

## KANSAS CITY CLINICAL ONCOLOGY PROGRAM

### A GENETIC RISK-STRATIFIED, RANDOMIZED PHASE II STUDY OF FOUR FLUDARABINE/ANTIBODY COMBINATIONS FOR PATIENTS WITH SYMPTOMATIC, PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only patients who choose to take part. Please take your time to make your decision. You may discuss your decision with your friends and family. You can also discuss it with your health care team.

You are being asked to take part in this study because you have chronic lymphocytic leukemia (CLL).

#### **Why is this study being done?**

The purpose of this study is to find out what effects (good and bad) treatment with four different therapies that include combinations of the drugs fludarabine, rituximab, cyclophosphamide, and lenalidomide have on you and your CLL provided you have low risk disease. The first three of these drugs are not experimental. Fludarabine and cyclophosphamide have been approved by the Food and Drug Administration (FDA) for the treatment of CLL, while rituximab is approved for the treatment of non-Hodgkin lymphoma and rheumatoid arthritis. The fourth agent, lenalidomide, however, has been studied in a variety of different diseases including multiple myeloma, myelodysplasia, and CLL. Lenalidomide has been approved by the FDA for use in multiple myeloma and in some patients with myelodysplastic syndrome (a group of malignant diseases of the bone marrow that usually causes a reduction in blood counts, resulting in anemia and an increased risk of infections and bleeding. In some patients this disease progresses to acute leukemia after a period of time.) The use of lenalidomide in CLL in this research study is considered investigational. Each of the four therapies proposed in this research study has been studied in patients diagnosed with CLL. If you are identified to have risk disease, you will be assigned to a three drug combination of fludarabine, cyclophosphamide, and rituximab that has been shown to be superior for these patients. After completion of this remission induction treatment you will receive lenalidomide consolidation therapy.

This research is being done because currently there is no proven cure for this type of cancer.

#### **How many people will take part in the study?**

About 405 people will take part in this study.

## What will happen if I take part in this research study?

### Medical Tests

The following tests must be done to make sure that you are eligible for this study. None of these tests are experimental. They are routine. Depending on when you last had them, you may need to repeat some of these tests:

- Blood tests, including a special test performed in a laboratory at the Ohio State University to determine whether your disease is high or low risk disease. You will not be billed for this special test.
- CT scan of the chest, abdomen, and pelvis
- Thyroid function tests
- Bone marrow aspirate and biopsy
- Pregnancy test (if you are of a woman of childbearing potential). If you are in Group B or Group D and receive the drug lenalidomide, a pregnancy test will be repeated 10-14 days prior to beginning lenalidomide consolidation therapy, 24 hours prior to beginning consolidation therapy, weekly during the first 28 days of treatment, then every 28 days if you have regular periods, at completion of lenalidomide consolidation therapy, and then 28 days after the last dose of consolidation therapy. If your periods are not regular, you will have pregnancy tests 10-14 days prior to beginning lenalidomide consolidation therapy, 24 hours prior to beginning consolidation therapy, weekly during the first 28 days of treatment, then every 14 days, at completion of lenalidomide consolidation therapy, and then 14 and 28 days after the last dose of consolidation therapy. In addition, you must either commit to continued abstinence from heterosexual intercourse or use two methods of birth control at the same time, at least 28 days before starting treatment, during treatment, and for at least 28 days after treatment has stopped. During their participation in the study, men must agree to use a condom if they have any sexual contact with a woman of childbearing potential, and for at least 28 days following completion of lenalidomide consolidation therapy, even if the man has undergone a successful vasectomy. See "Reproductive Risks" below for additional information.

Many of these tests will be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

### Treatment

You will be assigned to one of two disease risk groups, either low or high risk disease, based upon the special blood test described above. Because of the time needed to perform the special test, all patients initially will be "randomized" into one of the study groups A, B, or C described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group. After approximately one month of treatment, when the test results are known, if the results reveal that you have low risk disease, you will remain in the original study group to which you were randomized. Previous studies have suggested that patients that had high risk disease have had better outcomes when their chemotherapy regimen included the drug cyclophosphamide. Therefore, patients who initially were randomized to Arms A and B who test results reveal high risk disease will be

shifted to Arm D, which contains cyclophosphamide, after the first course. Patients who initially were randomized to Arm C whose test results reveal high risk disease will remain on Arm C because that treatment contains the drug cyclophosphamide. Patients on Arm D will test whether there is any benefit to giving the experimental drug lenalidomide after the fludarabine/cyclophosphamide/rituximab induction treatment.

**If you are in Group A (often called "Arm A"),** you will receive fludarabine and rituximab during induction therapy followed by observation.

**If you are in Group B (often called "Arm B"),** you will receive fludarabine and rituximab during induction therapy followed by consolidation therapy with lenalidomide.

**If you are in Group C (often called "Arm C"),** you will receive fludarabine, rituximab, and cyclophosphamide during induction therapy followed by observation.

**If you are in Group D (often called "Arm D"),** after receiving a month of the treatment in either Arms A or B, you will be re-assigned to Arm D to receive fludarabine, rituximab, and cyclophosphamide during induction therapy followed by consolidation therapy with lenalidomide.

See treatment diagram at the end of this document for an overview of the treatment plan.

Treatment on this study will consist of three parts: Remission Induction Therapy (Groups A, B, C and D), Consolidation Therapy (Groups B and D), and Follow-Up (Groups A, B, C and D). The details of all of the treatments for each group, for example, how often, and in what order the drugs are given, are described below.

In an effort to improve methods of diagnosis and treatment of patients with CLL, samples of blood and bone marrow will be obtained from all patients prior to treatment and several times throughout the course of therapy. Researchers will examine the particular characteristics of CLL cells and certain molecular and chromosomal features within these cells. In most instances, your participation will not involve any additional risk, as blood and bone marrow samples must be obtained for diagnosis and for following your disease. When these samples are drawn for diagnosis, routine follow-up, or if your doctor suspects that your disease may have returned, additional blood and bone marrow would be collected for this research. An additional 3 tablespoons of blood and 2 teaspoons of bone marrow would be obtained at most five times during the course of your therapy: prior to beginning your therapy; once approximately three months after completing your induction therapy; once, if you are in Arms B or D, two months after completing lenalidomide consolidation therapy; once approximately two years after study enrollment; and, finally, if your disease recurs or fails to respond to the treatment initially prescribed.

#### Remission Induction Therapy

During Remission Induction Therapy, two drugs, rituximab and fludarabine, will be used in combination in Groups A, B, and C. An additional drug, cyclophosphamide, will be added to these two drugs in Groups C and D. It is anticipated that Remission Induction Therapy for all patients will last approximately six months (that is, six 28-day cycles of therapy).

**If you are in Groups A and B**, rituximab will be given by intravenous (IV) infusion (that is, through a needle in a vein in your arm) over 4 hours on days 1, 3 and 5 of week 1, and then on the first day during weeks 5, 9, 13, 17, and 21. There will be a total of eight doses of rituximab during induction therapy (that is, three doses on days 1, 3 and 5 of week 1, and five additional doses on day 1 of weeks 5, 9, 13, 17, and 21). Fludarabine also will be given by IV infusion, but will be given over a period of 30 minutes each day for five days (days 1-5) during weeks 1, 5, 9, 13, 17, and 21. Some institutions may use an oral formulation of fludarabine where fludarabine will be given to you as a tablet to be taken by mouth each day for five days. You will also be given an oral (by mouth) medication, known as allopurinol, for at least the first 15 days of treatment to protect your kidneys from the dying leukemia cells.

**If you are in Groups C and D**, rituximab will be given by intravenous (IV) infusion (that is, through a needle in a vein in your arm) over 4 hours on days 1 and 3 of week 1, and then on the first day during weeks 5, 9, 13, 17, and 21. There will be a total of seven doses of rituximab during induction therapy. Fludarabine also will be given by IV infusion, but will be given over a period of 30 minutes each day for three days (days 1-3) during weeks 1, 5, 9, 13, 17, and 21. Some institutions may use an oral formulation of fludarabine where fludarabine will be given to you as a tablet to be taken by mouth each day for three days. Cyclophosphamide also will be given by IV infusion over 30 minutes each day for three days (days 1-3). You will also be given an oral (by mouth) medication, known as allopurinol, for at least the first 15 days of treatment to protect your kidneys from the dying leukemia cells.

About 3-4 weeks after your last dose of Remission Induction Therapy, you will undergo various blood tests, and a history and physical exam, as well as x-rays to determine whether your disease has responded to treatment. After a period of about twelve (12) weeks, you will again undergo various blood tests, a history and physical exam, as well as a bone marrow aspirate and biopsy, and x-rays to determine whether your disease has continued to respond to treatment.

You will be asked to have a bone marrow aspiration and biopsy performed at least once after completion of your treatment to allow the doctor to determine if the cancer has been destroyed in your bone marrow. A bone marrow aspiration is a procedure in which an area of the hip is numbed and a small sample of liquid bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone marrow tissue is removed through the needle. There may be some temporary pain or discomfort associated with these routine outpatient procedures, but they are necessary to determine whether you are responding to your therapy.

**Patients in Group A and C** will not receive any further therapy on this study.

**Remission Consolidation Therapy (Groups B and D only)**

If you have been assigned to Group B or D, and as long as there is no evidence that your disease has worsened, then Remission Induction Therapy will be followed by Remission Consolidation Therapy. If you are in Group B or D, you will receive lenalidomide orally (by mouth) daily for 21 days every 28 days. Each 28-day period will be known as a cycle of consolidation therapy. You will receive a minimum of 3 and a maximum of 6 cycles of consolidation therapy. If you do not experience significant side effects, your doctor may increase the dose of lenalidomide during the second or third month. You will be asked to record the dates and time of each dose of

lenalidomide on the CALGB 10404 Medication Calendar. You will be asked to bring the calendar with you to the clinic on the first day of each treatment cycle, as well as any unused or partial bottles of lenalidomide.

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 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, contact your doctor and seek emergency medical care if needed. You will be counseled at least every 28 days 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.

Depending on your health history or medication history, you may be at risk of blood clots as described below in the "risks" section. If you are considered to be at high risk, you may be given medicine (such as aspirin or heparin) to prevent clots from forming.

About 3-4 weeks after your last dose of Remission Consolidation Therapy, you will undergo various blood tests, and a history and physical exam, as well as x-rays to determine whether your disease has responded to treatment. After a period of about eight (8) weeks, you will again undergo various blood tests, a history and physical exam, as well as a bone marrow aspirate and biopsy, and x-rays to determine whether your disease has responded to treatment.

You will be asked to have a bone marrow aspiration and biopsy performed at least once after completion of your treatment to allow the doctor to determine if the cancer has been destroyed in your bone marrow. A bone marrow aspiration is a procedure in which an area of the hip is numbed and a small sample of liquid bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone marrow tissue is removed through the needle. There may be some temporary pain or discomfort associated with these routine outpatient procedures, but they are necessary to determine whether you are responding to your therapy.

## How long will I be in the study?

**If you are in Group A**, we think you will receive treatment on this study for approximately 6 months. After you have completed remission induction treatment on this study, you will be asked to return to the clinic for follow-up tests about four times per year for one year, and then twice a year thereafter for a maximum of fifteen years from the time you entered the study. If your disease should worsen after beginning treatment, you will be removed from the study and your physician will discuss other treatment options.

**If you are in Group B**, we think you will receive treatment on this study for approximately 15 months. After you have completed remission induction treatment on this study, you will be asked to return to the clinic for follow-up tests about four times per year for one year, and then twice a year thereafter for a maximum of fifteen years from the time you entered the study. If your

disease should worsen after beginning treatment, you will be removed from the study and your physician will discuss other treatment options.

**If you are in Group C**, we think you will receive treatment on this study for approximately 6 months. After you have completed remission induction treatment on this study, you will be asked to return to the clinic for follow-up tests about four times per year for one year, and then twice a year thereafter for a maximum of fifteen years from the time you entered the study. If your disease should worsen after beginning treatment, you will be removed from the study and your physician will discuss other treatment options.

**If you are in Group D**, we think you will receive treatment on this study for approximately 15 months. After you have completed remission induction treatment on this study, you will be asked to return to the clinic for follow-up tests about four times per year for one year, and then twice a year thereafter for a maximum of fifteen years from the time you entered the study. If your disease should worsen after beginning treatment, you will be removed from the study and your physician will discuss other treatment options.

## Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing, if necessary, could be most helpful for you.

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

## What side effects or risks can I expect from being in the study?

You may have side effects while on study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also the risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

### Risks and Side Effects During Induction Therapy (Patients in Group A, B, C and D)

Risks and side effects related to induction therapy with fludarabine, rituximab, and, where noted, cyclophosphamide (Groups C and D only) include those which are:

**Likely:**

- Lowered white blood cell count<sup>W</sup> (neutrophils/granulocytes) that may lead to infection.
  - Lowered platelets<sup>W</sup> which may lead to an increase in bruising or bleeding.
  - Lowered red blood cells<sup>W</sup> which may cause anemia, tiredness, or shortness of breath.
  - Lowered number of another type of white blood cells (lymphocytes) that may lead to infection.
  - Fatigue.
  - Nausea.
  - Vomiting.
  - Time away from work.
  - Infusion reactions with rituximab including fever, chills, and nausea which may be severe.
  - Hair loss (**if you are in Groups C or D only**).
  - “Shingles.” If you develop a condition known as shingles (Herpes zoster infection of the skin), a skin rash caused by the chicken pox virus, it will be important that you notify your physician immediately. There is a medication available to treat shingles effectively, but only if the medication is started within 24-48 hours after the rash has developed.
- <sup>W</sup> Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of chemotherapy given to you. Until your immune system has recovered from treatment, any blood products you may receive should be irradiated.

**Less Likely:**

- Allergic reaction.
- Severe allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- 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 virus may be at an increased risk of recurrence of the virus that may lead to severe liver damage that can be life threatening. You 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.
- Some viral infections may be worsened or reactivated from a “sleeping” state in patients taking rituximab.
- Stuffy or runny nose, sneezing.
- Sore throat.
- Abnormal fast heartbeat.

- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- High blood pressure.
- Excessive sweating.
- Flushing.
- Itching.
- Rash.
- Swelling of the lips, eyes, tongue, and throat which can be severe.
- Hives.
- Diarrhea.
- Swelling of the arms and/or legs.
- High blood sugar.
- Low blood potassium.
- Dizziness.
- Convulsion or seizure.
- Abdominal pain.
- Pain such as back, joint, and/or muscle pain.
- Headache.
- Wheezing.
- Cough.
- Shortness of breath.
- Inflammation of the lung which may cause difficulty breathing and difficulty getting oxygen.”
- Infertility or sterility **(if you are in Groups C or D only)**.
- Irregular menstrual periods **(if you are in Groups C or D only)**. Some women may not resume their periods.
- Abnormal production of a hormone that regulates salt and fluid excretion **(if you are in Groups C or D only)**.
- Increased production of tears associated with the administration of cyclophosphamide **(if you are in Groups C or D only)**.

- Metallic taste (**if you are in Groups C or D only, immediately after administration of cyclophosphamide**).
- Bladder irritation which may cause blood to appear in your urine (**if you are in Groups C or D only**). To minimize this side effect, patients are encouraged to drink fluids to promote frequent urination on the days of cyclophosphamide administration and one day afterwards.

#### **Rare But Serious:**

- Severe allergic reactions during rituximab infusion or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They have generally can be handled with medications and sometimes by slowing the rate of infusion. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Destruction of red blood cells that may lead to anemia. Should this occur, it can be treated with blood transfusions.
- Changes in vision or changes in degree of alertness both of which can be severe or fatal.
- Rash which may become severe.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of skin to separate from the middle layer.
- Severe lung dysfunction resulting in the ability to breathe which can be life-threatening.
- Allergic reactions to blood transfusions.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.
- Liver problems/liver failure.
- Another viral infection causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can cause severe disability or death.

#### **Risks and Side Effects During Consolidation Therapy (GROUPS B or D ONLY)**

Risks and side effects related to consolidation therapy with lenalidomide (Groups B or D only) include those which are:

#### **Likely:**

- Anemia
- Lowered platelets  $\psi$ , which may lead to an increase in bruising or bleeding.

- Lowered red blood cells $\psi$  which may cause tiredness, or shortness of breath.
- Decrease in the number of a type of white blood cell (neutrophil) that may lead to infection.
- Fatigue, tiredness
- Constipation
- Diarrhea

$\psi$  Should this occur, it can be treated with blood products (transfusions), and a reduction in the amount of chemotherapy given to you. Until your immune system has recovered from treatment, any blood products you may receive should be irradiated.

**Less Likely:**

- Lowered number of a type of white blood cells (lymphocytes) that may lead to infection.
- Fever
- Difficulty sleeping or falling asleep
- Chills, shivering
- Sweating
- Weight loss
- Abnormally low thyroid function
- Loss of appetite
- Rash or sores on the skin
- Itching
- Vomiting
- Nausea
- Infection
- Swelling of the arms and/or legs
- Dizziness
- Back pain
- Headache
- Joint or muscle pain
- Muscle spasm or cramp
- Cough
- Shortness of breath

- Formation or presence of a blood clot inside a blood vessel. Development of blood clots (for example, in the veins in your arms or legs) may be serious. Lenalidomide in combination with epoetin may increase the risk of these blood clots. Smoking and prolonged inactivity may also increase the risk.

#### **Rare But Serious:**

- Severe potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness.
- Abnormal blood level of a fat-digesting enzyme
- Inflammation of the pancreas causing pain
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (that is, the outer layer of skin) to separate from the dermis (that is, the middle layer).
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (that is, the outer layer of skin) to separate from the dermis (that is, the middle layer).
- A syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss, and associated with abnormal X-ray findings.
- Kidney failure
- Temporary growth of leukemia or worsening of leukemia-related problems
- Tumor lysis syndrome – a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.
- Death

#### **REPRODUCTIVE RISKS FOR MEN AND WOMEN**

The drugs used in this study may have a risk of causing malformations in an unborn child, especially when given in the early part of pregnancy. Therefore you should not become pregnant or father a baby while on this study. If you are a woman of childbearing potential, you will be required to have a pregnancy test at study entry. Childbearing potential means that a woman's uterus and/or both ovaries have not been removed, she has had at least one menstrual period in the past 24 months and/or her periods have stopped due to treatment of her disease.

**If you are a woman of childbearing potential in Groups B or D**, additional precautions, described below, must be taken.

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Women must not become pregnant while taking lenalidomide. You have been informed that the

risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking lenalidomide.

When taking lenalidomide, the drug is present in semen of healthy men at very low levels for three days after stopping the drug. For patients who may not be able to get rid of the drug, such as people with kidney problems, lenalidomide may be present for more than three days. To be safe, all men should use condoms when engaging in sexual intercourse while taking lenalidomide, when temporarily stopping lenalidomide, and for 28 days after permanently stopping lenalidomide treatment if their partner is either pregnant or able to have children.

Patients should not donate blood during study treatment or for 28 days following discontinuation of lenalidomide.

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 (or 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.

**FOR FEMALES OF CHILDBEARING POTENTIAL IN GROUPs B or D:**

If you are a woman of childbearing potential in Groups B or D, please read the following information thoroughly and initial 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 or able to get pregnant and not using two (2) reliable methods of birth control (one highly effective method and one additional effective method, as described below).

\_\_\_\_\_ If I am having sexual relations with a man, and I am of childbearing potential, I understand that I am able to get pregnant. I must use one highly effective method of birth control (intrauterine device (IUD), hormonal (birth control pills, injections, implants), tubal ligation, or partner's vasectomy) plus one additional effective method of birth control (latex condom, diaphragm, or cervical cap) at the SAME TIME.

\_\_\_\_\_ These birth control methods must be used during the following time periods: (1) for at least 28 days before starting lenalidomide therapy; (2) while participating in this study and during interruptions in therapy; and (3) for at least 28 days after lenalidomide has been stopped. I must use these birth control methods unless I completely abstain from heterosexual sexual contact. If a hormone 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 that if I am of childbearing potential I must have a pregnancy test done by my doctor within 10-14 days before starting lenalidomide therapy, and again 24 hours before

starting lenalidomide therapy. 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 whenever lenalidomide therapy is stopped, 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 whenever lenalidomide therapy is stopped, 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 that any left over 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 I have stopped taking lenalidomide.

**FOR ALL MALES IN GROUPS B or D:**

Please read the following information thoroughly and initial 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 it is not known whether lenalidomide is present in semen, my doctor 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 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 have been told by my doctor that I must not donate blood, sperm or semen while taking lenalidomide, and for at least 28 days after completing lenalidomide.

\_\_\_\_\_ I agree that any left over drug supply will be returned to the research site at each visit.

13 Approval Date: 11/10/11 to 11/9/12 09/30/11  
Assurance #: FWA00003582

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

**Risks and Side Effects Related to Bone Marrow Aspirations and Biopsies:** There may be some temporary pain or discomfort associated with these routine procedures at the site where the needle is inserted. The side effects associated with obtaining bone marrow samples include pain at the site of the procedure, as well as possible bleeding, bruising or swelling. There is also a very small chance that you could develop an infection at the site of the procedure. Bone marrow aspirations and biopsies will be necessary prior to beginning the study, after completing the induction and consolidation courses of treatment or if your leukemia should return.

**Secondary Malignancy:** A number of chemotherapy agents have a risk of causing another cancer (secondary malignancy). Fludarabine, rituximab, and cyclophosphamide in these doses are not known to markedly increase the risk of secondary malignancies, but may be shown at a later time to result in the development of these secondary malignancies.

Recently, in clinical trials of patients with another cancer, multiple myeloma, a higher number of new cancers has also been reported in patients treated with high doses of chemotherapy (induction therapy) and/or bone marrow transplant followed by prolonged lenalidomide therapy alone compared to those who received the high dose chemotherapy and/or transplant without the prolonged lenalidomide. It is not known if these new cancers were caused by lenalidomide or not.

We do not know at this time whether prolonged lenalidomide actually increases the risk of new cancers. The higher number of new cancers has not been seen in other patients receiving lenalidomide.

We will be carefully monitoring new cancers in on-going studies of lenalidomide and will inform you if there are any changes. We want you to be aware of this possibility and to continue to follow your doctors' recommendations for prevention and early detection of new cancers during and after you treatment.

For more information about risks and side effects, ask the researcher or contact

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## Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that the treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the combination of rituximab, fludarabine, and lenalidomide as a treatment for cancer. This information could help future cancer patients.

## What other choices do I have if I do not take part in this study?

Your other choices include:

- getting treatment or care for your chronic lymphocytic leukemia without being in a study
- taking part in another study for chronic lymphocytic leukemia
- getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

## Will my 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. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- Cancer and Leukemia Group B (CALGB)
- Eastern Cooperative Oncology Group (ECOG). Records of patient progress while on study will be kept in a confidential file at both the Eastern Cooperative Oncology Group and CALGB.
- National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)
- Southwest Oncology Group (SWOG)
- The National Cancer Institute (NCI), and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Celgene, the manufacturers of lenalidomide.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services or for purpose of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

## What are the costs of taking part in this study?

With the exception of lenalidomide used in Groups B or D during consolidation therapy (see below), all of the planned chemotherapy drugs in this research study (fludarabine, rituximab and cyclophosphamide) are commercially available. You and your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study, including costs of the supplies and personnel who give you the chemotherapy drugs used 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. Neither you nor your insurance company will be charged for any of the special research tests that will be done as part of this clinical trial.

The study agent in Arms B or D consolidation therapy, lenalidomide, will be provided free of charge by the Division of Cancer Treatment and Diagnosis, NCI, while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. 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 happens if I am injured because I took part in this study?

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.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Neither you nor your insurance company will be charged for any research tests required for your clinical care.

You will receive no payment for taking part in this study.

## 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 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.

### Whom do I call if I have questions or problems?

For questions about the study or a research-related injury, contact the researcher name(s) at \_\_\_\_\_ telephone number \_\_\_\_\_

For questions about your rights as a research participant, contact the Kansas City Clinical Oncology Program Institutional Review Board (which is a group of people who review the research to protect your rights) at 913-948-5588.

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person: (name) \_\_\_\_\_ (title) \_\_\_\_\_ (address) \_\_\_\_\_ (phone number) \_\_\_\_\_.

### Future Research Studies

In addition, we would like to keep some of the specimens that are left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information below to learn more about specimen research.

Your specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimen that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Cancer and Leukemia Group B may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

**Benefits**

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choice**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRBs phone number.

No matter what you decide to do, it will not affect your care.

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

Yes                      No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes                      No

3. Someone may contact me in the future to ask me to take part in more research.

Yes                      No

**Where can I get more information?**

You may call the NCI'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/clinical trials/](http://cancer.gov/clinical%20trials/)

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

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

**Release**

By signing this form you authorize KCCOP to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

Approval Date: <u>11/10/11</u> to <u>11/9/12</u> Assurance #: FWA00003582	09/30/11
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You will get a copy of this form. If you want more information about this study, ask your study doctor.

**Signature**

I have been given a copy of all 19 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_

Signature of Person Obtaining Consent \_\_\_\_\_

Date \_\_\_\_\_

**SWOG Additional Research Studies Consent Addendum**

(for SWOG participants only)

**Consent Form for Use of Specimens for Research**

Please note: This "Making Your Choice" section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study and are also registered to protocol S9910. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the Southwest Oncology Group Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

Your specimens will be kept at the following location:

Southwest Oncology Group Lymphoid and CML Repository  
Fred Hutchinson Cancer Research Center  
1100 Fairview Ave. N.  
D4-385  
Seattle, WA 98104  
Telephone: 206/667-2592  
E-mail: jradich@fhcrc.org