ADULT CONSENT - CLINICAL BIOMEDICAL
Phase I Consent

Title of this Research Study
A Phase I/II Study of the c-Met Inhibitor Cabozantinib as a Targeted Strategy to Reverse Resistance to the Proteasome Inhibitor Carfilzomib in Refractory Multiple Myeloma

Invitation
You are invited to take part in this research study. You have a copy of the following, which is meant to help you decide whether or not to take part:

- Informed consent form
- "What Do I need to Know Before Being in a Research Study?"
- The Rights of Research Subjects

Why are you being asked to be in this research study?
You are being asked to be in this study because you are 19 years of age or older and have multiple myeloma (MM) that has either come back or has not responded to treatment. You have also already progressed after prior treatment with Carfilzomib.

Up to 10 patients may be enrolled at UNMC/Nebraska Medicine. It is planned that up to 32 patients total will be enrolled in the study at UNMC and MD Anderson.

If you are pregnant, nursing an infant, or plan to become pregnant during this study, you may not be in this study.

What is the reason for doing this research study?
The purpose of Phase I of this research study is to find the highest dose of cabozantinib that can be given safely in combination with carfilzomib. To do this, a small number of subjects are given a low dose of the investigational medicine, and side effects are noted. If the side effects are tolerable, then the next group will receive a higher dose, and this will be repeated with successive groups until some subjects experience certain side effects. The particular dose you receive will depend on when you enter the study. The dose you receive will not increase.

Both drugs are FDA approved, but the combination of the two is experimental.

Carfilzomib is FDA approved to block cancer cells from repairing themselves in patients with Mulitple Myeloma (MM). Carfilzomib is designed to keep cancer cells

from repairing themselves. If the cancer cells cannot repair themselves, this may cause them to die.

Cabozantinib is FDA approved and commercially available for the treatment of medullary thyroid cancer. Cabozantinib is designed to stop the growth of cancer cells who signal through the c-Met signaling pathway in which might be over-active in MM and has become resistant to carfilzomib. This may reduce or stop the growth of cancer cells. Its use in this study is investigational.

What will be done during this research study?
We do not know the highest dose of cabozantinib that is safe. Phase I of this study is to determine the safest dose of cabozantinib in combination with carfilzomib. Different doses of cabozantinib will be given to see if there are good or bad side effects on you and your cancer.

To do this, a small number of subjects (3-6 patients per group) are given a low dose of the investigational medicine, and side effects are noted. If the side effects are tolerable, then the next group will receive a higher dose, and this will be repeated with successive groups until some subjects experience certain side effects. The particular dose you receive will depend on when you enter the study.

You will be made aware of what dose of cabozantinib your are receiving.

All subjects in this study will received a fixed dose of carfilzomib throughout the study.

The study investigator will review your medical history and current medications to determine if you might be eligible to participate in the study. If you choose to sign this informed consent form, you will continue with the screening process. Many of the tests may be the same as those you have already completed for the diagnosis of your multiple myeloma.

<u>Screening Visit</u>
Signing this consent form does not mean that you will be able to take part in this study. You will have screening tests to help the investigator decide if you are eligible to take part in this study. The screening process may take place over a period of up to 28 days. These may take more than one visit and will include the following:

- You will have a complete physical exam, including measurement of your height, weight, and vital signs (heart rate, blood pressure, and temperature).
- You will have a specific exam of your mouth (oral assessment)

- Your medical history will be recorded.
- Your actual health status and your well-being will be assessed. This is called a performance status assessment.
- You will have tests to check your heart function. These tests include an electrocardiogram (ECG) and echocardiogram (ECHO).
- Blood (about 2 tablespoons) and urine will be collected for routine tests. If urine is collected, you will be asked to collect your urine over a 24-hour period. You will be given a container for collection and will be told how to use and store it.
    - If you are able to become pregnant, your blood or urine will also be used for a pregnancy test. To take part in this study, you must not be pregnant.
- Blood (about 1 teaspoon) and/or urine will be collected to check the status of the disease, level of antibodies and your immune system.
- You will have a bone marrow aspiration and/or biopsy to check the status of the disease. To collect a bone marrow aspirate/biopsy, an area of the hip is numbed with anesthetic, and a small amount of bone marrow and/or bone is withdrawn through a large needle.
- You will have x-rays of your entire body to check for any bone fractures or tumors of the bone.
- You may have a CT scan or MRI scan to determine the size, locations of you cancer, if they are clinically indicated and have not already been done.
- In addition, we will draw a blood sample for research testing (2 teaspoons)
- Prior to starting study drug, medication diaries will be given to you. A member of the study staff will explain how to use the diaries. You will enter information about carfilzomib and cabozantinib that you take at home. You must bring the diaries with you whenever you come to the study clinic.

The study investigator will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study you will not be enrolled. Other options will be discussed with you.

Study Drug Administration
Every study cycle will be 28 days.

You will take cabozantinib pills by mouth on Days 1-28 of each 28-day study cycle. You will be given medication diaries. You should inform the study investigator and/or study staff of any missed doses of cabozantinib.

You will be asked to return any unused cabozantinib and empty bottles to the clinic at each study visit.

You will receive carfilzomib by vein over 10 minutes on Days 1, 2, 8, 9, 15, and 16 of each cycle.

You will be given a Drug Information sheet in addition to this consent form.

As part of pre-treatment medications, you will receive dexamethasone by mouth or by vein on Days 1,8,15 and 22 (for patients 75 years old or older you will receive dexamethasone by mouth or by vein on Days 1,2,8,9,15,16,22 and 23).

Study Visits
At all study visits, you will be asked about any other drugs you may be taking and about any side affects you may be having.

Prior to/On Day 1 of each cycle (If some of these tests were performed within 3 days before Cycle 1, they will not need to be done on Day 1 of Cycle 1)**:**

- You will have a physical exam, including measurement of your weight and vital signs.
- You will be asked about any side effects and other medication you have used.
- Your actual health status and your well-being will be assessed. This is called a performance status assessment
- You will complete a questionnaires about your nerve function and quality of life. Each of these questionnaires will take about 10 minutes to complete.
- You will have an electrocardiogram (EKG) to check your heart function
- Blood (about 2 tablespoons) will be drawn for routine tests.
- Blood (about 1 teaspoon) and/or urine will be collected to check the status of the disease. If urine is collected, you will be asked to collect your urine over a 24-hour period.

On Days 8 and 22 of Cycle 1:

- Blood (about 2 tablespoons) will be drawn for routine tests.

On Day 15 of Cycle 1:

- You will be have a brief physical exam, including measurement of vital signs.
- You will be asked about any side effects and other medication you have used.
- Your actual health status and your well-being will be assessed. This is called a performance status assessment.
- You will complete a questionnaire about your performance status of the

disease.
- Blood (about 2 tablespoons) will be drawn for routine tests.
- Blood (about 1 teaspoon) and/or urine will be collected to check the status of the disease.

On Days 1 of Cycles 2-3 and beyond
The assessments listed above for Day 1 will be performed. Additionally:
- Medication diaries will be reviewed and drug returns will be counted and new diaries will be given to you
- On Cycle 3 only, we will draw a blood sample for research testing (2 teaspoons)
- On Cycle 3 only, you will have a bone marrow biopsy/aspiration to check the status of the disease. Extra sample from the aspiration will be collected for the research samples.

On Days 15 of Cycles 2-3, and then beyond:
- You will complete a questionnaire about your performance status of the disease

If at any point the study tests show that the disease has changed (gotten worse or better), you may be asked to have additional imaging scans, blood and/or urine tests. You may also have an additional bone marrow aspiration and biopsy. The investigator will tell you more about any additional tests that need to be performed.

Length of Study
You may continue taking the study drugs for as long as the doctor thinks it is in your best interest. You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation on the study will be over once you have completed the End of Treatment visit.

<u>End of Treatment Visit</u>
About 30 days after your last dose of study drugs, the following tests and procedures will be performed:
- You will have a physical exam, including measurement of your vital signs.
- You will be asked about any side effects and other medication you have used.
- You will complete a questionnaire about your performance status of the disease
- You will complete a questionnaires about your nerve function and quality of

life.
- Blood (about 2 tablespoons) will be collected for routine tests.
- Blood (about 1 teaspoon) and/or urine will be collected to check the status of the disease. If urine is collected, you will be asked to collect your urine over a 24-hour period.

If you are able to become pregnant, you will have a blood (about 1 teaspoon) or urine pregnancy test. This test will be performed when you stop taking Cabozantinib and again about 30 days later.

Data collection after End of Treatment
We will ask to continue to collect information from you about how you are doing and effects of the study treatment on cancer following the end of study treatment.

What are the possible risks of being in this research study?
While on this study, you are at risk for side effects. These side effects will vary from person to person. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death. Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs.

The dose of the investigational medicine (cabozantinib) will be increased with each successive group of subjects to see what dose causes side effects. Therefore, depending on when you enter the study (which group you are in) you may experience more or new side effects not seen with lower doses.

Effects of Cabozantinib (XL184) in Humans
When participating in clinical studies with an investigational drug, cancer patients may experience side effects related to the drug. In studies of cabozantinib given alone, side effects related to cabozantinib have been reported in patients with many different types of cancer.

Side effects that occurred in less than 5% of patients but were considered medically important or severe or life-threatening and rarely fatal are listed in the next table. These events occurred in studies of cabozantinib given alone. If you are at the clinical site and notice any signs or symptoms of the side effects listed below, check with the staff in the clinic immediately; if you are no longer at the clinical site, call your doctor or go immediately to the nearest hospital.

Side Effects That Occurred in More than 20% of Cancer Patients Treated with Cabozantinib

- high blood pressure
- fatigue
- weakness
- changes in hair color
- hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering
- skin rash
- high blood levels of fat (possible heart disease and/or stroke)
- high blood sugar (possible diabetes)
- abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)
- underactive thyroid gland (possible weight gain, heart failure, and/or constipation)
- mouth blisters/sores (possible difficulty swallowing)
- mouth pain
- abnormal taste
- loss of appetite
- weight loss
- diarrhea
- nausea
- abdominal pain
- constipation
- vomiting
- low blood counts (red/white/platelets)
- abnormal liver or bone tests (possible liver damage and/or yellowing of the skin and/or eyes)
- abnormal kidney test (possible kidney damage)

Cabozantinib may cause low blood counts (red blood cells, white blood cells, and/or platelets).

- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low red blood cell count (anemia) may cause shortness of breath and/or fatigue. You may need a blood transfusion.

Side Effects That Occurred in 3 to 20% of Cancer Patients Treated with Cabozantinib

- blood clots in the veins
- low blood pressure (possible
- hole in the stomach or intestines (possibly leaking contents into the
- abnormal sensation (such as pins and needles)
- nerve damage

dizziness/fainting)
- headache
- dizziness
- anxiety
- dry skin
- skin redness
- skin thickening
- hair loss (partial or total)
- upset stomach
- hemorrhoids
- voice changes

abdomen)
- dehydration
- abnormal connections or passageways between organs or vessels (such as between different parts of the digestive system)
- difficulty swallowing
- pain (joint/arm/leg/chest muscle)
- muscle spasms

(possible numbness, pain, sensory function, and/or loss of motor function)
- difficulty breathing
- cough
- blockage in the lung (possible pain and/or shortness of breath)

Rare but serious (occurring in fewer than 3% of patients)

- brain damage that may be reversible (possible headache, confusion, seizures, and/or vision loss)
- blood clots in the arteries
- severe bleeding
- bone destruction (jaw bone)
- wound healing problems

You should not take St. John's Wort while on this study. In addition, you should not eat grapefruit, Seville (sour) oranges, star fruit, pomegranate, or products made with these fruits (including juice, jams, or candies) while you are taking cabozantinib.

Rare but Medically important Side Effects not listed above that Occurred ≥ 0.01% but < 0.1% of Cancer patients treated

- Air in the chest between lungs and chest wall
- Allergic reaction
- Hemolytic uremic syndrome (HUS) (anemia caused by the abnormal destruction of red blood cells)
- Blocked intestines
- Posterior reversible encephalopathy syndrome (PRES) (brain dysfunction caused by brain sweling)
- Cancer of the mouth or skin

- Damage to the outermost surface of the eye
- Inflammation and blockage of channels that carry bile from the liver
- Severe swelling of the mouth, lips, tongue, eyes and throat, or difficulty swallowing or breathing
- Very high blood pressure that comes on suddenly and quickly and which can lead to serious injury to the heart and brain

Effects of Carfilzomib in Humans

Carfilzomib may cause all, some, or none of the side effects listed below. These side effects can be mild but could also be serious and some may even result in death. There may also be unknown side effects from taking carfilzomib alone or with other drugs you may be taking.

Carfilzomib each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Very Common (may affect more than 1 in 10 patients)

- swelling of hands, feet or ankles
- headache
- high blood pressure
- shortness of breath
- muscle spasms
- fever
- fatigue and tiredness
- nausea/vomiting
- diarrhea
- constipation
- low blood cell counts (red, platelets, white)
- respiratory tract infections
- pneumonia
- decreased blood levels of potassium
- increased creatinine levels
- cough with phlegm
- bronchitis
- dizziness
- weakness
- numbness
- difficulty sleeping
- decreased appetite
- back pain
- joint pain
- pain in limbs (hands or feet)

Common (may affect up to 1 in 10 patients)

- fever associated with low white blood cell count
- chest pain
- heart attack
- heart failure and heart problems including rapid strong or irregular heartbeat
- chills
- pain
- stomach pain
- indigestion
- toothache
- ringing in the ears
- decreased blood levels of sodium, magnesium, protein, calcium or phosphate
- increased blood levels of calcium, uric acid, potassium, bilirubin, blood sugars, or c-reactive protein
- liver problems including an increase in your liver enzymes in the blood
- blood clot in the lungs
- nose bleed
- change in voice; hoarseness
- pain in throat
- wheezing
- pulmonary hypertension
- possible fluid in the lung
- rash
- itchy or redness of skin
- increase sweating
- runny nose or nasal congestion
- urinary tract infection
- inflammation of the nose and throat
- flu-like symptoms (influenza)
- lung infection
- serious infection in the blood
- viral infection
- flushing
- infection and/or irritation of the stomach and bowels
- feeling unwell
- blurred vision
- cataract
- infusion reactions such as pain, swelling, irritation or discomfort at site of injection
- low blood pressure
- blood clots in veins
- dehydration
- bone and muscle pain,
- muscle weakness
- aching muscles
- kidney problems, decreased ability to make urine and failure
- abnormal sensation (tingling) or decreased sensation in arms and legs
- anxiety

Uncommon (may affect up to 1 in 100 patients)

- sudden loss of heart function
- build-up of fluid around the heart
- bleeding, itchy skin, yellow skin, very pale stools caused by blocking of bile
- bleeding in the stomach and bowels
- multi-organ failure
- allergic reaction to

- severe increase in blood pressure
- stroke
- decreased blood supply to the heart
- bleeding around the brain
- bleeding in the lungs
- flow from the liver
- liver failure
- severe infection of the blood causing low blood pressure and low blood flow to organs. lung problems
- re-infection of the liver with hepatitis B virus
- carfilzomib
- breakdown products of the cancer cells entering the blood stream (Tumor Lysis Syndrome)
- Thrombotic thrombocytopenic purpura (TTP)
- Blockage of the intestines
- Inflammation of the pancreas gland
- Posterior reversible encephalopathy syndrome (PRES)

Rarely (may affect up to 1 in 1000 people)

- Hemolytic uremic syndrome (HUS)
- Thrombotic microangiopathy
- Swelling and irritation of the lining around the heart
- Swelling of the throat
- Hole in the stomach, small intestines or large bowel
- Infection of the back of the eye (cytomegalovirus)

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

- Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML).
- Tenderness of pain in the abdomen that gets more intense with motion or touch, abdominal bloating or distention, nausea and vomiting, diarrhea, constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs
- Blurred or double vision, vision loss, difficulty speaking, weakness in an arm or a leg, a change in the way you walk, problems with your balance, persistent nmbness, decreased sensation or loss of sensation, decreased alertness, memory loss or confusion which may be symptoms of a central

nervous system infection known as Progressive Multifuocal Leukoencephalopathy (PML).

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

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

Other Risks
Blood draws
Blood draws may cause pain, bleeding , and/or bruising. You may fa int and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Bone marrow aspirations/biopsies
Bone marrow biopsies and aspirations may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the aspiration/biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration/biopsy site.

CT Scans
CT scans involve exposure to radiation. Although the amount of radiation exposure is higher than a typical x-ray, the risk of harmful effects from a single exam is very small. The dye that is injected into a vein for the scan is usually well tolerated. Some people feel dizzy or queasy or get a headache with it or notice a cold feeling near the injection site. There is a chance of having an allergic reaction to the dye that rarely can be serious and life threatening. Your radiologist will obtain a separate informed consent explaining this procedure in specific detail.

Questionnaires
Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study

chair.

It is possible that other rare side effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

Pregnancy Risks

It is possible that the medicines used in this study could injure a fetus if you, or your partner, becomes pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test within 10-14 days and 24 hours before entering the study.

* 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).

If you have regular or no menstrual cycles, you will then have pregnancy tests every week for the first 28 days, then every 28 days while taking cabozantinib, again when taken off of cabozantinib therapy and 28 days after having stopped taking cabozantinib. If you have irregular menstrual cycles, you will have pregnancy tests every week for the first 28 days, then every 14 days while taking cabozantinib.

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use TWO appropriate method(s) of birth control every time you have sex, or you must not have sex. Both male and females must agree to use a medically accepted barrier method of birth control (contraception) plus one additional highly effective method of birth control (contraception) at the SAME TIME.

<u>Highly Effective Methods:</u>

- Intrauterine device (IUD) or intrauterine system [IUS])

- Additional Effective Methods
- Tubal ligation
- Male vasectomy

If an IUD method is not medically possible for you, you may use another highly effective method or two barrier methods AT THE SAME TIME.

These birth control methods must be used during the following time periods related to this study:
1) for at least 28 days before starting cabozantinib therapy;
2) while participating in the study; during interruptions in therapy and
3) for at least 4 months after cabozantinib has been stopped

Because of the nature of this research, methods of natural family planning are not, by themselves, sufficiently reliable to avoid pregnancy.

Special Note: Certain HIV-protease inhibitors, griseofulvin, modafinil, pencillins , rifampin, rifabutin , phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort may reduce the effectiveness of hormonal contraceptives during and up to one month after discontinuation of these concomitant therapies. Therefore, females of childbearing potential requiring treatment with one or more of these drugs must choose ONE non-hormonal method as the highly effective method of birth control (IUD, tubal ligation, partner's vasectomy) along with ONE of the additional effective methods (latex condom, diaphragm, cervical cap) or abstain from heterosexual contact while taking cabozantinib.

<u>FOR ALL MALES</u>
You must NEVER have unprotected sexual contact with a female who can become pregnant. Because it is not known whether cabozantinib is present in semen, you must completely abstain from sexual contact with females who are pregnant or able to become pregnant, or use a latex condom every time you engage in any sexual contact with females who are pregnant or may become pregnant. You must do this while taking cabozantinib and for 28 days after you stop taking cabozantinib, even if you have had a successful vasectomy.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to avoid pregnancy for 4 months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for 4 months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

What are the possible benefits to you?
Phase I of the study will be looking for the highest dose of cabozantinib that can be given safely. You may not get any benefit from being in this research study.

What are the possible benefits to other people?
Future patients may benefit from what is learned. Specifically, in the current study, we aim to treat the patients with MM who progressed on carfilzomib. It is hoped that by treating patients with cabozantinib, this may improve response to the carfilzomib therapy that has proven to result in improved outcomes in MM patients.

What are the alternatives to being in this research study?
You may choose not to take part in this study. You may choose to receive standard of-care therapy for the disease The standard-of-care options that are available to you will be based on what therapies you may have already had. The study doctor and your regular doctor will discuss the options with you in more detail. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

What will being in this research study cost you?
The investigational drug, cabozantinib is provided by the manufacturer, Exelixis, at no cost to you for the entire time you are on the study. Some tests and procedures that you may receive as part of this study and are for research purposes only will be without cost to you. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner.

However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration.

You will be responsible for any applicable insurance deductibles and co-payments. If you wish to speak with a financial counselor about your insurance coverage and

benefits, let the investigator or other study personnel know. A contact for personal assistance will be made available for you.

Will you be paid for being in this research study?
You will not be paid to be in this research study.

Who is paying for this research?
This research is being paid for by grant funds from Amgen. The Institution receives money from Amgen and study drug from Exelixis to conduct this study.

Dr. Muhamed Baljevic, the Principal Investigator of this study, receives money as an independent consultant for participating on an Advisory Board for Amgen, Inc..

What should you do if you are injured or have a medical problem during this research study?
Your welfare is the main concern of every member of the research team. If you are injured or have a medical problem as a direct result of being in this study, you should immediately contact one of the people listed at the end of this consent form. Emergency medical treatment for this injury or problem will be available at the Nebraska Medical Center. If there is not sufficient time, you should seek care from a local health care provider.

The Institution has no plans to pay for any required treatment or provide other compensation. If you have insurance, your insurance company may or may not pay the costs of medical treatment. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay for the medical treatment.

Agreeing to this does not mean you have given up any of your legal rights.

How will information about you be protected?
You have rights regarding the protection and privacy of your medical information collected before and during this research. This medical information is called "protected health information" (PHI). PHI used in this study may include your medical record number, address, birth date, medical history, the results of physical exams, blood tests, x-rays as well as the results of other diagnostic medical or research procedures. Only the minimum amount of PHI will be collected for this research. Your research and medical records will be maintained in a secure manner.

Who will have access to information about you?
By signing this consent form, you are allowing the research team to have access to

your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study at the Institution.

Your PHI will be used only for the purpose(s) described in the section "What is the reason for doing this research study?"

You are also allowing the research team to share your PHI, as necessary, with other people or groups listed below:

- The UNMC Institutional Review Board (IRB)
- Institutional officials designated by the UNMC IRB
- Federal law requires that your information may be shared with these groups:
    - The HHS Office of Human Research Protections (OHRP)
    - The Food and Drug Administration (FDA)
- The HIPAA Privacy Rule requires the following groups to protect your PHI:
    - Researchers at MD Anderson.
    - Your health insurance company
    - The Fred and Pamela Buffett Cancer Center Scientific Review Committee (SRC)

Your PHI may also be shared with the following groups. However, these organization(s) do not have the same obligation to protect your PHI:

- Exelixis Corporation, the manufacturer of cabozantinib and Amgen, which provides funds the Institution to conduct this research
- The National Cancer Institute's (NCI) Clinical Trial Reporting Program

There is currently no plan to end this study. Your information may be kept and used indefinitely.

You may cancel your authorization for further collection of PHI for use in this research at any time by contacting the principal investigator in writing. However, the PHI which is included in the research data obtained to date may still be used. If you cancel this authorization, you will no longer be able to participate in this research.

How will results of the research be made available to you during and after the study is finished?

In most cases, the results of the research can be made available to you when the study is completed, and all the results are analyzed by the investigator or the sponsor of the research. The information from this study may be published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

If you want the results of the study, contact the Principal Investigator at the phone number given at the end of this form or by writing to the Principal Investigator at the following address:Dr. Muhamed Baljevic, 986840 Nebraska Medical Center, Omaha, NE 68198-6840

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen if you decide not to be in this research study?
You can decide not to be in this research study. Deciding not to be in this research will not affect your medical care or your relationship with the investigator or the Institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

What will happen if you decide to stop participating once you start?
You can stop participating in this research (withdraw) at any time by contacting the Principal Investigator or any of the research staff.

Deciding to withdraw will otherwise not affect your care or your relationship with the investigator or this institution. You will not lose any benefits to which you are entitled.

For your safety, please talk to the research team before you stop taking any study drugs or stop other related procedures. They will advise you how to withdraw safely. If you withdraw you may be asked to undergo some additional tests. You do NOT have to agree to do these tests.

You may be taken off the study if you do not follow instructions of the investigator or the research team.

You may also be taken off the study if

- your disease progresses after two cycles
- you have unacceptable side effects from the study treatment
- the investigator determines that you condition has changed and that the study treatment is unacceptable
- you are unable to continue to have the ability to provide consent for yourself
- your response to treatment qualifies you for another therapy, such as high dose therapy with autologus stem cell transplant.

Any research data obtained to date may still be used in the research.

Will you be given any important information during the study?
You will be informed promptly if the research team gets any new information during this research study that may affect whether you would want to continue being in the study.

What should you do if you have any questions about the study?
You have been given a copy of "*What Do I Need to Know Before Being in a Research Study?*" If you have any questions at any time about this study, you should contact the Principal Investigator or any of the study personnel listed on this consent form or any other documents that you have been given.

What are your rights as a research participant?
You have rights as a research subject. These rights have been explained in this consent form and in The Rights of Research Subjects that you have been given. If you have any questions concerning your rights, or want to discuss problems, concerns, obtain information or offer input, or make a complaint about the research, you can contact any of the following:

- The investigator or other study personnel
- Institutional Review Board (IRB)
    - Telephone: (402) 559-6463.
    - Email: IRBORA@unmc.edu
    - Mail: UNMC Institutional Review Board, 987830 Nebraska Medical Center, Omaha, NE 68198-7830
- Research Subject Advocate
    - Telephone: (402) 559-6941
    - Email: unmcrsa@unmc.edu

Optional Storage of Your Samples
The researchers doing this study are interested in doing research now on the blood and bone marrow aspirate samples collected from you to better understand the nature of cancer and how patients respond to treatment. Rapid advances in technology make it impossible to predict what new tests or studies may be possible in the future.

The collection of these research samples will be before you begin treatment and before cycle 3 are a necessary part of this study and will be used only for these purposes. The samples will not be sold.

However, with your permission should these research samples not be used for this study then we would like to ask you if you will allow them to be saved and stored for

future use. The samples will be kept until they are used up or destroyed.

Most future research studies will focus on cancer, specifically multiple myeloma. This may also include research on inherited traits also known as hereditary genetic testing (to find out if cancer runs in your family).

Reports about any research tests done with your samples will not be given to you or your oncologist, or family doctor. These reports will not be put in your medical records.

Confidentiality of Samples
To protect your identity, the information that will be on your research blood and tissue samples will be limited to your pathology identification number and participant code, which may include your initials.

To protect your identity, the information that will be on your blood samples will be limited to the participant code, which may include your initials.

Withdrawal of Required Samples
If you agree to allow the investigators to store your research samples and then decide you no longer want your samples to be used for future research, you should tell the investigator. The investigator will ensure the samples stored are destroyed. If tests have already been done on your sample(s) it will not be possible to withdraw those results. However, no further testing will be done.

This research may not benefit you, but may help people in the future who have the same kind of cancer as you have. You can indicate your wish to participate in this additional research, and have your samples stored for future research purposes when signing this consent form. You may decide not to participate in the "optional" study and still participate in this main study.

_____ You agree to allow storage and use of bone marrow aspirate and blood samples taken from you for future research.

_____ You do not agree to storage and use of bone marrow aspirate and blood samples to be stored for future research.

Documentation of informed consent
You are freely making a decision whether to be in this research study. Signing this form means that:

- You have read and understood this consent form.
- You have had the consent form explained to you.
- You have been given a copy of The Rights of Research Subjects
- You have had your questions answered.
- You have decided to be in the research study.
- If you have any questions during the study, you have been directed to talk to one of the investigators listed below on this consent form.
- You will be given a signed and dated copy of this consent form to keep.

Printed Name of Subject _____

Signature of Subject _____

Date _____

My signature certifies that all the elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the subject possesses the legal capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Printed Name of Person obtaining consent _____

Signature of Person obtaining consent _____

Date _____

Authorized Study Personnel
Principal
* Baljevic, Muhamed
phone: 402-559-8562
alt #: 402-559-8013
degree: MD

Secondary
* Holstein, Sarah
phone: 402-559-6660
alt #: 402-559-8013
degree: MD

What Do I Need To Know Before Being In A Research Study?

You have been invited to be in a **research study**. Research studies are also called "clinical trials" or "protocols." **Research** is an organized plan designed to get new knowledge about a disease or the normal function of the body. The people who are in the research are called **research subjects**. The **investigator** is the person who is running the research study. You will get information from the investigator and the research team, and then you will be asked to give your **consent** to be in the research.

This sheet will help you think of questions to ask the investigator or his/her staff. You should know all these answers before you decide about being in the research.

What is the **purpose** of the research? Why is the investigator doing the research?

What are the **risks** of the research? What bad things could happen?

What are the possible **benefits** of the research? How might this help me?

How is this research different than the care or treatment I would get if I wasnˆt in the research? Are there other treatments I could get?

Does **everyone** in this research study get the same treatment?

Will being in the research **cost** me anything extra?

Do I have to be in this research study? Will the doctor still take care of me if I say **no**?

Can I **stop** being in the research once Iˆve started? How?

Who will look at my **records**?

How do I reach the investigator if I have more **questions**?

Who do I call if I have questions about being a **research subject**?

Make sure all your questions are answered before you decide whether or not to be in this research.

THE RIGHTS OF RESEARCH SUBJECTS
AS A RESEARCH SUBJECT YOU HAVE THE RIGHT ˆ

ˆ to be told everything you need to know about the research before you are asked to decide whether or not to take part in the research study. The research will be explained to you in a way that assures you understand enough to decide whether or not to take part.

ˆ to freely decide whether or not to take part in the research.

ˆ to decide not to be in the research, or to stop participating in the research at any time. This will not affect your medical care or your relationship with the investigator or the Nebraska Medical Center. Your doctor will still take care of you.

ˆ to ask questions about the research at any time. The investigator will answer your questions honestly and completely.

ˆ to know that your safety and welfare will always come first. The investigator will display the highest possible degree of skill and care throughout this research. Any risks or discomforts will be minimized as much as possible.

ˆ to privacy and confidentiality. The investigator will treat information about you carefully, and will respect your privacy.

... to keep all the legal rights you have now. You are not giving up any of your legal rights by taking part in this research study.

ˆ to be treated with dignity and respect at all times

The Institutional Review Board is responsible for assuring that your rights and welfare are protected. If you have any questions about your rights, contact the Institutional Review Board at (402) 559-6463.