Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

You are being asked to take part in this study because you have asymptomatic high-risk smoldering multiple myeloma.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time when making your decision, and discuss it with your friends and family.

WHY IS THIS STUDY BEING DONE?

This research study is being done because there is no current therapy proven to benefit patients with high-risk asymptomatic myeloma, a type of blood cell cancer that has not yet damaged body tissue and organs to the point where symptoms are noticeable. These patients are not treated unless their disease progresses to symptomatic myeloma.

The purpose of this study is to find out what effects (good and bad) the use of the drug lenalidomide has on you and your multiple myeloma, and to compare this with patients that receive no therapy. Currently, the accepted treatment for asymptomatic myeloma is to receive no therapy. However, not all patients with asymptomatic (smoldering) myeloma have the same outcome. There are 3 groups of patients as identified by the Mayo clinic group that have different predicted outcomes. Because the 3 groups can have very long delays between the identification of smoldering myeloma and the requirement for treatment, not all patients are eligible for this study. Only patients with ”high-risk” smoldering myeloma are considered eligible for this study as these are all patients whose risk of developing myeloma that requires therapy is the highest.

Lenalidomide is a drug that has shown benefit and is approved for use in patients whose myeloma has been resistant to other therapies. The mechanism by which lenalidomide works in myeloma is still unclear, but it is felt that the drug works by making your own immune system (your body’s natural defense against disease) work better against the myeloma cells. It may also have additional direct effects on the myeloma cells. Though lenalidomide is an approved drug for symptomatic myeloma and myelodysplastic syndrome (diseases of blood and bone), it is experimental for the asymptomatic patients who will participate in this study.

One recent trial suggests that early therapy of smoldering myeloma with lenalidomide and dexamethasone may prolong survival. However, additional data are needed to be definitive, and some methods of risk evaluation used in that trial are not widely available. The relative value of lenalidomide and dexamethasone is also not clear.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 224 people will take part in this study.

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

This study will compare the results of patients given a standard dose of lenalidomide with patients who undergo observation (no treatment). The first 44 patients to register to the study will be placed on “Arm A” (Phase II) and will receive treatment with lenalidomide.

After the phase II portion has ended, the phase III portion will begin and new patients will be selected to receive one of two treatments, “Arm A,” lenalidomide, or “Arm B,” observation. The treatment “arm” you are put on will be decided randomly. You and your doctor will NOT be able to choose which treatment you receive.

If you take part in this study, you will have the following tests and procedures. Some of these tests would be done even if you do not take part in the study.

Tests

- Blood tests
- Urine tests
- Bone marrow biopsy
- X-rays
- Electrocardiograms
- MRI (Magnetic Resonance Imaging, like a type of highly detailed x-ray) scans will be performed on all patients before they begin treatment or observation as part of the research to see if this test helps predict clinical outcomes in patients with asymptomatic myeloma. MRI tests are recommended as a part of standard clinical care. Some people feel claustrophobia or discomfort for a short period of time during the procedure.

While you are receiving treatment, your blood and urine tests will be repeated once a month to assess the effect of treatment on your myeloma.

While on this study, you will be required to keep a pill diary.

Procedures

Arm A: If you are assigned to Arm A, you will be treated with lenalidomide. You will take 25 mg of lenalidomide once a day by mouth for 21 days (days 1-21), followed by a week off with no lenalidomide (days 22-28). This 28-day period is considered "one cycle." If there are no

signs to suggest worsening of your myeloma, you will receive treatment until the drug is no longer working.

Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew, or open the capsules.

If you miss a dose of lenalidomide, take it as soon as you remember on the same day. If you miss taking your dose for the entire day, take your regular dose the next scheduled day (do NOT take double your regular dose to make up for the missed dose).

If you take more than the prescribed dose of lenalidomide you should seek emergency medical care if needed and contact study staff immediately.

Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

Only enough lenalidomide for one cycle of therapy will be supplied to you each cycle.

You will also receive one aspirin per day while receiving this treatment to prevent complications known to be caused by both your myeloma and the treatment drug. Specifically, these complications involve blood clots in the legs and lungs. **If you notice swelling in your legs, contact your doctor immediately.** Your doctor may choose to use other drugs to prevent these complications instead of aspirin. Aspirin may cause irritation of the stomach wall and should not be taken on an empty stomach.

Arm B: Currently, the standard of care for patients with asymptomatic myeloma is to be closely monitored and receive no treatment until symptoms that are caused by myeloma begin to develop. If you are assigned to Arm B, you will not receive lenalidomide, and will instead be monitored more closely than what is considered standard.

Both Arms: Patients on Arm A and Arm B will be required to complete a Quality of Life (QOL) assessment before starting treatment or observation and every 6 cycles until cycle 48. QOL will also be assessed at the end of treatment or observation. Patients on both Arm A and Arm B will complete the QOL assessment in the same way and on the same schedule.

HOW LONG WILL I BE IN THE STUDY?

If you agree to take part in this study and are randomized to receive lenalidomide treatment, you will be on the study treatment for as long as your disease does not progress; possibly for two years or more. If you don't have serious side effects and your disease does not show signs of worsening, you may continue treatment at the discretion of your treating physician. Alternatively, you may be on the study treatment for less than 4 months if your multiple myeloma worsens and you begin to develop symptoms caused by your myeloma or you have serious side effects. Regardless of which arm of the study you are on, once you complete the study, we would like to keep track of your medical condition for 10 years to look at the long-term effects of the study.

Your doctor may decide to take you off this study treatment if you have excessive side effects, if your condition worsens, if new information becomes available that may affect your decision to continue your participation, or for any reason felt to be in your best interests.

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?

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

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

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

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

Here are important points about side effects:

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

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

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

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

Risks and side effects related to the lenalidomide include:

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

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

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

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

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

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

Pregnancy:

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Preliminary findings from a monkey study appear to indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Because of this risk, all patients taking lenalidomide must read the following statements that apply to them according to gender and menopausal status.

FOR FEMALES WHO *ARE ABLE* TO BECOME PREGNANT*

* Any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months.

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

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

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

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

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

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

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

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

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

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

_____: I agree any unused drug supply will be returned to the research site at each visit.

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

Study patients who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

FOR ALL MALES

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

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

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

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

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

_____: I agree any unused drug supply will be returned to the research site at each visit.

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

FOR FEMALES THAT ARE *NOT* ABLE TO BECOME PREGNANT

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

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

_____: I certify that I am not now pregnant, nor am I of child bearing potential as I have been in a natural menopause for at least 24 months (been through the change in life without even 1 menstrual period for the past 24 months); or I had my uterus removed (hysterectomy) or had both my ovaries removed (bilateral oophorectomy).

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

_____: I agree any unused drug supply will be returned to the research site at each visit.

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

FOR ALL PATIENTS

You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the “Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies” with each new supply of lenalidomide as a reminder of these safety issues.

Risks of Bone Marrow Tests:

There may be infection, bleeding or bruising at the site of the bone marrow biopsy or aspiration, as well as possible inflammation of the vein or infection. A bone marrow aspiration is a procedure in which an area of the hip is numbed and a small sample of bone marrow fluid is withdrawn. A bone marrow biopsy is similar except a sample of bone marrow tissue is removed through the needle. There may be temporary pain or discomfort at the bone marrow site. However, a local anesthetic is routinely used to numb the skin, and care will be taken to avoid these complications. Bone marrow studies carry very minimal risk to the patient.

SECOND PRIMARY RISKS OF LENALIDOMIDE

Sometimes a second primary cancer arises after patients have undergone cancer therapy, including therapy using chemotherapeutic agents used to treat multiple myeloma. Recently, in clinical trials of patients with newly diagnosed multiple myeloma, a higher number of second cancers has also been reported in patients treated with high doses of chemotherapy (induction therapy) and/or stem cell transplant followed by prolonged (maintenance) lenalidomide therapy compared to those who received induction therapy and/or transplant without maintenance lenalidomide.

We do not know at this time whether prolonged lenalidomide therapy in this clinical setting actually increases the risk of second primary cancers. No increase in second primary cancers has been observed in patients receiving lenalidomide therapy who have relapsed multiple myeloma or other types of cancer.

We will be carefully monitoring these events (second primary cancers) in on-going studies of lenalidomide therapy and will inform you if there are any changes. We want you to be aware of this possibility and to continue to follow standard medical advice for prevention and early detection of other cancers during and after your treatment.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you.

Possible benefits include improvement in the symptoms related to your cancer, and prolonged survival.

We hope the information learned from this study will benefit other patients' myeloma in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have this option:

- Monitoring. Currently patients with asymptomatic myeloma are closely monitored without active treatment until they show signs of developing symptoms caused by their myeloma.

Please talk to your doctor about this.

WHAT ABOUT CONFIDENTIALITY?

This study is being conducted by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN). ECOG-ACRIN is a cancer group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

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

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

Finally, you should understand that your doctor and ECOG-ACRIN are not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others, and the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Montana Cancer Consortium
- The ECOG-ACRIN Cancer Research Group
- National Cancer Institute
- Food and Drug Administration
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute to provide greater access to cancer trials.
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers, distributors, and/or their representatives
- Designated laboratories and reviewers

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

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

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

The aspirin which is used to prevent blood clots is available over the counter, and will be paid for by you. If your doctor prescribes alternate medications, they will be billed to your insurance. Please discuss this with your doctor.

The costs of additional laboratory tests, such as pregnancy tests for patients on Arm A, might not be covered by your insurance.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

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

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the lenalidomide to the NCI for some reason. If this would occur, other possible options are:

- **You might be able to get the lenalidomide from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.**
- **If there is no lenalidomide available at all, no one will be able to get more and the study would close.**

If a problem with getting lenalidomide occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.
No funds have been set aside to compensate you in the event of injury.

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

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

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

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study, or choosing not to take part, will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

Additional specimen collection (not for diagnostic purposes) will not occur until you have consented for the study.
For questions about your rights while in this study, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor. Contact information for your study doctor is listed on the consent cover page.

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

WHERE CAN I GET MORE INFORMATION?

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

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI Web sites

For comprehensive clinical trials information go to http://cancer.gov/clinicaltrials.

For accurate cancer information go to http://cancer.gov/cancerinformation.

You will get a copy of this form. Upon request, you will also receive a copy of the protocol (full study plan).

ABOUT USING SPECIMENS FOR RESEARCH

If you participate in the clinical trial, we would also like samples of your **blood and bone marrow** to be used for research studies. These samples are referred

to as “specimens”. These specimens and the health information collected during your participation in the clinical trial can be used to help doctors and scientists learn more about caring for and treating people with cancer and other diseases.

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

You will not receive any payments for allowing your specimens to be used for these research studies, even if your specimens are used to help develop commercial products or tests someday. You or your insurance company will not be billed for the research studies performed using your specimens.

How Will My Specimens Be Used For Research?

There are two types of projects:

- Laboratory Research projects: These research studies are already planned and the project details are written into the study plan. They are approved by ECOG-ACRIN and NCI, and have been reviewed by the researchers’ Institutional Review Board (IRB). An IRB is a group of people who review research to protect patient rights.
- Future Research projects: Specimens are stored in central locations for use in future research. The type of projects they will be used for are not yet known. Future projects must be approved by ECOG-ACRIN and have been reviewed by the researchers’ IRB.

Researchers may study the differences and similarities of the cells or parts of the cells in the specimens, such as normal cells, tumor cells, proteins, and genetic material. The level of drug in the specimens may be studied. Some projects may study characteristics that are passed on in families (inheritable). The study of inheritable traits is a type of genetic research. To better understand the results, the researcher may compare the test results to the information collected from your participation in the clinical trial (such as your age, side effects you experience, and your cancer’s response to treatment).

Additional information on the importance of donating your specimens for research and how specimens are used for research can be found on the patient advocacy website (www.researchadvocacy.org) and on the NCI website at www.cancer.gov/clinicaltrials/.

Where will my specimens be stored and who has access to them?

If you agree to allow your specimens to be used for the research projects, your

specimens will be sent to research laboratories for testing. After these tests are completed, the researchers will send any left over specimens to a repository (bank) where, if you agree, they will be stored for use by other researchers. The stored specimens will be kept indefinitely or until they are used up.

Because your specimens are valuable, researchers must present their projects for review and approval to scientific reviewers appointed by the ECOG-ACRIN Cancer Research Group. Any research done on the specimens must also be reviewed by the researcher's IRB. Some projects may also require approval by the National Cancer Institute (NCI).

Will personal information be associated with the specimens?

The specimens sent to research laboratories and repositories will have some identifying information, such as initials and where the specimens were collected. To protect your identity, your specimens and any related information will receive a unique identification code. Researchers approved to use the specimens for future research will only receive the code that is attached to your specimen. Any information from your research records that is approved to go to these researchers will also receive a code.

Any research or information that is published, presented at scientific meetings or made public in any other way will use only coded information.

This could include genetic data. Current safety rules are followed to safeguard your privacy. Your name or contact information will not be in the database.

How will information related to your specimens be protected?

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

1. Your specimens and information receive a unique code. For future research projects, researchers only receive coded specimens and information, and will not be able to see the key that links the code to you. Only approved people in ECOG-ACRIN can match you to the code on your specimens and related information.
2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include *password protected access to databases and keeping freezers that contain specimens in a locked area.*
3. Research studies are reviewed for the quality of the science and for patient protection before specimens are given to researchers. To make sure the research follows the rules of ECOG-ACRIN and state or federal laws, records from research studies can be reviewed by ECOG-ACRIN, by the sponsor, and by government agencies.
4. Rules for publications: If research results are published, you will not be identified by name or any other personally identifiable information.

5. ECOG-ACRIN also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the specimen bank or database. What this means is that *ECOG-ACRIN* cannot be forced to disclose your identity to any third party. It is possible that for some criminal proceedings, the Certificate of Confidentiality could be over-ridden.

What are the risks?

There are very few risks to you if your specimens and data are used for this type of research. The greatest risk, although rare, is the loss of confidentiality caused by unauthorized release or misuse of information from your research records.

We will do everything possible to make sure that the information in your research records are kept private.

Risk from participating in genetic research: Your genetic information is unique to you. You do share some genetic information with your family members. Although rare, there are examples where health insurers or employers have denied insurance or employment based on results from genetic testing. Some states have laws that help to protect against genetic discrimination. A recent federal law (Genetic Information Non-Discrimination Act, GINA) will help reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about the GINA Law, you can find information about it on the internet or ask the study staff.

How we will address these risks: We have several safeguards in place to prevent misuse of research results by any third party including insurers or employers: your research results will not be sent to you or your doctor and will not be placed in your medical record; insurers or employers will not be authorized to view any research records; and all information will be coded. As stated before, we also have a Certificate of Confidentiality from the US government, which protects your information from forced disclosure by civil, criminal, administrative, legislative or other proceeding. We believe that the risks to you and your family are very low.

Benefits

The research that may be done with your specimens will probably not benefit you directly. It may help researchers learn more about what causes cancer and other diseases, how to prevent them, and how to select the most appropriate treatment for future patients who have these diseases.

Changing your mind about letting us use your specimens

If at any time you decide you no longer want your specimens used for research, please give your doctor or study nurse a signed note stating your decision. They will contact ECOG-ACRIN and tell us about your decision.

If your specimens were already sent from the repository and are being used for a project when you withdraw your consent, your specimens and accompanying data will still be used for that approved project. Once you choose to end your participation, no further specimens or related information will be sent to researchers from the repository for any new research projects.

Specimens will NOT be returned to you. Depending on the type of specimen, it will be marked as not for research use or destroyed.

Voluntary Participation

The choice to participate in the optional laboratory research projects or to allow your specimens to be stored for future research is completely up to you. **No matter what you decide to do, your decision will not affect your medical care.** You can participate in the treatment part of the study without participating in these research projects.

Please read the research study descriptions below, review the questions carefully and circle "Yes" or "No". If you circle "Yes", you are indicating you understand:

- Coded information collected from your medical records may be given to researchers to perform these studies.
- The research results from your specimens will not be given to you or your doctor, they will not be placed in your medical record and they will not affect your medical care.
- Your specimens may be used in genetic research.
- The risks associated with allowing your specimens to be used in research, including the possible risks associated with genetic research.
- You will not receive any payment for the use of your specimens for these projects. You or your insurance will not be billed for any of these research studies.
- That at any time, you can end your participation in the projects and any remaining specimens or information will not be used for new research.

If you do not agree with any of the statements above, indicate "No" to ALL the questions below.

If you have any questions, please talk to your doctor or nurse. Contact information for your study doctor is listed on the consent cover page.

LABORATORY RESEARCH STUDIES

This study includes one or more laboratory tests that will analyze samples of your blood and bone marrow. These samples will be collected at preregistration

(before you start treatment) and when you discontinue the study or if your cancer get worse, whichever occurs first. Blood will be collected from your vein using a needle according to standard procedures for routine blood sampling. In most cases the blood will be collected at the time you are going through your routine blood draws. There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed.

The blood samples (approximately four (4) tablespoons per time point) will be collected using a needle to draw some blood out of your vein. The bone marrow will be collected from bone using a needle, with the risk of a small amount of bleeding at the biopsy site. The bone marrow samples will be collected as part of your routine clinical care. The bone marrow samples (approximately three (3) tablespoons per time point), along with slides and cores, will be obtained at the time of the bone marrow biopsies scheduled for the treatment aspect of this study. No additional biopsies will be done to obtain this material. The blood and bone marrow samples will be sent to central laboratories where tests will be performed. The tests are for research purposes only and the results will not be given to you or your doctor and will not affect your care. Researchers will perform these tests in order to understand how your treatment procedures attack your cancer cells. They hope this will help them better understand your type of cancer.

Please review the points listed in the “Voluntary Participation” section above, then read the questions below and circle “Yes” or “No”.

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

Yes No

USING SPECIMENS FOR FUTURE RESEARCH

We would like to keep some of your samples for future research.

This means any specimens left over from the laboratory studies will be stored for future research.

We would like to collect additional blood for banking for future research. Blood will be collected from your vein using a needle according to standard procedures for routine blood sampling. In most cases the blood will be collected at the time you are going through your routine blood draws. There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Approximately two (2) teaspoons of blood will be collected at each of the following time points: preregistration and when you discontinue treatment or if your cancer gets worse, whichever occurs first.

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

Alzheimer's disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the ECOG-ACRIN Cancer Research Group. Any research done on the specimens must also be reviewed by the researcher's Institutional Review Board.

Please review the points listed in the "Voluntary Participation" and the risks associated with allowing your specimens to be used for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle "Yes" or "No".

I agree to provide additional blood for research.

Yes No

My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer.

Yes No

My specimens may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, or heart disease).

Yes No

PERMISSION TO CONTACT YOU IN THE FUTURE

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

Someone from this institution may contact me in the future to ask me to take part in more research.

Yes No

Phase II Study Plan

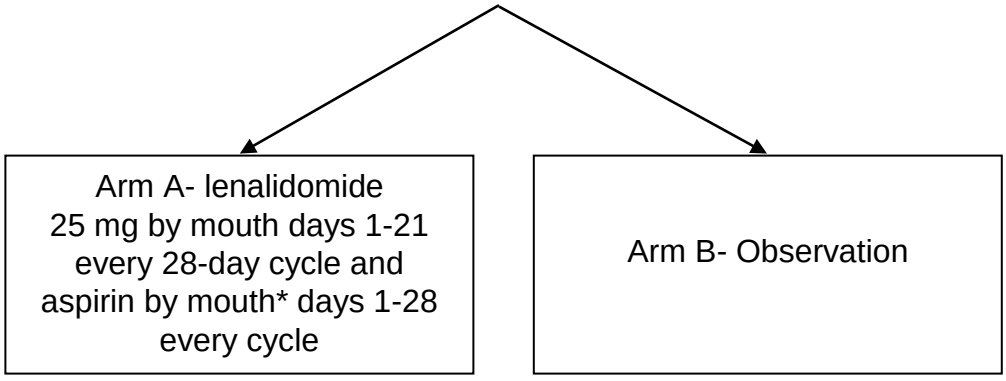
You will be assigned to
Arm A (lenalidomide)

Arm A- lenalidomide 25 mg by mouth days 1-21 every 28-day cycle and aspirin 325 mg by mouth* days 1-28 every cycle

- If your myeloma gets worse while on Arm A you will come off the study.
- If your disease gets worse at any point you will stop taking the drug and you will discuss future treatment with your doctor.
- 44 patients will be accrued to the Phase II part of the study.

Phase III Study Plan

You will be randomly
assigned to
Arm A (lenalidomide), or
Arm B (observation).



- If your myeloma gets worse while on Arm A you will come off the study.
- If your disease gets worse at any point you will stop taking the drug and you will discuss future treatment with your doctor.

* Or alternative drug prescribed to prevent deep vein thrombosis, a serious blood clotting disorder. For the Phase III study, the dose of aspirin is up to your doctor, but is suggested to be 75-325 mg/day, depending on your health.

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) or TTY: 1-800-332-8615

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

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

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

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

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)