ or body part, as from illness or lack of fluid;
- Kidney failure or inability of the kidneys to remove waste from the body.

The following events have been reported from clinical studies and post-marketing experience:

- Rare treatment-emergent adverse events of angioedema (an allergic skin disease which includes small areas of swelling involving the skin and/or the lining of the nose, mouth, stomach, and intestines) and serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to separation of the top layer of skin (could be body-wide) which have been reported with lenalidomide during commercial use. These events have the potential to result in death. Medical journals have reported patients with allergic skin reaction with thalidomide who also developed the same type of reaction with lenalidomide.
- 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.
- Tumor lysis syndrome (TLS) and tumor flare reaction (TFR) have commonly been observed in patients with Chronic Lymphocytic Leukemia (CLL), and uncommonly in patients with other lymphomas, who were treated with lenalidomide. There have been rare reports of TLS in patients with Multiple Myeloma (MM) treated with lenalidomide, and no reports in patients with Myelodysplastic Syndrome (MDS) treated with lenalidomide. Tumor lysis syndrome is a metabolic complication caused by the break-down products of dying cancer cells. Complications include hyperkalemia (high potassium), hyperphosphatemia (high phosphorus), hyperuricemia and hyperuricosuria (high uric acid in blood and urine), hypocalcemia (low calcium), and consequent acute uric acid nephropathy and acute renal failure (kidney damage). Tumor lysis syndrome can occur with or without treatment of cancer. Tumor flare reaction is a condition that

involves any of the following: increase in size of the cancerous lymph nodes, rash and slight fever.

- The rare adverse event of rhabdomyolysis has been seen with lenalidomide treatment. This is a serious condition involving destruction of skeletal muscle that can lead to kidney damage. Signs and symptoms include dark, red or cola colored urine, muscle tenderness and stiffness, aching (myalgia) or weakness.

Hematological Toxicity

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

Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has demonstrated an increased risk of deep vein thrombosis (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 new cancers

According to researchers, patients with cancer have a higher risk for 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 lenalidomide for a long period of time after induction therapy (treatment as first step to reducing the number of cancer cells) with or without bone marrow transplant than in patients who received placebo for a long period of time after induction therapy with or without bone marrow transplant Placebo treated patients experienced earlier progression of their myeloma in all of these trials and therefore went off study earlier. At this point it is not known if this explains the higher reported rate of secondary cancers in lenalidomide treated patients or if lenalidomide contributed to the development of secondary cancers. Patients should make their doctors aware of their medical history and of any concerns they may have regarding their own increased risk of other cancers.

Other Risks

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.

Vidaza® (azacitidine):

Most common side effects/adverse reactions in trials that used a higher monthly dose given in the first week in patients with the bone marrow cancer myelodysplastic syndrome (these are the percentages of individuals who have had these side effects as reported by the drug manufacturer).

- nausea, 70.5%
- anemia, 69.5%
- thrombocytopenia (too few platelets that could cause bleeding), 65.5%
- vomiting, 54.1%
- fever, 51.8%
- leukopenia (too few white blood cells that fight infection), 48.2%
- diarrhea, 36.4%
- fatigue, 35.9%
- injection site redness and swelling, 35.0%
- constipation, 33.6%
- neutropenia (too few neutrophils—a type of white blood cell), 32.3%
- bruising, 30.5%

Other less common side effects/adverse reactions

- dizziness, 18.6%
- chest pain, l6.4%
- febrile neutropenia [too few neutrophils (a white blood cell) and a fever], 16.4%
- muscle aches, 15.9%
- injection site reaction, 13.6%
- aggravated fatigue, 12.7%
- malaise (vague bodily discomfort and fatigue), 10.9%

Dexamethasone*:*

The most common side effects of dexamethasone include infection, insomnia, seizures, muscle weakness, particularly the thigh muscles, irritability and mood swings, dependence with withdrawal syndrome, weight gain, increased appetite, diabetes mellitus (high blood sugar), high blood pressure, thromboembolism (blood clot formation in a large blood vessel and distribution of pieces of blood clots that break off via the blood stream, usually to the lungs), peptic ulcers, pancreatitits (inflammation of the pancreas), infection in your mouth and fluid retention.

For more information about any of the risks and side effects, ask the Study Doctor.

Measures that may be used if white blood cells and/or platelets are lowered on therapy

Myeloma and previous therapy can limit platelet and white blood cell production by your bone marrow. Since both lenalidomide and azacitidine can potentially lower white blood cells and platelets your doctor may advise measures that make their administration safer without reducing their dose until an antimyeloma effect may improve your bone marrow function.

Your doctor may advise the use of G-CSF, which helps the bone marrow produce white blood cells, if your white blood cells should drop while receiving azacitidine and / or lenalidomide. G-CSF can cause flu-like side effects that include fever, muscle, and bone aches.

Platelet transfusions may be advised by your doctor if your platelets drop with the use of azacitidine and / or lenalidomide and your doctor feels that full doses of azacitidine and lenalidomide give you the best chance for getting the myeloma under control and thereby among other things may restore your bone marrow's ability to produce enough platelets. The risks of platelet transfusions would be discussed with you separately by your doctor. In general they include transfusions reactions which are usually mild and include rashes, fever, rigors, and muscle aches, but extremely rarely they can be severe and life threatening requiring hospital and intensive care unit admission. Other very rare side effects from platelet transfusions with today's blood product quality control are infections with bacteria or viruses.

Possible Side effects of blood draws

The risk of blood drawing commonly includes discomfort, pain, redness, swelling, and/or bruising where the blood is taken from your arm. Sometimes bleeding can occur at the place where blood is drawn. Fainting and infection are rare occurrences.

Possible Side effects of bone marrow aspiration and biopsy

With the bone marrow aspiration and biopsy you may feel a slight burning sensation with the local anesthetic. Pressure may be felt as the needle is inserted into the bone. There is a sharp sucking sensation as the marrow is aspirated, which lasts for only a few moments.

There may be some bleeding, swelling, and bruises at the puncture site. More serious risks, such as serious bleeding or infection, are very rare. Bleeding may be stopped with direct pressure and a cool compress to the area as soon as possible to reduce swelling. Do not place ice directly on the skin.

Radiation Risks (X-ray/Chest X-ray/Skeletal Survey):
While you are in this research study, chest x-rays and skeletal surveys (x-rays of the bones) may be used to evaluate your disease. The total amount of radiation that you will get from these tests is relatively small and is not likely to be harmful to you or affect your disease.

A Skeletal Survey:
Is a series of X-rays. The standard set of X-rays includes X-rays of the skull, entire spine, pelvis, ribs, and legs. X-rays are beams of energy that create shadows of internal structures when they pass through the body. The beams pass through skin and muscle, but are blocked by the bones and teeth. Their shadows are captured on photographic film and called x-rays.

Examiners sometimes inject substances that give contrast to soft tissues. These materials include barium, dyes, and radioactive mixtures. The skeletal survey will take approximately 1 hour. X-rays are fairly safe, but excessive use can pose some health risks. The effects of radiation from repeated x-rays collect over a lifetime. Too much exposure can lead to serious illness. These include blood disorders, cataracts, skin problems, and cancer. However, healthcare providers are aware of these risks. They consider the person's total exposure before x-ray tests.

12-Lead Electrocardiogram

An electrocardiogram — also called an ECG or EKG — records these electrical signals as they travel through your heart. Your doctor can look for patterns among these heartbeats and rhythms to diagnose various heart conditions. An electrocardiogram is a painless, noninvasive way to diagnose many common types of heart disease. An electrocardiogram is a safe procedure. There may be minor discomfort when the electrodes are removed. Rarely, a reaction to the electrodes may cause redness or swelling of the skin. During a stress test, exercise or medication — not the ECG — may trigger heart distress.

If any physician other than the study physician prescribes medication for you, even if it is for another condition, you must inform the study staff. In addition, you must report all over the counter medications, herbal preparations and nutritional supplements that you are taking. This is important because the interaction of some medications and supplements may cause serious side effects.

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 **RevAssist®** program.

Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules. Lenalidomide is best tolerated if taken with or after food, best with dinner since it can cause fatigue. It can also be taken on an empty stomach but sometimes this can cause nausea. It should be stored at room temperature in a dry place, away from direct sunlight and protected from excessive heat or cold.

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.

Dexamethasone should be taken with breakfast as one dose of the appropriate number of tablets on day 1, 8, 15, and 22 of the first six 28-day cycles. If you miss a dexamethasone dose you may take it later that day with food, but to avoid difficulty sleeping you should avoid taking it after 2pm. If you have not taken dexamethasone by 2pm, you may wait until the next day and take it with breakfast then. Please call your study nurse if you miss a dexamethasone dose.

You should document your lenalidomide and dexamethasone intake on a diary that will be given to you.

Reproductive Health/Sexual Activity

Pregnancy Risk:

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. For this reason, lenalidomide is provided to patients under a special distribution program called **RevAssist®.**

In order to participate in this study you must 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.

Pregnancy Risk – Females:
If you are a female of childbearing potential*, you will be required to have two negative pregnancy tests: the first test within 10-14 days before lenalidomide is prescribed and the second test within 24 hours before lenalidomide is prescribed.

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

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.

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

5. Benefits

You may or may not receive any benefits from your participation in this study. By taking part in this study you may contribute new information that will help and benefit other people who have a similar medical problem in the future

6. Alternatives to Participation

If you do not take part in this study, you have several alternatives to choose from, including the following that you should discuss with your doctor:

- Getting treatment or care for your cancer without being in a study such as:
  - Chemotherapy
  - Bone marrow or stem cell transplantation
  - Radiation therapy
  - High-dose myeloablative therapy – High-dose chemotherapy
  - Glucocorticoids like dexamethasone or prednisone with or without lenalidomide
  - Other anti-myeloma drugs like bortezomib (Velcade®) or thalidomide (Thalomid®)
- 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.

You should talk to your doctor about your choices for managing your healthcare needs before you decide if you will take part in this study

7. Costs and Compensation

Celgene will provide lenalidomide and azacitidine, free of charge. You and/or your insurance company will not be charged for any treatments or tests performed strictly for this study, that are not considered to be standard of care for myeloma. You and/or your insurance company are responsible for the costs of any other treatments, diagnostic and laboratory studies, hospital or clinic visits done while you are on the study. You will not be paid to participate in this study and you will not be compensated for travel, parking, meals, or other similar expenses.

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

8. Research-Related Injury

If you experience physical injury or illness as a result of participating in this research study, medical care is available at the Cleveland Clinic or elsewhere; however, the Cleveland Clinic has no plans to provide free care or compensation for lost wages. You are not waiving any legal rights by signing this form.

If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at *216-444-2924*.

9. Privacy and Confidentiality

This section explains how your medical and health records might be used and disclosed if you agree to participate in this study. If you do not sign this form you will not be able to participate in this study.

Every effort will be made to maintain the confidentiality of your study records. Agents of the United States Food and Drug Administration and Celgene Corporation, their agent or designee will be allowed to inspect sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name.

In order to obtain lenalidomide free of charge from Celgene, your name, address, phone, date of birth and the fact that you are participating in this trial will be disclosed to Celgene and its agents or vendors that supply lenalidomide and administer the RevAssist® program. By signing this consent form you agree to this disclosure.

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to ***Frederic Reu, MD, Ehsan Malek, MD and Sub-Investigators*** and their research staff at Cleveland Clinic and University Hospitals Case Medical Center for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- **Study supporter *(Celgene Corporation)***
- **The Food and Drug Administration**
- **The Department of Health and Human Services**
- **Your insurance company**
- **The National Committee for Quality Assurance**
- **The Cleveland Clinic and/or University Hospitals Case Medical Center**

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to Frederic Reu, MD, The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195 or Ehsan Malek, MD at University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, Ohio 44106**.** Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic and/or University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

10. Voluntary Participation

Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Termination of Participation

You understand that your participation is voluntary and you may refuse to participate. You may discontinue your participation AT ANY TIME, without penalty or loss of benefits to which you are otherwise entitled. You also understand that the investigator has the right to withdraw you from the study AT ANY TIME. You understand that your withdrawal from the study may be for reasons related solely to you (e.g. not following study-related directions from the Investigator; a serious adverse reaction) or because the entire study has been terminated. You understand that the study or the Investigator's participation in the study may be terminated at any time.

11. Questions About the Research

If you have any questions, you can ask the Principal Investigator and/or research staff. *FREDERIC REU, MD 216-636-0200 OR EHSAN MALEK, MD 216-844-3951*

Emergency and After-hours Contact Information

If you are a Cleveland Clinic patient, you should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

If you are a University Hospitals patient, you should call your doctors telephone number, this will be directed to the operator who will call your doctor or a covering doctor at home.

If you have questions about your rights as a research subject, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924.

Where Can I Get More Information?

You may call the National Cancer Institute's Cancer Information Services at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI website 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 study doctor.

US National Institutes of Health (NIH) Clinical Trial Database

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

12. Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the

investigator(s) or sponsor(s) are not relieved of any liability they may have. A signed copy of this consent form will be provided to you.

_____	_____	_____
Signature of Participant	***Date***	***Printed Name of Participant***

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____	_____
Signature of Person Obtaining Consent	***Date***

_____

Printed Name of Person Obtaining Consent