UNIVERSITY OF CALIFORNIA, DAVIS
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: UCDCC#253: A Phase I/II Study of PiC-D (Ixazomib in Combination with Pomalidomide, Clarithromycin and Dexamethasone) in Patients with Relapsed or Refractory Multiple Myeloma [Protocol version 11.0 dated: 08/28/19]

Principal Investigator: Joseph Tuscano, MD
Department: Internal Medicine

CALIFORNIA SUBJECT'S BILL OF RIGHTS FOR BIOMEDICAL RESEARCH STUDIES

The rights below are the rights of every person who is asked to be in a medical research study. As an experimental subject, you have the right to:

- Be informed of the nature and purpose of the research study.
- Be given an explanation of the procedures to be followed, and any drug or device to be used.
- Be given a description of common or important discomforts and risks reasonably to be expected from the study.
- Be given an explanation of any benefits you might expect.
- Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be helpful, and their risks and benefits compared to this study.
- Be informed of the types of medical treatment, if any, that are available if complications should arise.
- Be given an opportunity to ask any questions concerning the study or the procedures involved.
- Be instructed that consent to participate in the study may be withdrawn at any time, and you may discontinue participation in the study at any time without it being held against you.
- Be given a signed and dated copy of this document.
- Be given the opportunity to decide to consent or not to consent to the study without force, fraud, deceit, duress, coercion, or undue influence.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

For study participants at UC Davis: If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team [redacted] If you are unable to the reach the Principal Investigator of this study, please contact the clinical research coordinator (CRC) responsible for your care. The CRC's contact information will be provided to you. The CRC will assist you in contacting another investigator for this study.

In addition to the phone number above, there is a 24-hour emergency telephone number for the UC Davis Medical Center (UCDMC) Hospital Operator. It is [redacted] If you call the UCDMC Hospital Operator, tell the Operator you are participating in a research study and you wish to talk to the medical oncologist on call. In the case of an emergency, dial 911 from any phone.

UC Davis Contact information (including the 24-hour emergency number) is summarized below:
Joseph Tuscano, MD [redacted]
24-hour phone number: [redacted] **(ask for the medical oncologist on call)**

For study participants at UC Irvine: If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at (714) 456-8653. If you are unable to the reach the Principal Investigator of this study, please contact the clinical research coordinator (CRC) responsible for your care. The CRC's contact information will be provided to you. The CRC will assist you in contacting another investigator for this study. In the case of an emergency, dial 911 from any phone.

UC Irvine Contact information is summarized below:
Elizabeth Brem, MD [redacted]
Pager number: [redacted]

For study participants at UC San Diego: If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at [redacted]. If you are unable to the reach the Principal Investigator of this study, please contact the clinical research coordinator (CRC) responsible for your care. The CRC's contact information will be provided to you. The CRC will assist you in contacting another investigator for this study. In the case of an emergency, dial 911 from any phone.

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UC San Diego Contact information is summarized below:
Caitlin Costello, MD [redacted]

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-admin/.You may talk to an IRB staff member at [redacted] hs-IRBAdmin@ucdavis.edu, or [redacted] Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

INTRODUCTION

This is a research study. Research studies only include subjects who choose to participate. Your study doctor will explain the clinical trial to you. As a study participant you have the right to know about the procedures that will be used in this research study so that you can make the decision whether or not to participate. The information presented here is to make you better informed so that you may give or withhold your consent to participate in this research study. Please take your time to make your decision and discuss it with your family, friends, or with your personal physician. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have multiple myeloma that has relapsed or been treated before with a chemotherapy regimen and your disease has returned. We hope to learn more about your type of cancer. You must be 18 years of age or older. In order to participate in this study, it will be necessary to give your written consent.

The drugs being used in this study are ixazomib, clarithromycin, pomalidomide, and dexamethasone. Ixazomib (otherwise referred to as MLN9708) is an investigational drug or experimental agent that has not yet been approved by the Food and Drug Administration (FDA). Ixazomib may stop the growth of cancer by interfering with proteasomes (the protein breakdown mechanism in the cells). Clarithromycin, pomalidomide, and dexamethasone are standard drugs that can change and regulate the immune system and may stop cancer cells from growing. The combination of drugs used in this study is experimental.

Dr. Tuscano at UC Davis is the author and sponsor of this of this study and is the coordinating site for this study. He is also the chemotherapy doctor and principal investigator who is overseeing this study at UC Davis. UC San Diego and UC Irvine will also be participating in this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study will be completed in two parts. First part (phase I) is to determine the dose of clarithromycin. The second part (phase II) is to determine the effects, good and/or bad, of the study drugs ixazomib in combination with pomalidomide, clarithromycin, and dexamethasone on you and your multiple myeloma.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 52 patients will participate on this study here at UC Davis and UCSD and UCI (our participating sites).

BEFORE YOU BEGIN THE STUDY

If you choose to take part in this study and sign this informed consent form, you will complete "pre-study screening tests" to determine if you meet the study requirements. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. Tests that are not part of regular cancer care and are being done only because you are in this study are marked as *** *for research only*. The pre-study screening tests are listed below.

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Pre-study Screening Tests:

- Physical examinations including vital signs
- Demographics (questions about your age, gender, race, ethnicity, etc.)
- Weight and height
- Measure your general well being
- Tests to check the heart if you have a medical history of heart problems (electrocardiogram [ECG or EKG], a test that measure heart rhythm)
- Urine tests
- CT scan (if your doctor thinks it is necessary)
- Pregnancy testing (One (1) within 2 weeks before starting treatment and one (1) within 24 hours before starting treatment; see "Reproductive Risks" later in this form)
- Questionnaires measuring your quality of life. These questionnaires will take approximately 15-20 minutes to complete. *** *For research only*
- Blood tests for HIV (human immunodeficiency virus – about 1 tablespoon will be drawn)
- Blood draw for blood counts, kidney function, liver function, and chemistries (about 2-3 teaspoons will be drawn)
- Blood draw testing for multiple myeloma markers (substances in the blood that are elevated in people with cancer) and research PK sampling about 2 tablespoon of blood will be drawn)
- Blood clotting tests (about 1-2 teaspoons will be drawn)
    - ❖ *(A total of 5-6 tablespoons of blood will be drawn on the pre-study screening visit)*

To be performed within 42 days of starting the study:

- A skeletal survey: This is a series of x-rays of your bones to assess any bone damage caused by multiple myeloma.

To be performed within 100 days of starting the study:

- A bone marrow aspirate and biopsy: A bone marrow aspirate is a test in which the skin is numbed, and a needle is inserted into the bone underneath to get a sample of the liquid bone marrow. A bone marrow biopsy is collected at the same time as the aspirate and is a small piece of bone marrow tissue

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

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

You will receive treatment over 28 days in this study. This period of time is called a “cycle”.

Your study team will provide you with medication diaries that will help you know when you need to take your medications. Please keep track of when you took each on the diaries. This will help you remember when you took your medications. It will also help your study doctor understand how much of the medication you are taking. Please bring these drug diaries, along with any unused pills/capsules/bottles with you to every study visit. You can contact the study team any time should you have questions about your medications.

It is very important that you inform your study team of any changes to your current medications, as some medications may interact with the study drugs.

This study is split into two phases, which are based on the dose of clarithromycin. In the phase I part a small group of patients will be given a dose of clarithromycin in combination with pomalidomide, ixazomib, and dexamethasone to see how well it is tolerated. If that dose is also tolerated, it becomes the prescribed dose (the “maximum tolerated dose”, or “MTD”) for the next phase – phase II. If the dose is not tolerated, then a lower dose is used. None of the other drugs – pomalidomide, ixazomib, and dexamethasone – will be escalated (however, these medications may be lowered due to age [for dexamethasone] or side effects cause by these drugs). In phase II, the MTD dose of clarithromycin determined in phase I will be used for all patients in combination with pomalidomide, ixazomib, and dexamethasone. You will be told which phase of the study you are enrolling to prior to your participation.

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Clarithromycin

Once a day dosing

You should take clarithromycin once a day at the same time each day. Clarithromycin tablets may be taken with or without food. If more than 12 hours have elapsed before you remember to take the next dose, you must skip the dose for that day. You should NOT take 2 doses to make up for the one that you missed. Clarithromycin may interact with some drugs, so you must report to your doctor the use of any other medications.

Twice a day dosing

You should take clarithromycin twice a day at the same time each day, 12 hours apart. Clarithromycin tablets may be taken with or without food. If more than 12 hours have elapsed before you remember to take the next dose, you must skip the dose for that day. You should NOT take 2 doses to make up for the one that you missed. Clarithromycin may interact with some drugs, so you must report to your doctor the use of any other medications.

You will continue to take clarithromycin for as long as you are benefitting from it and you are not experiencing unmanageable side effects.

Cycle 1

For Cycle 1 only, you will receive clarithromycin on days 15-21 of the 28 day cycle.

Cycles 2-6

For Cycles 2-6, you will receive clarithromycin on days 1-21 of the 28 day cycle.

Cycles 7 and beyond

For the "maintenance" cycles (which are Cycles 7 and beyond), you will receive clarithromycin on days 1-28 of the 28 day cycle.

On research blood or PK sampling days, cycle 1 days 1 and 8 (phase 1) and cycles 2-3 day 1 (phase 2) clarithromycin with be administered immediately prior to pomalidomide and ixazomib.

Pomalidomide

Take pomalidomide at home, preferably at night about the same time each day. You will take pomalidomide by mouth once daily for the first 21 days of the 28-day treatment cycle followed by a 7-day rest period.

Ixazomib

Take ixazomib at home. You will take ixazomib by mouth once a week for the first 3 weeks of the 28-day treatment cycle (days 1, 8, and 15).

Dexamethasone

Take dexamethasone at home with food, preferably in the morning. You will take dexamethasone by mouth once a week, beginning on day 1 of each treatment cycle (on days 1, 8, 15, and 22 of the 28-day cycle). The dose of dexamethasone will be lowered if you are over 75 years of age.

Treatment cycles will be continued as long as you are tolerating treatment (not experiencing unmanageable side effects) and are benefitting from it.

Please see the table of tests and procedures on the chart which further explains what will happen if you participate in this study.

	Screen	Cycle 1				Cycles 2-6		Maintenance Cycles	End of Treatment	Follow-Up
		D1	D8	D15	D22	D1	D15	D1		
Tests & Observations										
Sign this consent form	X									
Demographics	X									
Physical examination and medical history	X	X				X	X	X	X	

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	Screen	Cycle 1				Cycles 2-6		Maintenance Cycles	End of Treatment	Follow-Up
		D1	D8	D15	D22	D1	D15	D1		
Tests & Observations										
Vital signs	X	X				X	X	X	X	
Weight	X	X				X	X	X	X	
Performance status	X	X				X	X	X	X	
Height	X									
Evaluation of any side effects you are having		X.....							X	
Review of any other medications you are taking	X.....								X	
ECG	X									
QOL questionnaires	X					X		X	X	X
Laboratory Studies										
Blood tests for blood counts	X	X	X	X	X	X	X	X	X	
Blood tests to measure viral loads (HIV)	X					X		X	X	
Blood tests for chemistries	X	X		X		X	X	X	X	
Blood tests for blood clotting	X									
Blood or urine pregnancy test	X	X	X	X	X	X		X	X	
Blood test for multiple myeloma markers	X									
Staging										
Tumor measurements by CT or MRI	X					X		X	X	
Skeletal survey	X								X	
Bone marrow aspiration & biopsy	X					X		X	X	
M-protein assessments	X					X		X	X	X
Treatment										
Pomalidomide		Days 1-21				Days 1-21		Days 1-21		
Ixazomib		Day 1, 8, 15				Days 1, 8, 15		Days 1, 8, 15		
Clarithromycin		Days 15-21				Days 1-21		Days 1-28		
Dexamethasone		Days 1, 8, 15, 22				Days 1, 8, 15, 22		Days 1, 8, 15, 22		
For research only studies performed on your blood specimens and correlative studies for future use										
Blood for research studies PK and correlative (future use) *** *For research only.* these will be discussed at the end of this consent form		X		X		X			X	
Follow-up										
Follow-up to check your status										X

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WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY? (Continued)

PK Research Sampling (Phase I)								
		Post-dose in Cycle 1 on days 1 and 15						
		HOURS						
	Pre-dose	0.5	1.0	1.5	2	4	8	24
PK research sampling	X	X	X	X	X	X	X	X

	PK Research Sampling (Phase 2)
	Cycles 2 and 3 on day 1
	2-6 hours after dose
PK	X

Study location: This study is currently enrolling at the sites listed below. Your treatment will be administered (given) at the site of your enrollment.

UC Davis Medical Center
2315 Stockton Blvd.
Sacramento, CA 95817

UC Davis Cancer Center
4501 X Street
Sacramento, CA 95817

UC San Diego Cancer Center
3855 Health Sciences Drive[redacted]
La Jolla, CA 92093-0698

UC Irvine Health Chao Family Comprehensive Cancer Center
101 The City Drive South
[redacted]
Orange, CA

HOW LONG WILL I BE IN THE STUDY?

You will be asked to participate for as long as your cancer is not growing and you are not having any unmanageable side effects. After you are finished with the study treatment, your doctor will ask you to visit the office for follow-up exams for at least once. After that, we will continue to collect follow-up information about your cancer and any further treatment you receive for every 3 months, up to 3 years from the time you enrolled in this study.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop the study at any time and it will not be held against you. Tell your study doctor if you are thinking about stopping or decide to stop. Your doctor will tell you how to stop safely. It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment 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.

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

There may be other reasons to stop your participation in this study that are not known at this time. If you stop participating in the study, or the study ends, you will stop receiving the study drug(s) and may be asked to come back for final tests and procedures. If you choose to stop taking the study drug before the study ends, you should discuss the following options with the study doctor:

- Continue to visit the study doctor for study related procedures or tests.
- Stop study related visits but allow the study doctor or his/her study staff to obtain information about your health by reviewing your medical records, by contacting you, a family member or a legal representative, or through other means as allowed by local law
- You can completely leave the study and have no more contact with the study doctor and his/her study staff for study related procedures or questions as of the date of your request.

If you stop being in the research, already collected data may not be removed from the study database.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

POSSIBLE DISCOMFORTS AND RISKS OF IXAZOMIB

There are risks to taking part in any research study. During the study, you may have problems or discomforts and risks from ixazomib alone, ixazomib and other drug combinations, and/or study procedures. The more commonly occurring discomforts and risks are listed below, as are the rare but serious discomforts and risks. You should discuss these with your study doctor. There is always the possibility that unknown risks may occur, however your doctor will watch closely for problems or discomforts and risks. Many discomforts and risks go away shortly after treatment is stopped or with treatment for the discomforts and risks, but in some cases discomforts and risks may be serious, long-lasting or permanent and may even result in hospitalization. There is also the risk of death.

If any discomforts and risks occur, you must tell your study doctor or study staff, even if you do not think they are related to the study drug.

POTENTIAL DISCOMFORTS AND RISKS OF IXAZOMIB

Based on studies of ixazomib, it is possible to predict some of the discomforts and risks. However, it is possible that ixazomib may cause risks that have not yet been observed in patients. The following risks might be seen:

- Low platelet count which may increase the chance of bleeding
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
- Nausea
- Vomiting
- Diarrhea
- Numbness or tingling or pain feelings in hands and feet
- Swelling or fluid buildup in the arms or legs
- Flu-like symptoms and other upper respiratory tract infections
- Arthralgia or joint pain
- Lung infections including pneumonia or pneumonitis
- Herpes Zoster that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time

Other discomforts and risks reported in studies with ixazomib, which may have been due to your disease, ixazomib, other medications, or some combination of these include:

- Not feeling like eating
- Electrolyte imbalance (blood chemical imbalance)

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POTENTIAL DISCOMFORTS AND RISKS OF IXAZOMIB (continued)

Other discomforts and risks reported in studies with ixazomib, which may have been due to your disease, ixazomib, other medications, or some combination of these include:

- Loss of water from the body (dehydration) because of vomiting and/or loose stools
- High blood creatinine and renal failure which means your kidneys are having trouble working well. Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
- Feeling short of breath or difficulty breathing
- Feeling tired or weak
- Chills
- Cough
- Fever
- Headache
- Pain in the abdomen or back
- Muscle weakness
- Feeling dizzy or dizziness
- Lowered blood pressure that can commonly cause you to feel lightheaded, faint or pass out when you stand up
- Lowered white blood cells called lymphocytes
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Constipation
- Pain (muscular) in extremities

Some discomforts and risks that occur with lesser frequency (<1%) than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience and because these events occurred while patients were receiving other drugs as well, we do not know if ixazomib causes such problems. Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens - Johnson syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute febrile neutrophilic dermatosis (Sweet's syndrome)) and pemphigus vulgaris have been reported in MLN9708 studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.

In addition, two rare neurological conditions have been reported in patients on ixazomib (frequency <1%). .Posterior reversible encephalopathy syndrome has also been reported with ixazomib with lesser frequency (<1%). This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible. Transverse myelitis, also a rare condition (<1%), is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving ixazomib. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether ixazomib causes transverse myelitis, however, as it happened to a patient receiving ixazomib, we are not able to exclude the possibility that ixazomib may have contributed to transverse myelitis.

Progressive multifocal leukoencephalopathy, (PML) is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1 %) in patients taking MLN9708. It is not known whether MLN9708 may contribute to the development of PML.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells, and result in blood clots in small vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These

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disorders can occasionally be fatal. TMA, TTP, and HUS have been seen rarely (<0.1%) in patients treated with MLN9708.

Overdose has been reported in patients taking ixazomib. Reports of accidental overdose have been associated with risks such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. It is important to take only one dose of ixazomib at a time, and only at the prescribed interval.

Additionally, it is worth noting that:

- Ixazomib, should not be taken if you have ever had an allergic reaction to the active substance or any of the inactive ingredients used in its formulation..
- The following side effects may also be a risk with MLN9708 because they have been reported with another proteasome inhibitor, Velcade, in patients with diseases requiring this type of treatment, or in patients who receive MLN9708 in combination with other drugs for cancer treatment:
- Rapid death of cancer cells that may let large amounts of the cells into the blood that injure organs, such as kidneys (this is referred to as tumor lysis syndrome);
- Worsening of your heart function (congestive heart failure) that may require additional drugs for treatment or hospitalization;
- Disorders of your lung that could be serious enough to result in death
- Other drugs and supplements may affect the way ixazomib works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

Reproductive risks of ixazomib

Female subjects: We do not know if the study drug **ixazomib** will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study.

You must have a negative pregnancy test prior to enrolling in the study.
Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see examples below).

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex or non-latex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

You must use birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male subjects: We do not know if using ixazomib will affect sperm. Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period (including interruptions in treatment). Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non-latex condom with a spermicidal agent) during the entire study drug treatment period, and for 90 days after completing study drug treatment. Or, you should completely avoid having heterosexual intercourse.

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Highly effective methods	Other effective methods (barrier methods)
Vasectomy	Latex or non-latex condom with or without a spermicidal agent
	Diaphragm with spermicide; Cervical cap with spermicide; Sponge with spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.
If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

If you become or think you might be pregnant during the study, tell your study doctor immediately. Tell your study doctor right away if you or your partner becomes pregnant during the study or within 90 days after the last dose of study drug. The study doctor or research staff will advise you of the possible risks to your unborn child and will make an effort to contact your partner to get her permission to collect information about the pregnancy. In order for us to follow you or your partner after pregnancy occurs, you or your pregnant partner will be asked to sign a separate consent form.

RISKS OF POMALIDOMIDE
Pomalidomide (CC-4047) has been studied in healthy volunteers and in subjects with cancer of the blood and other organs of the body as well as in subjects with other diseases. As with any other experimental treatment there may be side effects or risks that are unknown or cannot be predicted at this time.

The following is a list of important side effects reported with pomalidomide. In some cases, side effects can be serious, long-lasting, may never go away or can cause death. This list is not complete but your study doctor will answer any questions you might have and provide you with more information.

Very Common (Greater than 10% chance this may happen):

- Decrease in the number of platelets, the cells that help your blood to clot
- Changes in bowel movement
- Cough
- Decrease in the cells carrying oxygen to your body
- Decreased appetite
- Fever
- Low number of white blood cells (with or without a fever, which may increase your chances of infection)
- Muscle cramp
- Nausea
- Pain
- Pneumonia (infection in the lungs)
- Shortness of breath
- Swelling including arms and legs
- Tiredness

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RISKS OF POMALIDOMIDE (continued)

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

- Infection
- Dizziness
- Vomiting
- Rash
- Abnormal shaking
- Changes in sensations including decreased sense of touch, burning sensation or tingling
- Sore throat
- Kidneys not working well
- Confused
- Abnormal blood test results
- Less alert
- Blood clots in legs or lungs
- Difficulty in passing urine
- Itching
- Abnormally low number of red blood cells (which can lead to fatigue or shortness of breath)
- Low number of white blood cells (with or without a fever)
- Pain

Uncommon (Between 0.1- 1% chance that this may happen):

- Abnormal blood test results

Other important risks of pomalidomide
Events that do not meet the criteria for inclusion into above criteria but are considered important enough for you to be made aware.

- New cancers (including acute myeloid leukemia (AML) (a cancer of the bone marrow which affects your white blood cells have been seen in diseases where AML is considered to be part of the disease progression), Adrenal carcinoma (cancer of the adrenal gland), Bladder transitional cell carcinoma (cancer of the urinary bladder), Renal cell carcinoma (kidney cancer), myelodysplastic syndrome (MDS: a group of diseases that affect your blood and bone marrow), Skin cancers, and Thyroid cancer
- Inflammation of your lungs
- Tumor lysis syndrome (TLS) Rapid death of cancer cells where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage
- Pomalidomide in combination with dexamethasone increases the risk of blood clots in the veins of your legs and lungs. Therefore, aspirin, warfarin, low molecular weight heparin shots (for example, lovenox) or other appropriate blood thinner will be required to prevent this complication, provided your platelet count is high enough. Your study doctor will discuss the risks and benefits of the different blood thinners.

Additional important precautions
Other than the subject, females who are able to become pregnant and males who are able to father a child should not touch or handle the pomalidomide capsules or the powder they contain.

We do not know if pomalidomide has any effect on your being able to have a child in the future, please speak with your doctor about family planning options for the future.

You must agree to abstain from donating blood or semen while taking pomalidomide (even if you temporarily stop your medication) for at least 1 week after the last dose of pomalidomide.

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Please let your study doctor know all of your present and past diseases and allergies and any medication you may be taking including over-the-counter medications, vitamins, herbal, homeopathic or holistic medications or treatments. This is important because a possible interaction with some medications, vitamins, and remedies may cause serious side effects, and/or may still be unknown.

Pregnancy risks of pomalidomide

Pomalidomide was found to cause birth defects in an experimental study in animals. Pomalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Pomalidomide is therefore considered to have the potential to cause birth defects in humans. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females **must not** become pregnant while taking pomalidomide.

Certain drugs such as HIV-protease inhibitors, griseofulvin, modafinil, penicillins, 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. Please speak to your study doctor if you are taking any of these medications.

RISKS OF DEXAMETHASONE

Likely:

- Stomach and throat ulcers (holes) or worsening or irritation of existing ulcers
- Inflammation of the pancreas
- Increased weight around the stomach
- Puffiness (especially in the face)
- Retaining of salt and fluids which could cause an increase in blood pressure
- A possible rise in the blood sugar
- Problems with the level of potassium in the blood
- Muscle weakness
- Brittle bones
- Menstrual changes
- Mood swings
- Depression
- Trouble with sleeping
- Changes in personality
- Increased risk of infections

Less Likely:

- Itching, and other allergic reactions (including severe allergic reactions)
- Convulsions and dizziness
- If you are more prone to heart disease, you may experience heart failure
- Participants with glaucoma (build-up of pressure inside the eye) or a family history of glaucoma may experience a rise of inner eye pressure or glaucoma.
- Dexamethasone given for more than one year at doses of 15 mg or greater may cause cataracts (clouding of the normally clear lens of your eye)
- Dexamethasone may also affect the skin by causing stretch marks (stomach, lower back, breasts, and groin area), slow wound healing, increased sweating and easy bruising
- Continued use (more than 25 mg for 2 weeks) can lower the function of the adrenal glands
- This drug may also alter the body's defense system increasing the chance of infections

Rare, but Serious:

- A tear in the bowel that will make the contents of the bowel leak into the abdominal cavity and cause infection and pain, and could lead to death

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RISKS OF CLARITHROMYCIN

The following is a list of important side effects reported with clarithromycin. In some cases, side effects can be serious, long-lasting, may never go away or can cause death. This list is not complete but your study doctor will answer any questions you might have and provide you with more information.

Common risks:

- Diarrhea
- Nausea
- Vomiting
- Stomach pain
- Heartburn
- Gas
- Change in taste
- Headache

Other important risks of clarithromycin:

- Rash
- Hives
- Itching
- Swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles or lower legs
- Difficulty breathing or swallowing
- Hoarseness
- Peeling or blistering skin
- Fever
- Yellowing of the skin or eyes

Other important risks of clarithromycin:

- Extreme tiredness
- Unusual bleeding or bruising
- Lack of energy
- Loss of appetite
- Pain in the upper right part of the stomach
- Dark-colored urine
- Flu-like symptoms
- Muscle weakness such as difficulty chewing, talking, or performing daily activities
- Double vision
- Fast, pounding, or irregular heartbeat. Rarely, a disruption in heart rhythm can cause cardiac death.
- Antibiotic resistant infections (bacterial infections that will not longer respond to treatment with antibiotics), including clostridium difficile, a bacterial infection that can cause symptoms such as watery diarrhea, abdominal pain and/or tenderness, nausea, loss of appetite, and fever.

General Risks:

Blood draw risks: Routine laboratory tests and the research blood draws may result in bruising, infection and minor pain or discomfort comparable to a needle prick

Bone Marrow Aspiration risks: Risks of bone marrow aspiration include bleeding, and/or bruising after the procedure is completed. Also, soreness in the area may occur and last for a few days afterwards. Rarely an infection can develop.

Bone Marrow Biopsy risks: A bone marrow biopsy can be extremely painful. Individuals have reported a sharp pain or discomfort upon removal of the biopsy needle. A bone marrow biopsy may result in fainting, inflammation (irritation or infection) of the area surrounding the puncture site, bruising, or bleeding at the site of puncture. A few individuals have an allergy or a side effect from the pain or anti-anxiety medication, if given.

CT scan risks: If contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). Having a CT scan may mean some added

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discomfort. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time.

EKG (ECG) risks: Since EKG is done without entering the body and does not use dyes or x-rays, there is no pain or risk associated with having an EKG. Mild irritation, slight redness, and itching at the places on the skin where the recording patches are placed may occur. This skin irritation usually disappears when the patches are removed.

HIV testing risks: Being tested for HIV may cause anxiety regardless of the test results. Receiving positive results may make you very upset. If other people learn about the positive test results, you may have trouble obtaining insurance or employment.

IV inserted in the vein risks: Inserting a needle into a vein to inject medication may cause inflammation, pain, bruising, bleeding, or infection.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during the examination. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. The risks to a fetus from MRI are unknown; pregnant women cannot participate in this study.

Radiological risks: This study involves a radiation exposure from PET/CT scans, and x-rays from skeletal surveys that is higher than other diagnostic tests using ionizing radiation. The exposure to radiation from this procedure might result in a slight increase in cancer risk in normal healthy individuals. However, since you already have cancer, a risk estimate cannot be accurately determined.

Skeletal Survey Risks: The x-rays are painless. Changing positions for different x-ray views may be uncomfortable. The test will take about one hour.

Unknown Risks:
This research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may not benefit from taking part in this research. The information we get from this study may help us to learn more about this study treatment, and this may help future cancer patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your alternative is not to take part in this study. If you choose not to take part in this study, your future care will not be affected. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Participating in a different study, if available
- 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.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

This clinical study may only be performed by collecting and using your medical information. The medical information that will be collected from you if you participate in the study includes:

- Information used to determine your eligibility to participate in the study, including routine medical history, physical examination, x-rays, electrocardiogram, blood and urine tests, and CT and MRI scans.

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- Information that is created or collected from you during your participation in the study, including the results of the tests and procedures listed above and any other procedures performed during the study
- Information contained in your underlying medical records related to your medical history and treatment.

The above information may identify you by name, address, telephone number, social security number, health plan number, study number, date of birth, dates relating to various medical procedures, or other identifying information. In an effort to maintain confidentiality, your study records and samples (if sent outside the hospital) will be identified only by a number and initials. You will not be personally identified in any reports or publications that may result from this research study. Because of the research goals of this study, however, your study records cannot be kept absolutely confidential. The study personnel, Millennium, Celgene or its agents may need to review your medical records to make sure that the information recorded by the study staff is correct. In addition, in order to review the study findings, the Food and Drug Administration (FDA) and other regulatory agencies and the Institutional Review Board (IRB) may also need to review your medical records.

If you sign this form and participate in the study, the study personnel will be authorized to provide access to your medical records to the parties listed below. In addition, by signing this form you are authorizing the study personnel to use the information described above to carry out the purposes of the research study and to disclose that information to the parties listed below for their use in carrying out the purposes of the study. If you choose not to authorize these uses and disclosures of your information, you will not be able to participate in the study.

- The investigators involved in the conduct of this study and their designees
- The UC Davis Comprehensive Cancer Center's Data and Safety Monitoring Committee
- The Food and Drug Administration (FDA)
- The UC Davis Institutional Review Board (IRB)
- The pharmaceutical company that is providing MLN9708 (Millennium Pharmaceuticals: A Takeda Oncology Company)
- Celgene Corporation, correlative research funding

Once your information is disclosed to Millennium, Celgene, the IRB/IEC or government agencies as described above, there is a potential that your medical information will be re-disclosed and will no longer be protected by United States federal privacy regulations. The laws of your state may provide further protection.

Your access to your underlying medical records will not be affected by the study. You have the right to see and copy the medical information collected from you in the course of the study for as long as that information is maintained by the study personnel and other entities subject to federal privacy regulation.

You may revoke your authorization at any time by sending a written request to Joseph Tuscano, MD at UC Davis Cancer Center. If you revoke your authorization, your participation in the study will end and the study personnel will stop collecting medical information from you. In addition, study personnel will stop using your information and will stop disclosing your information to the parties described above, except to the extent study personnel have relied on information that has already been collected from you. For example, the study personnel may need to use or disclose information obtained before you revoked your authorization in order to preserve the scientific integrity of the study.

If you agree to participate in this research study, a signed copy of this consent document and the privacy authorization form may be filed in your electronic medical record (EMR) and your study participation may be added to your EMR. This information will be used for your care and treatment and for healthcare operations, which may include billing and payment. Federal and state privacy laws give patients the right to access information about their care and treatment contained in their medical record. During this study, you may not be able to access certain information related to this study in your EMR until the study is complete to ensure that the study remains unbiased. If necessary for your care, this information will be provided to you or your physician.

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 study results. You can search this Web site at any time.

You will be asked to sign a separate form to give your permission for us to access protected health information (e.g., your medical record).

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WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you promptly tell the person in charge of this research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or may be billed to your insurance company just like other medical costs. The University does not normally provide any other form of compensation for injury. For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at hs-IRBAdmin@ucdavis.edu.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Millennium Pharmaceuticals: A Takeda Oncology Company will provide ixazomib free of charge for this study. Every effort will be made to ensure adequate supplies of ixazomib for all participants. If ixazomib becomes commercially available for this indication, you may be asked to purchase subsequent supplies.

There will be no charge to you or your insurance company for processing the research blood draws or research studies on your tumor biopsy tissue and blood tests. Celgene will provide funding for the peripheral blood for correlative studies. They will be paid for by the study. However, if the specimens are obtained during a standard diagnostic procedure, that procedure will be charged to you or you insurance company in the usual way.

Dexamethasone, pomalidomide, and clarithromycin are commercially available and will be billed to you and/or your insurance company.

You or your insurance carrier will be responsible for the associated costs of the study including, but not limited to, the costs of the dexamethasone, pomalidomide, and clarithromycin, all routine laboratory tests, x-rays, scans, clinic visits or hospital stays. However, you or your insurance carrier will not be asked to bear the cost of any tests or procedures done solely for research purposes.

Whenever possible, pre-authorization will be obtained. If the costs are not covered, these costs will be discussed prior to proceeding with the study.

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

WILL I BE COMPENSATED FOR BEING IN THIS STUDY?

You will not be compensated for your participation in this study.

Your participation in this research study may contribute to the development of commercial products from which Millennium Pharmaceuticals, Inc. or others, may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

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 willingness to continue in the study.

DOES THE RESEARCHER HAVE A FINANCIAL INTEREST IN THIS RESEARCH STUDY?

The Principal Investigator does not have any personal or financial interest in this study.

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WILL SPECIMENS (tissue, blood, urine or other body materials) TAKEN FROM ME BE USED FOR FUTURE RESEARCH PURPOSES?

You have had a biopsy to see if you have cancer. Your doctor removed some body tissue to do some tests. The results of these tests were given to you by your doctor and are being used to plan your care.

We would like to keep some of the biopsy and blood sample that is left for correlative studies for future research purposes. Your specimen(s) will only be used for research purposes. If you agree, these specimen(s) will be kept and used to learn more about your disease as well as other diseases.

The research that may be done with your specimen(s) will not benefit you directly nor have an effect on your care. It might help people who have your disease and other diseases in the future. Any reports about the research, done with your specimen(s), will not be shared with you or your doctor and the reports will not be put in your health record.

Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. To help protect your privacy, people outside the research process will not have access to results about any one person.

The benefits of research using specimens include learning more about what causes diseases, how to prevent them, how to treat them, and how to cure them. There are very few risks to you. The greatest risk is the release of information from your health records which may be necessary for us to obtain along with your specimens. We will protect your records so that your name, address, and phone number will be kept private.

WILL SPECIMENS (tissue, blood, urine or other body materials) TAKEN FROM ME BE USED FOR FUTURE RESEARCH PURPOSES? (continued)

Your samples will be kept at UC Davis indefinitely unless you decide to withdraw your permission for the use of your samples, in which case your samples will be destroyed.

May I Change My Mind About the Use of My Samples?

Yes. You may change your mind at any time. If you want to withdraw your consent for the use of your samples during the study, tell your study doctor that you no longer want your samples stored or used for research. If you want to withdraw your consent after the close of the study, follow the instructions provided to you by the study doctor. Then, any samples that remain will be destroyed. If you change your mind and your samples have already been tested, those results will still remain as part of the overall research data. In the event of your death or loss of competence, your specimens and data will continue to be used. If you withdraw or discontinue from the main study, your samples will continue to be stored and used for research unless you specifically ask that they be destroyed.

Bio-specimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

Please read each question below and think about your choice. After reading each question, initial next to "YES" or "NO". If you have any questions, please discuss this with the researcher.

My tissue and blood may be kept for use in future research: YES_____ NO_____

Someone may contact me in the future to ask me to use my specimens in future research: YES_____ NO_____

For further information on the use of specimens for future research purposes and your rights as a research participant, please visit: http://research.ucdavis.edu/IRBAdmin/Participants.

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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/

VOLUNTARY CONSENT:

My signature below will indicate that I have decided to participate in this study as a research subject. I have read and understand the information above. I understand that I will be given a signed and dated copy of this consent form and the Bill of Rights.

Signature of Subject	Printed Name of Subject	Date

Signature of Person Obtaining Consent	Printed Name of Person Obtaining Consent	Date

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SIGN BELOW ONLY IF A WITNESS WILL OBSERVE THE CONSENT PROCESS (for use with IRB "Short Form")

Signature of Witness to Consent Process	Printed Name of Witness	Date

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