PRINCIPAL INVESTIGATOR: Kathryn Lurain, M.D.

STUDY TITLE: Phase I/II Study of Lenalidomide Combined with Modified DA-EPOCH and Rituximab (EPOCH-R^2) in Primary Effusion Lymphoma or KSHV-associated Large Cell Lymphoma

STUDY SITE: NIH Clinical Center

Cohort: Standard

Consent Version: 06/06/2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

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

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

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

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

This study is being performed to evaluate a new treatment for aggressive B cell lymphomas caused by Kaposi sarcoma herpesvirus (KSHV). These lymphomas include primary effusion lymphoma

(PEL) or a related cancer, Kaposi sarcoma-associated herpesvirus (KSHV) -associated large cell lymphoma, which are rare diseases with no standard therapy. Given their similarities, we will refer to both types of lymphoma as PEL. This study is divided into two parts. In part 1, or phase 1, we will test the safety of the combination chemotherapy regimen DA-EPOCH-R, which refers to dose adjusted etoposide (E), prednisone (P), vincristine (O), cyclophosphamide (C), doxorubicin (H), rituximab (R) and lenalidomide (brand name Revlimid (R)). DA-EPOCH-R (i.e., the study regimen without lenalidomide) is commonly used for the treatment of other aggressive lymphomas, including lymphomas occurring in people with HIV. The addition of lenalidomide to DA-EPOCH-R, which has been approved by the FDA for the treatment of multiple myeloma, is being tested in this study to see if it can be combined safely with DA-EPOCH-R in PEL. Data from the laboratory show that lenalidomide may be effective in treating PEL.

During the Phase I portion of the study, different doses of lenalidomide will be evaluated in combination with the DA-EPOCH-R chemotherapy regimen to see which lenalidomide dose is best in this combination for treating people with PEL. The 6 drugs in DA-EPOCH-R have been approved by the FDA for the treatment of cancer; however, the combination of the drugs in DA-EPOCH-R has not been approved specifically in this combination with lenalidomide.

In the second part, or phase 2, which will be performed after Phase I has been completed, we will treat additional patients with the DA-EPOCH-R using the dose of lenalidomide identified in Part 1 to get a better idea of how patients with PEL do in the long run after receiving DA-EPOCH-R chemotherapy.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have PEL.

How many people will take part in this study?

Up to 36 participants will take part in this study. Of these, up to 18 will be part of the dose finding portion of the study; up to an additional 18 participants will be enrolled once the highest safe dose has been found.

Before you begin the study

Before you can enroll on the study, you will have standard tests and procedures such as blood tests, imaging studies and physical exam to be certain you are eligible to be in the study. These tests will be described in a separate consent.

Description of Research Study

If you are eligible and consent to participate in this study, you will undergo tests to determine the stage, or extent, of your disease. Some participants may have additional KSHV associated tumors, such as Kaposi sarcoma (KS) or multicentric Castleman disease (MCD), and if your doctor determines you have one or both of these conditions, they will be evaluated as well. Staging tests that are part of routine medical care will include blood tests, body scans, magnetic resonance imaging (MRI) of your head, a lumbar puncture (also known as a spinal tap), and a bone marrow biopsy. Some participants may require additional skin or lymph node biopsies to evaluate for KS or KSHV-associated MCD. Some participants may have fluid around their lungs, intestines, or

heart; these are called effusions. If you have an effusion, you will undergo a special procedure to remove the effusions for special studies and to help you feel better. In some cases, a small rubber tube called a catheter may be placed so that we can drain your effusion from time to time until they improve with treatment. Additional descriptions of the different tests and procedures that will be performed on this study are noted below.

Once we have determined the extent and severity of your lymphoma, you will start by taking a pill called lenalidomide alone for 10 days.

After the first 5 days of lenalidomide, you will go on to receive the combination of medications called DA-EPOCH-R, which is given as follows: the drug rituximab or a biosimilar drug will be given by IV infusion on the first day of DA-EPOCH-R combination over several hours. (During the first cycle only, rituximab is given after 3 days of lenalidomide). A biosimilar drug is very similar to another drug (called a reference drug) that has already approved by the FDA and is shown to be as safe as, work as well as, and work in the same way as the reference drug. The rituximab biosimilar drug has been shown by the FDA to have no clinically meaningful difference. (We will refer to rituximab or its biosimilars as "rituximab" for the remainder of this consent). When the rituximab IV infusion is complete, the drugs doxorubicin, etoposide, and vincristine will each be given by continuous IV infusion over the next 4 days (that is, continuously for a total of 96 hours). Cyclophosphamide will be given by IV infusion on Day 10 after you have received the previous chemotherapy drugs. Prednisone and lenalidomide will be given by mouth on each day for 5 days. The DA-EPOCH-R therapy will be repeated every twenty-one (21) days, which is known as a "cycle" of therapy. Most people will receive a total of 6 cycles of treatment.

IV drugs on this study will be given through a "central line", a catheter (or tube) placed in the large vein in the arm or in your chest. We usually remove the catheter after each cycle but on occasion it can be left in for several cycles.

We will provide you with a pill diary to record the times that you take lenalidomide at home and any side effects that you experience. Please make sure that you bring the diary with you at each visit.

You will receive the drug filgrastim or a biosimilar drug by subcutaneous (under the skin) injection starting on Day 11 of each combination therapy cycle to increase white blood cell counts. The filgrastim biosimilar drug has been shown by the FDA to have no clinically meaningful difference. (We will refer to filgrastim or its biosimilars as "filgrastim' for the remainder of this consent). Filgrastim will be continued until your white blood counts have reached acceptable levels. The dose of doxorubicin, etoposide, and/or cyclophosphamide may be "adjusted" up or down each cycle depending on your white blood cell count (WBC) and/or platelet count.

To reduce the risk of the lymphoma spreading to your central nervous system (CNS), you will also receive eight doses of a drug known as methotrexate injected into the spinal fluid. You will receive this treatment on Days 1 and 5 of cycles 3-6 of combination therapy.

Participants who have HIV will usually be kept on HIV medications, although your study doctor may need to change the antiretroviral pills you take to make sure that they do not increase the risk of side effects from chemotherapy. Participants will also need to take aspirin or a blood thinner to prevent blood clots while they are taking lenalidomide.

Tests performed during the study

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following tests and procedures. Some of the tests are done to check for side effects and to see how your disease is responding to the study drugs. Other tests are done for research. Risks for the research procedures are discussed in the section on Procedure Risks.

Clinical and Safety Testing

These tests will be done at least once during every cycle during all parts of the study. An asterisk indicates that they may be done more often than that during some cycles (up to 4 times).

- Medical history and physical examination*
- Routine blood tests*
- Urine tests (including 24-hour urine collection)
- Pregnancy test (if you are a female who can have children)
- Testing of stool for blood
- Blood tests to determine levels of certain viruses if it is shown at screening that you are positive (EBV, HIV, HBV, HCV, CMV)
- Photography and measurement of KS lesions, if you have KS
- Lumbar puncture (spinal tap). This collection of fluid from the area around your spinal cord will only occur on cycles when you receive methotrexate. Fluid collected from this procedure will also be used in research testing.

These tests are done once during the study before you have taken any study drug

- Bone marrow biopsy. This test will be done at the same time as the bone marrow aspiration for research. Please see description below in the Procedure Risks portion of the consent.
- Pulmonary function tests. These tests, which usually involve deep inhalation and exhalation, determine how well your lungs work.
- Bronchoscopy/Endoscopy (only if your chest x ray or stool tests are abnormal). These tests involve the use to flexible tubes with cameras attached to help us view your airways (bronchoscopy) or your digestive tract (endoscopy).
- Eye Examination. This test may involve dilation of your pupils which may cause you to be sensitive to light for the rest of the day.

Research Evaluations

Research testing will be done on your blood, pleural effusion fluid, CSF, saliva and lung cells to help us determine how your body processes lenalidomide when given alone and as part of DA-EPOCH-R, the effects of the drugs on your body, how your immune system is responding to therapy, the level of various viruses in your body fluids, and testing to see whether you have any genes that are associated with how your body processes medications. These genes account for only a small portion of your DNA, and are not known to cause disease. Testing for them will not be enough to allow anyone to identify you based on your DNA.

These tests will be done at least once during every cycle during all parts of the study. An asterisk indicates that they may be done more often than that during some cycles (up to 2 times).

- Blood for research tests*
- Testing of pleural effusion fluids*
- Saliva collection

These tests are done once during the study before you have taken any study drug at the same time they are being done for medical reasons:

- Bone marrow aspiration
- Bronchoalveolar lavage (fluid taking from the lung during bronchoscopy only in patients with significant lung disease noted during the staging evaluation)

When you are finished taking the drugs

After you have completed your study therapy, your doctor will continue to watch you for side effects and follow your condition every three months for one year and then every 3 – 6 months for four years. The following will be performed at each follow up visit:

Clinical Evaluations

- History and physical exam (including assessment of your disease symptoms)
- Routine blood tests
- Urinalysis
- Viral levels
- Testing of stool for blood (only if results were positive while on study therapy)
- CT Scan of neck, chest, abdomen and pelvis
- FDG PET Scan

After this period is over, we may contact you yearly by telephone to see how you are doing.

Risks or Discomforts of Participation

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

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

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

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

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

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

Risks and discomforts of Lenalidomide

Very common (occurring in ≥ 10% of patients)
• Fatigue or feeling tired • Low blood pressure • Anemia or a decrease in red blood cells that can cause tiredness • Decrease in white blood cells with or without fever that can make you more prone to infections (leukopenia, neutropenia, febrile neutropenia, granulocytopenia, lymphopenia) • Thrombocytopenia or a decrease in platelets which can cause you to bruise or bleed easily • Pulmonary embolism (a sudden blockage of a blood vessel in the lung) • Constipation or difficulty moving your bowels • Diarrhea or loose/frequent bowel movements • Heartburn • Nausea and vomiting • Gastroenteritis (inflammation of the stomach and intestines) • Loss of appetite; weight loss • Dehydration • Abdominal and stomach pain • Back, bone, joint, arm, legs, and muscle pain • Muscle spasms • Muscle weakness • Swelling (including arms and legs) • Neuropathy (weakness, numbness, tingling and pain including in the hands and feet); • Abnormal touch sensation, such as burning or prickling • Depression; difficulty sleeping or staying asleep • Chills; fever • Flu • Dry mouth • Nasopharyngitis (inflammation of the nasal passages and throat) • Nose bleeds • Sore throat • Cough

Very common (occurring in ≥ 10% of patients)
• Shortness of breath or difficulty catching your breath • Upper respiratory tract infection; bronchitis, pneumonia • Itching, dry skin, rash • Lack or loss of strength; dizziness • Headache • Inflammation of the mouth • Abnormal liver function tests • Urinary tract infection • Elevated or reduced blood sugar • Reduced blood calcium, sodium, potassium • Kidney problems, including kidney failure. Signs of kidney problems may include decrease in the amount of urine, blood in your urine, ankle swelling • Blood clot which may cause swelling, pain, shortness of breath • Blurred vision; cloudiness of the eye (cataract) • Progression of the disease being studied • Change in taste • Tremors (shaking movements)

Common (occurring in ≥ 1% and < 10 % of patients)
• Hemolytic anemia (blood condition that occurs when your red blood cells are destroyed faster than they can be replaced) • Pancytopenia (low levels of all types of blood cells – white blood cells, red blood cells and platelets) • Temporary loss of consciousness • Mood disorder • Abnormal heart rhythm (atrial fibrillation, tachycardia) • Heart failure • Myocardial ischemia (lack of blood flow getting to your heart), which can lead to serious damage to heart muscle (heart attack) • Throat pain • Upper abdominal pain • High blood pressure • Sepsis or an infection of the blood • Joint infection • Lung problems (lung infection, lower respiratory tract infection, respiratory distress) - symptoms may include new or worsening cough, chest pain, shortness of breath, rapid breathing • Herpes simplex and zoster (shingles), including ophthalmic herpes zoster (shingles of the face and eyes)

- Meningitis (inflammation of the protective membranes covering the brain and spinal cord)
- Kidney injury
- Liver disease which may cause yellowing of eyes and skin, itching, dark urine, abdominal pain
- Blood clots
- Gastrointestinal bleeding
- Small intestine blockage
- Infection of the colon
- Inflammation of the blood vessels
- Chest pain
- Skin infection – skin may be swollen red, painful, warm
- Diabetes (high blood sugar)
- Elevated blood calcium
- Elevated uric acid in the blood (gout)
- Excess stores of iron in the body
- Loss of balance; increased risks of falls
- Bruising
- Redness of the skin
- Toothache
- Low phosphate in the blood
- Low magnesium in the blood
- Neck pain
- Secondary primary blood and skin cancers (when another cancer, other than PEL, occurs)
- Loss of blood flow to part of the brain
- Altered sense of touch
- Drowsiness and an unusual lack of energy and mental alertness
- Nerve pain
- Abnormal voice
- Hypoxia, which is low oxygen in the blood
- Increased sweating; night sweats
- Tumor lysis syndrome: a metabolic complication that can occur during or without treatment of cancer. These complications are caused by the break-down products of dying cancer cells and include high potassium, high phosphorus, high uric acid in blood and urine, low calcium, and consequent kidney damage.

Uncommon (occurring in ≥ 0.1% and < 1% of patients)

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- Appendicitis
- Pyelonephritis (kidney infection
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): severe, adverse,

delayed hypersensitivity drug reactions causing rash and facial swelling. DRESS can progress to severely affect organs, most often the liver, kidneys, lungs and heart.
- Inflammation of the colon caused by the bacteria, clostridium difficile – signs may include watery diarrhea, fever, loss of appetite, nausea, pain, tiredness
- Infective bursitis (infection of a fluid-filled sac that cushions a join)
- Worsening of Chronic Obstructive Pulmonary Disease (COPD) symptoms

Rare (occurring in ≥ 0.01% and < 0.1% of patients)

- Angioedema or an allergic skin disease characterized by patches of swelling involving the skin and/or the lining of your nose, mouth, and gastrointestinal tract
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to detachment of the top layer of skin (could be body- wide).
- Rhabdomyolysis: a serious condition involving destruction of skeletal muscle that can lead to kidney failure. Signs and symptoms include dark, red or cola colored urine, muscle tenderness and stiffness, aching (myalgia) or weakness.
- Anaphylaxis (a severe allergic reaction that can lead to low blood pressure, breathing difficulty, and rapid heartbeat)

Risks and discomforts of Rituximab

Common, some may be serious (Occurring in 20% -100% of patients)

- Nausea
- Reaction during or following infusion of the drug (Reactions may include fever, chills, nausea, itching, rash, swelling of the hands, feet or face, low blood pressure, dizziness, headache and difficulty breathing. Reactions can be treated, and are usually temporary.)
- Infection, especially when white blood cell count is low
- Numbness and tingling of the arms and legs
- Tiredness

Occasional, some may be serious (Occurring in 4% -20% of patients)

- Anemia which may require blood transfusions
- Bruising, bleeding
- Abnormal heartbeat
- Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Sores in eye
- A tear or a hole in the stomach that may require surgery
- Diarrhea, vomiting
- Pain
- Swelling of the body

Occasional, some may be serious (Occurring in 4% -20% of patients)
• Hepatitis which may cause yellow eyes and skin • Dizziness, headache • Kidney damage which may require dialysis • Cough • Scarring of the lungs • Stuffy nose • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

Rare, but serious (< 3% of patients)
• Damage to the brain which may cause changes in thinking • Heart stops beating

Risks and discomforts of DA-EPOCH

Likely:	
• Lowered white blood cell count that may lead to infection. • Lowered platelets which may lead to an increase in bruising or bleeding. • Lowered red blood cells which may cause anemia, tiredness, or shortness of breath. • Should low counts occur, they can be treated with blood products (transfusions), antibiotics, and there may be a reduction in the amount of drug given to you. • Constipation.	• Fatigue or tiredness. Tingling of fingers and/or toes. • Hair loss. • Fever and/or chills. • Urine colored red for a day or two after the doxorubicin infusion. • Fingernail and toenail changes. • Tearing or dry eyes. • Runny nose. • Bony pain.

Less Likely:	
• Nausea and/or vomiting. • Loss of appetite, change in taste and weight loss. • Temporary shortness of breath or dizziness while receiving rituximab. • Headaches. • Muscle aches and muscle weakness. • Hoarseness or pain in the jaw. • Elevated blood sugar levels. • Elevated or decreased blood pressure. • Confusion.	• Mouth & throat sores. Temporary irritation to the mouth may lead to mouth ulcers (similar to canker sores). Medications to numb the mouth may ease the mouth discomfort. • Stomach ulcers. • Skin rashes and/or dry skin. • Loss of control of muscles or reflexes. • Abnormalities in blood results such as elevated liver enzymes, low blood protein and low blood calcium. • Mood changes such as agitation or depression. • Trouble sleeping.

Rare, but serious:	
• Severe constipation may result in abdominal pain and cramping. • A tear in the large or small bowel • Bladder irritation with painful and bloody urine. • Damage to the heart muscle. • Skin rash that may be serious and life-threatening. • Allergic reaction that may be severe or life-threatening. Symptoms may include difficulty breathing, low blood pressure, fast heart rate, and sweating. • Severe neutropenia and associated infections have previously resulted in death in EPOCH-R regimens.	• Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Patients who may have had prior exposure to the hepatitis B and C virus may be at an increased risk of recurrence of the virus that may lead to severe liver damage that can be life-threatening. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection, and you will be treated, if appropriate, by your doctor.

Risks and Discomforts of Filgrastim

Common, some may be serious (Occurring in 20% -100% of patients)
• Nausea, vomiting • Pain in bone

Occasional, some may be serious (Occurring in 4% -20% of patients)
• Anemia which may cause tiredness, or may require transfusion • Damage to the lungs which may cause shortness of breath • Internal bleeding which may cause coughing up blood • Swelling or tenderness of vessels

Rare, but serious (< 3% of patients)
• Rupture of the spleen leading to bleeding in the belly

Procedure Risks

Saliva Collection

You will be asked to rinse with mouthwash and then provide your spit in a special container. Your saliva will be tested for the amount of KSHV present. There are no physical risks associated with saliva collection.

Blood sampling

Taking blood may cause some discomfort, bleeding or bruising where the needle enters the body, and in rare cases, it may result in fainting. There is a small risk of infection. Some people have not felt well when having their blood taken. Some people have felt dizzy while having their blood drawn or after. Let the nurse know if you would prefer to lie down while you have your blood drawn. Up to 9 ½ tablespoons of research blood may be collected at any visit but no more than 37 tablespoons in an 8 week period.

Urine collection

No physical risks are associated with urine collection.

Stool collection

No physical risks are associated with stool collection.

Electrocardiogram

Some skin irritation can occur where the ECG/EKG electrodes are placed. The test is completely painless, and generally takes less than a minute to perform.

Echocardiogram

There is no physical risk involved with echocardiogram. Side effects of an echocardiogram are discomfort from the transducer being firmly placed against the chest.

Eye exam

Eye exams can be uncomfortable but usually safe for most people. Risks of complication may include rare reactions to eye drops that may cause dry mouth, flushing, dizziness, nausea, vomiting, or narrow-angle glaucoma.

Pulmonary function tests (PFTs)

Pulmonary function tests (PFTs) are a group of tests that measure how well your lungs work. This includes how well you're able to breathe and how effective your lungs are able to bring oxygen to the rest of your body. PFTs are usually safe for most people. However, because the test may require you to breathe in and out quickly, you may feel dizzy and there's a risk that you may faint. If you have asthma, the test may cause you to have an asthma attack. In very rare cases, PFTs may cause a collapsed lung.

Endoscopy/bronchoscopy

Risks of endoscopy include infection, bleeding, or perforation of the duodenum, esophagus, or stomach.

Risks of bronchoscopy include bleeding, infection, bronchial perforation, bronchospasm (tightening of your airways in your lungs), laryngospasm (closure of the vocal cords), lung collapse.

Bronchoalveolar lavage

This procedure is done during a bronchoscopy if you have abnormalities noted in your lungs. Bronchoalveolar lavage is a way to collect fluid and collect cells from your lungs to look for infections or evidence of cancer in your lungs. A flexible tube with a camera at the end (bronchoscope) will then be passed through your mouth or nose down into your lungs. In some cases, the doctor doing this procedure may be able to see KS in your lungs. Fluid is squirted into a small part of the lung and immediately suctioned out, washing off cells lining the airways. The collected fluid will be tested for infections and evaluated for cancer.

The procedure may involve some discomfort as the tube is inserted, but we will numb your nose and throat with lidocaine or similar drug and give you a sedative to make it as comfortable as possible for you. Beyond discomfort, there are very few side effects related to this procedure. In rare instances, patients have developed cough, temporary chills, fevers and muscle aches and a temporary decrease in lung function.

Effusion collection

Fluid in the space around your lungs (pleural effusions), intestines (peritoneal effusion) or heart (pericardial effusion) will be collected so that we may determine the presence of viruses and immune cells present. If there is fluid present, a needle or plastic tube will be inserted into the space and the fluid will be drawn out. In some cases, a temporary tube will be left in place so that fluid can be drained again without repeating.

There may be pain, bleeding, bruising in the area where the needle or tube was inserted. Your doctor may give you a numbing medicine to reduce the pain before inserting the needle/tube. On rare occasions, bleeding may occur in or around the organ sampled. In the case of fluid around the lungs, it is also possible that the needle makes a hole in the lungs. The hole usually seals itself, but the lung may collapse and your doctor may have to insert another tube to reinflate your lungs.

Bone marrow biopsy and aspiration

This involves inserting a needle into a large bone such as the pelvis and removing a small amount of bone marrow fluid (aspiration) and a sample of solid bone marrow tissue (biopsy). The aspiration is usually performed first with a smaller needle than is used in the biopsy.

A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow aspiration/biopsy. The needle will go through the skin into the bone and may produce a brief, sharp pain. As the sample is taken from the bone, there may be a brief, sharp pain. This procedure may cause some discomfort, however not all participants experience discomfort.

The possible side effects associated with a bone marrow aspiration/biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.

Lumbar puncture

The lumbar puncture (LP) may cause pain at the site where the needle goes in and the spinal fluid is taken. There is a small risk of infection or bleeding. After the LP you may get a headache. About a third of adults report a headache after an LP. To minimize the risk of a headache, the doctor will use a small needle and may prescribe bed rest for one or more hours after the procedure. If a headache occurs, it is usually mild and can be controlled by bed rest, drinking lots of fluids and a pain pill, such as acetaminophen. Rarely, the headache is severe and may require additional treatment with a "blood patch". In this procedure, a small amount of your own blood is injected into the lumbar puncture site. This procedure is generally effective in stopping the headache. A rare but serious complication of a LP, if it is done when the pressure inside the head is higher than normal (such as when a brain tumor is present), is known as medullary herniation which can result in death. Increased intracranial pressure is very unlikely to be present. The LP will not be done if there are any clinical indications that you have increased intracranial pressure, a skin infection in the lower back area, or bone malformation of the lower back (including severe scoliosis) which would make a LP difficult.

Local Anesthesia

Potential side effects include drowsiness, headaches, blurred vision, twitching muscles or shivering, continuing numbness, weakness, or pins and needles sensation. These side effects usually go away quickly.

Conscious sedation

You may receive conscious sedation before undergoing a biopsy and you will be informed of the additional risks prior to undergoing the procedure. Conscious sedation is usually given to help someone relax and minimize discomfort. It can be given as a pill, a shot, an IV or even inhaled. You may have to wait up to an hour to start feel the effects depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. You will be monitored throughout the procedure.

Risks: If received, the most common risks of conscious sedation last up to a few hours after being given can include drowsiness, feeling slow or sluggish, low blood pressure, headache, and nausea.

Imaging

You may receive a contrast agent injected into your arm as part of your scan. Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives but can also result in a serious life-threatening emergency from difficulty breathing. If this occurs, it is treatable. You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach. Please ask the study doctor if you have questions about the risks of these scans.

MRI

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

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

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

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

Risks from gadolinium

During part of the MRI you may receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for both research and medical purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000

people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body.

Ultrasound

The ultrasound procedure will take about 15- 30 minutes. Ultrasound has extremely minimal risk with no use of ionizing radiation or adverse heating or pressure effects in tissue in the way that it is being utilized.

Medical photography

Every effort will be made not to include identifying features (such as your eyes or face) in the photographs, but complete anonymity may not be possible. The photographs taken may be used in presentations and publications about the study.

What are the risks of radiation from being in the study?

During your participation in this research study, you may be exposed to radiation from up to 3 CT scans, up to 4 FDG PET/CT scans, up to 3 chest x-ray/year. The amount of radiation exposure from these procedures is equal to approximately 8.73 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The scans that you get in this study will expose you to the roughly the same amount of radiation as 97 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.9 out of 100 (0.9%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

Reproductive Risks

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

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

Precautions

Birth Control

Female Participants

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how the study regimen would affect your baby or your unborn child. If you are a woman who can become pregnant, you will need to practice complete abstinence or use two reliable forms of birth control for at least 28 days before starting study treatment, during study treatment including during dose interruptions, and for at least 28 days after you finish study treatment. The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. **If you think that you are pregnant, you should tell your study doctor or nurse at once.**

Highly effective methods:

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

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

* 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 therapies.

Male participants

If you are man, you must agree to complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female who can become pregnant while participating in the

study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy. **If you think that your partner is pregnant, you should tell your study doctor or nurse at once.**

Additional Important Precautions

Handling of Lenalidomide

Other than the participant, females who are able to become pregnant and males who are able to father a child, should not touch or handle the lenalidomide capsules or the powder they contain.

- We do not know if lenalidomide 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 sperm while taking lenalidomide (even if you temporarily stop your medication) for at least 1 week after the last dose of lenalidomide.

Medication History

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.

Supportive Care

Your health care team will provide care to help lessen side effects. This may include medications to help soften your stool, medications (such as aspirin, enoxaparin or heparin) to help prevent blood clots, medications to treat/prevent various types of viral, bacterial and fungal infections, blood transfusions if needed. You may also be provided with nutritional counseling and support.

Potential Benefits of Participation

The aim of this study is to see how this experimental treatment affects survival in participants with your disease as well as to see how safe the experimental treatment is. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

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

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the

cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

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

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

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

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

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

Conflict of Interest

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

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

The National Institutes of Health and the research team for this study are using lenalidomide developed by Celgene Corporation through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply

to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

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

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

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

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

You will not receive compensation for participation in this study.

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

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

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

Will taking part in this research study cost you anything?

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

If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

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

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

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

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

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

POLICY REGARDING RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Kathryn Lurain, MD, Kathryn.lurain@nih.gov at 301-250-5156. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

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

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking participant or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate participant**

Signature of Witness	Print Name of Witness	Date

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

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

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