A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL negative B lineage Acute Lymphoblastic Leukemia in Adults

This is a clinical trial, a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation.

You are being asked to take part in this study because you are between the ages of 30 and 70 years and have been recently diagnosed with a subtype of acute lymphoblastic leukemia (ALL) that is known as BCR-ABL negative B-lineage ALL.

Why is this study being done?

This study in being done to determine what affects (good and bad) the therapy blinatumomab has on your type of cancer (BCR/ABL negative ALL). This investigational therapy will be added to what has traditionally been used to treat your specific sub-type of ALL. Studies are being done in ALL and other blood cancers with blinatumomab. It is hoped that blinatumomab will target your B-cell ALL and destroy these specific cells, but it has not yet been proven.

Blinatumomab has been approved in the United States for several years for treatment of recurrent or resistant ALL. In late March 2018, blinatumomab was given a second new approved indication by the United States Food and Drug Administration (FDA) for treatment of B-lineage ALL patients in remission, but who have MRD positive cells present in their bone marrow. However, it is still not known if blinatumomab is better than chemotherapy in this setting.

How many people will take part in the study?

About 488 people will take part in this study.

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

Before you begin the study:

This study is for people with B-lineage ALL without a gene called BCR/ABL. All of the patients on this study will have a blood test to see if they have this specific sub-type of ALL.

You will also need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor**.**

- Physical exam with weight
- Complete blood count (a type of blood test)
- Chemistries (blood test)
- Chest x-ray
- ECG (used to measure your heart activity)
- MUGA or echocardiogram
- Lumbar puncture (procedure where a needle is used to remove fluid from your spinal canal)
- Marrow aspiration and biopsy (marrow will be taken from your hip bones using a needle)
- Urine or serum (blood) test to check if you are pregnant (women of childbearing potential only)
- HLA-typing to see if you might have a suitable donor for a bone marrow transplant

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures at different time points throughout the study. They are part of regular cancer care.

- Physical exam with weight
- Complete blood count (a type of blood test)
- Chemistries (blood test)
- Marrow aspiration and biopsy (marrow will be taken from your bones using a needle)
- Lumbar puncture (procedure where a needle is used to remove fluid from your spinal canal)
- ECG

At this time you will also likely have a special tube placed in your vein (called a catheter) that goes into a central vein in your chest, so that you can receive chemotherapy, blood transfusions and other medications such as antibiotics as needed. Blood for testing can also be drawn from this catheter.

In addition to these tests, if you are assigned to receive blinatumomab, you will perform a writing test which will be evaluated by medical staff and completed at the time of visits for blinatumomab bag changes or weekly clinical visits for evidence of early signs of neurologic toxicity. This is not part of regular cancer care.

Steps in this treatment study

There are several steps of treatment in this study. They are called induction, intensification, consolidation, and maintenance. In these study steps you will be getting standard chemotherapy treatments that may or may not be combined with an investigational cancer drug called blinatumomab. Your doctor may recommend you to have a blood or marrow transplant (BMT) at a later date after randomization to the blinatumomab/no blinatumomab arms, if you have a suitable donor.

Testing for levels of leukemia cells in the bone marrow will be done at several time points in the course of this study. This is known as Minimal Residual Disease (MRD) and will be tested by the ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL) with a specialized technique (called multiparameter flow cytometry). There is no single best way to do this test. The LTRL will do the test in a way agreed upon by research doctors and the NCI. MRD results will be reported back to your doctor. During the study the ECOG-ACRIN Data Monitoring Committee, which looks at the study for safety issues, may restrict the use of blinatumomab to MRD positive or MRD negative patients if it seems the drug is not working well in one group. We think the risk of a false positive or false negative test result is very low. Even if the test result is wrong, you would still receive the standard of care treatment on this study.

Induction treatment:

In the first part of this study (induction chemotherapy) you will receive multiple chemotherapy drugs by injection into a vein or into a muscle. Induction treatment will take up to 3 months. To prevent the leukemia from appearing around the spinal cord later you will also receive injections of chemotherapy into the spinal canal in your lower back or through a reservoir placed under the skin in your head. These chemotherapy drugs are given at various time points and include daunorubicin by vein, vincristine by vein, pegaspargase by vein or into the muscle, dexamethasone by mouth, cytarabine by vein and into the spinal canal, methotrexate into the spinal canal, cyclophosphamide into a vein, and 6-mercaptopurine by mouth. Also, a drug named rituximab will be given by vein if your leukemia expresses a certain protein and you and your doctor have decided to have it. If you develop an allergic reaction to pegaspargase, asparaginase erwinia will be used instead. If leukemia cells are found in the spinal fluid around your spinal cord, extra injections of chemotherapy into the spinal canal will be needed and you will also receive radiation therapy to your head later in the course of your treatment. Bone marrow biopsies will be done at the end of the first month of induction treatment and at the completion of induction therapy to see how your leukemia has responded to the treatment. If you have not achieved a remission (significant reduction in the amount of leukemia in your bone marrow and blood) at this time, your doctor will recommend alternative treatment to you outside of this study. If you have achieved a remission, your treatment on this study will continue.

Intensification treatment:

This part of the treatment is to treat residual leukemia cells in your bone marrow and blood that are not easily seen and also helps prevent the leukemia from appearing in your spinal

fluid. You will receive 2 high doses of methotrexate into a vein a week apart and after the second dose of methotrexate you will receive a dose of pegaspargase into a vein or muscle. If you develop an allergic reaction to pegaspargase, asparaginase erwinia will be used instead.

After each dose of methotrexate, you will receive a total of 16 doses of leucovorin calcium, 4 into a vein and 12 by mouth, over a four day period. You will then be observed and monitored while your blood counts decrease and recover.

After the study treatment step called ‘intensification”, it will be determined if you are MRD negative or positive and if you are MRD negative, you will be "randomized" into one of the study groups 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 either group. If you are determined to be MRD positive, you will be assigned to receive blinatumomab and not randomized.

Blinatumomab treatment arm and subsequent treatment:

If you are randomized to the blinatumomab group, you will initially receive two cycles of blinatumomab. Blinatumomab is given as a continuous intravenous infusion. Each cycle is 28 days long, and there is a two week treatment-free break before the beginning of cycle two of blinatumomab making each cycle a total of six weeks in length. It is recommended that you be hospitalized for at least the first 3 days of blinatumomab treatment with the first cycle and for at least two days for the second cycle. Following the hospitalization, you may receive the blinatumomab for the remaining cycle in the outpatient setting. The IV bag will be changed anywhere between one and seven days as per institutional policy and guidelines. If you have a suitable donor your doctor may recommend you have a blood or marrow transplant after receiving therapy with blinatumomab, or you may proceed directly to consolidation chemotherapy

Consolidation therapy will consist of three 28-day cycles of chemotherapy and one 42-day cycle of chemotherapy using standard chemotherapy drugs. You will have regular blood tests to see if your leukemia is responding to the drugs. Before the 4th cycle of consolidation chemotherapy, you will receive an additional 4 week treatment with blinatumomab. After this cycle of blinatumomab you will have another cycle of chemotherapy lasting approximately 28 days and then have another 4 week treatment with blinatumomab. It is recommended that you be hospitalized for at least the first two days of each of these cycles of blinatumomab.

After you are finished with the consolidation chemotherapy you will then proceed to maintenance therapy. Maintenance therapy consists of less intense standard chemotherapy drugs, and will continue for about two and a half years as counted from the start of intensification therapy.

It is recommended that patients refrain from driving or operating heavy machinery while on treatment with blinatumomab.

No blinatumomab treatment arm and subsequent treatments:

If you are randomized to the "No blinatumomab" group, you may proceed directly to a blood or marrow transplant if you have a suitable donor, or you may proceed directly to consolidation chemotherapy. Consolidation therapy will consist of three 28-day cycles of chemotherapy and one 42-day cycle of chemotherapy using standard chemotherapy drugs. You will have regular blood, bone marrow and spinal fluid tests to see if your leukemia is responding to the drugs.

After you are finished with the consolidation chemotherapy you will then proceed to maintenance therapy. Maintenance therapy consists of standard chemotherapy drugs, and will continue for about two and a half years as counted from the start of intensification therapy.

Blood or marrow transplantation:

Based on your age and the individual features of your leukemia, your doctor may recommend that you undergo a BMT. If you have a suitable donor and you achieve a remission or disappearance of your ALL after your induction and intensification treatment (and blinatumomab if you are randomized to receive it) you will be offered a stem cell transplant. Before the transplant you may receive up to one or more cycles of consolidation treatment.

If you choose to have a stem cell transplant, then immediately before the transplant you will receive treatments to alter your immune system so that the transplant is more likely to work. You will receive chemotherapy drugs, through the vein daily for approximately a week and may also receive radiation. A day or two later you will receive stem cells collected from your donor and transfused by vein. The day of the transplant is called "day 0".

After day 0 you may receive additional treatments to help prevent graft versus host disease, a reaction of the immune cells of the donor against the tissues in your body. You may also receive daily antibiotics by mouth to help prevent infection.

After the transplant you will be monitored closely at least once or twice a week for up to 3 months for signs of graft-versus-host-disease described below under "Risks." You will also be monitored for signs of infection. You will be treated with anti-rejection medications to prevent or treat graft – versus – host disease or antibiotics if appropriate. You will get blood tests regularly for the first 4-6 months to determine how well the donor transplant has taken, and then every 3 months for the first year after the transplant. You will also undergo a bone marrow biopsy at 3 months after the transplant and then as needed afterwards to monitor your leukemia and to determine how well the transplant has taken.

Consolidation treatment:

If you do not undergo a BMT, you will receive four cycles of consolidation chemotherapy to consolidate the remission you have achieved in order to prevent the leukemia from returning. Each consolidation cycle will last 4-6 weeks including recovery of your blood counts and will include the chemotherapy drugs cytarabine by vein, etoposide by vein, pegaspargase by vein or injection into the muscle, methotrexate into the spinal canal, daunorubicin by vein, vincristine by vein, dexamethasone by mouth, and 6-mercaptopurine by mouth. Also, a drug named rituximab will be given by vein if your leukemia expresses a certain protein and you

and your doctor have decided to have it. If you develop an allergic reaction to pegaspargase, asparaginase erwinia will be used instead.

If you were originally randomized to receive blinatumomab after intensification, you will receive two more four week cycles of blinatumomab given by continuous infusion through a vein, one four week cycle given before the last cycle of consolidation chemotherapy treatment and one after the last cycle of consolidation chemotherapy.

Maintenance treatment:

After you are finished with the consolidation chemotherapy you will then proceed to maintenance therapy. Maintenance therapy consists of standard chemotherapy drugs, and will continue for about two and a half years as counted from the start of intensification therapy. The chemotherapy drugs will include vincristine by vein every 3 months, prednisone by mouth for five days every 3 months, 6-mercaptopurine by mouth daily, methotrexate by mouth or by vein weekly, and methotrexate into the spinal canal every 3 months.

Pills Diary

Some of the medicines used on the trial will come in pill form. You will be asked to use the Pills Diary to write down when you are taking the pills, and if you have any comments you may make them in the Pills Diary. You will be asked to bring your Pills Diary with you to your visits to your study doctors and/or nurses.

Central Review

Samples of your bone marrow and/or blood and pictures of your chromosomes (karyotypes) will be forwarded to central laboratories to be examined by central reviewers to verify your diagnosis and determine if you can participate in this clinical study.

Approximately six (6) to eight (8) teaspoons of blood and/or one (1) teaspoon of bone marrow, along with smears, will be collected before you begin treatment during pre-registration. Smears will also be submitted at the end of cycles one (1) and two (2) of induction chemotherapy, prior to randomization (at the end of intensification) after the first two (2) cycles of blinatumomab or after two (2) cycles of consolidation, and if your cancer gets worse (relapse).

The chromosome studies will be done before you begin treatment, at the end of cycles one (1) and two (2) of induction chemotherapy, and if your cancer gets worse (relapse) and will determine whether cytogenetic data, that is, the genetic status of your leukemia, is affected by the therapy given and if this information can be used to determine responses to therapy.

Laboratory Research Studies

This study includes laboratory tests that will analyze samples of your bone marrow and blood. The blood samples will be collected at the same time blood is being collected for tests to monitor your health. In most cases an additional needle stick will not be required to collect the blood samples. The blood samples will be collected by using a needle to draw some blood from a vein in your arm. Additional tubes of blood (approximately one (1) teaspoon) will be collected at the following time points from patients on Arm C (blinatumomab arm):

- Post randomization, before you begin treatment
- Prior to cycle three (3) of treatment
- Prior to cycle four (4) of consolidation with blinatumomab (cycle 3 of blinatumomab)
- Before the start of maintenance (at the end of consolidation).

There can be mild pain, or some bleeding and bruising when the blood is drawn. Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but should only last a few minutes after the blood is drawn.

The blood samples will be sent to a laboratory where tests will be performed. Researchers will perform these tests to see if your body is building antibodies to blinatumomab. This is very rare, but would mean that you should stop taking blinatumomab. If you do have antibodies to blinatumomab more blood will be collected every three (3) months until you test negative or for at least one (1) year. More frequent blood collections (e.g. every month) may be requested if there are safety concerns.

The bone marrow will be collected from bone using a needle, with the risk of a small amount of bleeding and slight bruising at the biopsy site. Approximately one (1) teaspoon of bone marrow will be collected at the following time points:

- The end of cycle one (1) of induction chemotherapy
- Prior to randomization (at the end of intensification)
- After the first two (2) cycles of blinatumomab or after two (2) cycles of consolidation
- 100 days post transplant
- Before the start of maintenance (at the end of consolidation).

If you have a stem cell transplant after only one (1) cycle of blinatumomab you will also have bone marrow collected just prior to the stem cell transplant.

The bone marrow samples will be from aspirates used to diagnose and monitor your disease. No additional procedures will be done to obtain the bone marrow.

Researchers will perform these tests to evaluate your response to treatment and assess whether there are residual leukemic cells present.

Methotrexate Shortage

If a national shortage of methotrexate were to occur, we may substitute it with cytarabine during your treatment plan. Other research has found that these regimens will be equally beneficial to the methotrexate regimens. You doctor may answer questions you have regarding the different treatments.

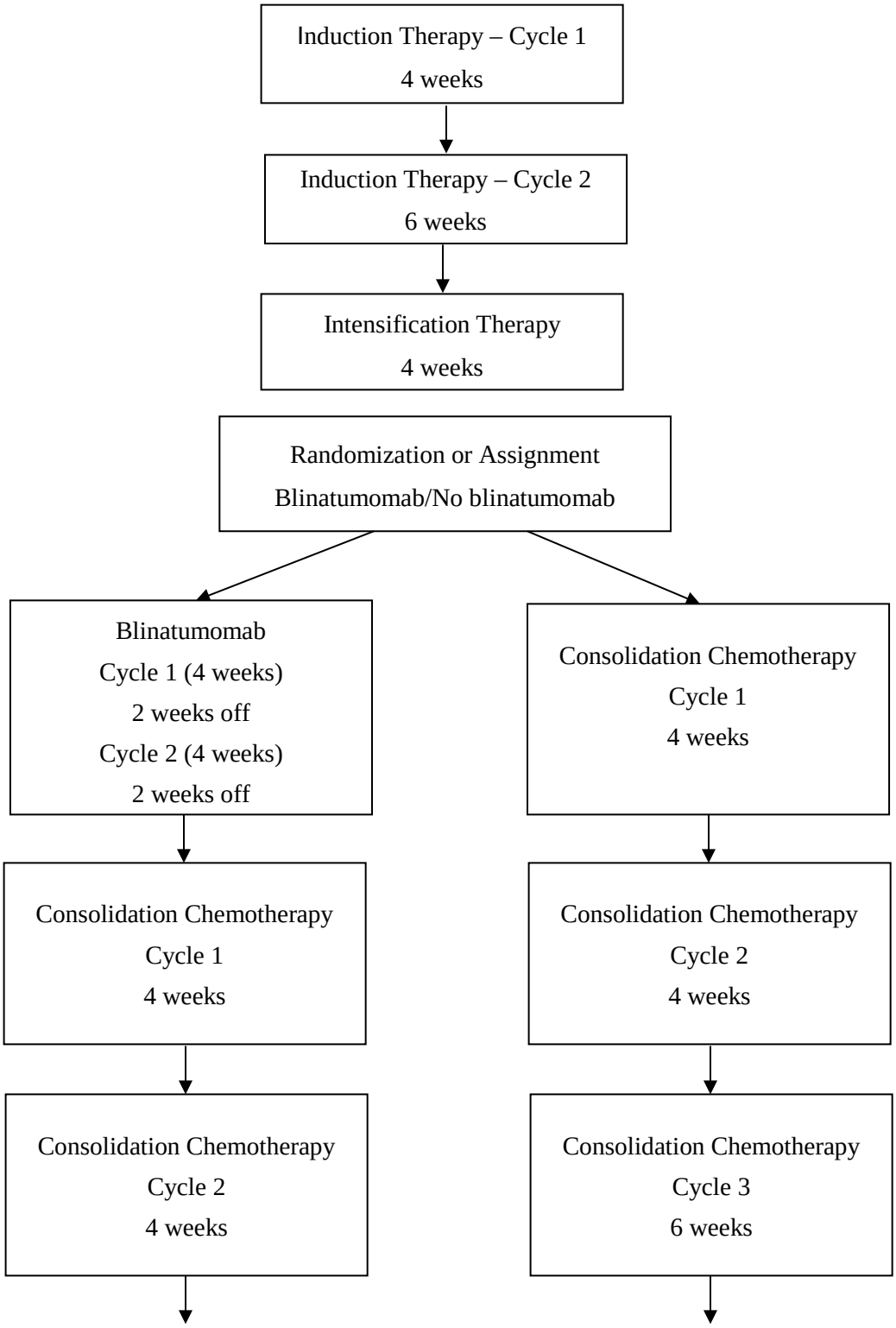
When I Am Finished With Study Treatment

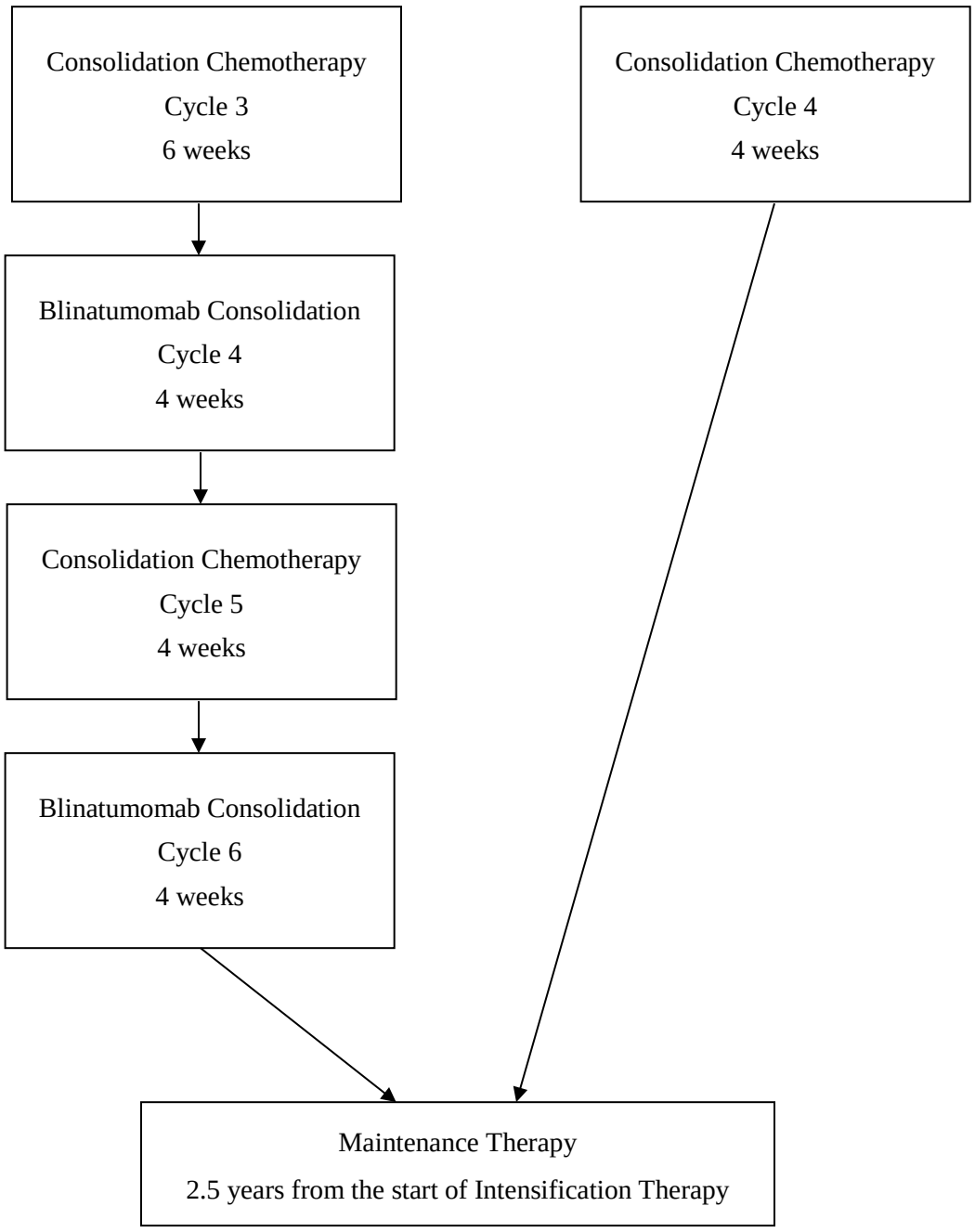
After you have completed all treatment, your doctor will ask you to return for follow-up exams regularly. You will be asked to have a bone marrow biopsy 3 months after finishing treatment and possibly at other times that your doctor may recommend. You will have blood

tests at least every 3 months initially, then every 6 months when you are 2 to 5 years out from the start of treatment and then at least yearly between 6 and 10 years from the start of treatment. Your doctor may recommend more frequent monitoring and additional testing as needed depending on your individual situation.

Study plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.




Consolidation Chemotherapy
Cycle 3
6 weeks
Consolidation Chemotherapy
Cycle 4
4 weeks
Blinatumomab Consolidation
Cycle 4
4 weeks
Consolidation Chemotherapy
Cycle 5
4 weeks
Blinatumomab Consolidation
Cycle 6
4 weeks
Maintenance Therapy
2.5 years from the start of Intensification Therapy

How long will I be in the study?

You will be asked to take the chemotherapy drugs with or without blinatumomab for about 3 years. After you are finished the doctor will ask you to visit the office for follow-up exams regularly. You will be followed to see how you do for up to 10 years after you enroll in the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the 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 doctor if you are thinking about stopping so any risks from the *chemotherapy drugs* or the bone marrow transplant can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The 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?

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 blinatumomab 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.

Blinatumomab side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving blinatumomab, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea • Tiredness, fever • Infection, especially when white blood cell count is low • Bruising, bleeding • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving blinatumomab, from 4 to 20 may have:
• Blood clot which may cause swelling, pain, shortness of breath • Abnormal heartbeat • Bloating, constipation, vomiting • Pain • Sores in the mouth which may cause difficulty swallowing • Chills • Swelling of the body • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Weight gain • Weight loss, loss of appetite • Kidney damage which may require dialysis • Muscle weakness • Difficulty walking, talking, sleeping • Change(s) in thinking patterns or voice • Dizziness, confusion • Trouble with memory

- Abnormal body movement
- Feeling of "pins and needles" in arms and legs
- Seizure
- Worry
- Internal bleeding which may cause black tarry stool, blood in vomit, or blood in urine
- Cough, shortness of breath
- Nose bleed
- Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles
- Increased sweating
- Itching, rash
- Flushing
- High blood pressure which may cause headaches, dizziness, blurred vision
- Low blood pressure which may cause feeling faint

RARE, AND SERIOUS

In 100 people receiving blinatumomab, 3 or fewer may have:

- Air trapped in internal organs that may cause discomfort or pain
- Bleeding of the mouth
- Bleeding in the brain
- Damage to organs (brain, lungs, others) which may cause shortness of breath
- Damage to the brain or nerves which may result in confusion, restlessness, worry, or sensing things that are not there
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Mini stroke
- Restlessness
- Sensing things that are not there
- Change in personality
- State of mind that involves a "loss of contact with reality"

Daunorubicin side effects may include:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Daunorubicin, more than 20 and up to 100 may have:

- Hair loss
- Nausea, vomiting
- Pink or red colored urine, sweat, or saliva

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, from 4 to 20 may have:
• Damage to the heart which may cause shortness of breath, tiredness • Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Pain and sores in mouth and throat • Dark discoloration of the nail, skin • Loss of nails • Redness and pain at the site of previous radiation • Swelling and redness at the site of injection • Diarrhea

RARE, AND SERIOUS In 100 people receiving Daunorubicin, 3 or fewer may have:
• Cancer of the bone marrow (leukemia) cause by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Cytarabine side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, more than 20 and up to 100 may have:
• Blood clot • Rash • Swelling in the rectum which may cause rectal pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Anemia which may cause tiredness, or may require blood transfusions • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Numbness and tingling of the arms and legs • Severe blood infection • Kidney damage which may cause swelling, may require dialysis • Headache • Chest pain • Hair loss • Liver damage which may cause yellowing of skin or eyes • Swelling and redness of the eye

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• None

Vincristine side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Vincristine, more than 20 and up to 100 may have:
• Constipation • Hair loss • Pain or redness at the site of injection • Numbness and tingling of fingers or toes • Headache, jaw pain and/or muscle pain • Weakness and difficulty walking • Swelling of lower legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Vincristine, from 4 to 20 may have:
• Anemia which may cause tiredness, or may require transfusion • Drooping eyelids • Hoarseness

RARE, AND SERIOUS In 100 people receiving Vincristine, 3 or fewer may have:
• Seizure

Dexamethasone side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Dexamethasone, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness • Skin changes, rash, acne • Swelling of the body, tiredness, bruising • Weight gain in belly, face, back and shoulders • In children and adolescents: decreased height • Pain in belly • Infection • Damage to the bone which may cause joint pain or loss of motion • Bleeding of the eye • Glaucoma • Difficulty sleeping • Mood swings • Diabetes • Increased appetite and weight gain • Loss of bone tissue

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Dexamethasone, from 4 to 20 may have:
• Cloudiness of the eye, visual disturbances • Non-healing wound • Heartburn • Kidney stones

RARE, AND SERIOUS In 100 people receiving Dexamethasone, 3 or fewer may have:
• Blurred vision • Bleeding from sores in stomach • Broken bones

Pegaspargase side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Pegaspargase, more than 20 and up to 100 may have:
• Nausea, vomiting • Chills, fever • Pain • Swelling of the body • Tiredness • Blockage of the airway which may cause cough, wheezing • Hives, rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Pegaspargase, from 4 to 20 may have:
• Liver damage which may cause yellowing of eyes and skin • Anemia which may cause tiredness, or may require blood transfusions • Infection, especially when white blood cell count is low • Abnormal heart beat • Bruising, bleeding • Night sweats • Headache • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS In 100 people receiving Pegaspargase, 3 or fewer may have:
• Blood clot • Damage to the pancreas

Asparaginase Erwinia side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Asparaginase Erwinia, more than 20 and up to 100 may have:
• None

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Asparaginase Erwinia, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS In 100 people receiving Asparaginase Erwinia, 3 or fewer may have:
• Blood clot • Nausea • Diabetes • Pain in belly • Vomiting • Mini stroke • Bleeding

Methotrexate side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Methotrexate, more than 20 and up to 100 may have:
• Increased risk of sunburn, rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Methotrexate, from 4 to 20 may have:
• Scarring of the lungs which may cause shortness of breath • Fluid around heart • Internal bleeding which may cause belly pain, black tarry stool, blood in vomit • Nausea, vomiting, diarrhea • Sores in mouth which may cause difficulty swallowing • Liver damage which may cause yellowing of eyes and skin • Scarring of the liver • Hepatitis • Hair loss • Bruising, bleeding • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require transfusion • A new cancer resulting from treatment of earlier cancer • Confusion

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Methotrexate, from 4 to 20 may have:
• Seizure • Kidney damage which may require dialysis • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving Methotrexate, 3 or fewer may have:
• Dizziness • Damage to the brain which may cause tiredness, or changes in thinking

Cyclophosphamide side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• Hair loss • Nausea, vomiting, loss of appetite • Sores in mouth • Infection, especially when white blood cell count is low • Absence of menstrual period which may decrease the ability to have children • Blood in urine

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, from 4 to 20 may have:
• Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Loss or absence of sperm which may lead to an inability to father children • Stuffy nose • Fluid around the heart

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy • Swelling of the body including the brain which may cause dizziness, confusion • Scarring of the lungs

6-Mercaptopurine side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Mercaptopurine, more than 20 and up to 100 may have:
• Damage to the liver which may cause belly pain, bleeding • Rash • Loss of appetite • Fatigue

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Mercaptopurine, from 4 to 20 may have:
• Pain • Sores in stomach • Fever • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require transfusion • Bruising, bleeding • Absence or decrease sperm which may impact ability to father children

RARE, AND SERIOUS In 100 people receiving Mercaptopurine, 3 or fewer may have:
• Damage to the pancreas causing abdominal pain • Liver damage which may cause confusion, yellowing of eyes and skin, swelling • Damage to the lungs which may result in shortness of breath • A new cancer resulting from treatment of earlier cancer

Etoposide side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Etoposide, more than 20 and up to 100 may have:
• Hair loss

COMMON, SOME MAY BE SERIOUS In 100 people receiving Etoposide, more than 20 and up to 100 may have:
• Chills • Sores in mouth which may cause difficulty swallowing • Diarrhea, loss of appetite, nausea, vomiting • Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Tiredness • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Etoposide, from 4 to 20 may have:
• Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness • Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body • Liver damage which may cause yellowing of eyes and skin, swelling

RARE, AND SERIOUS In 100 people receiving Etoposide, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Leucovorin Calcium side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Leucovorin, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Leucovorin, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS In 100 people receiving Leucovorin, 3 or fewer may have:
• None

Prednisone side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• In children and adolescents: decreased height • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, tiredness, bruising • High blood pressure which may cause headaches, dizziness, blurred vision • Pain in belly • Increased appetite and weight gain • Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Prednisone, from 4 to 20 may have:
• Cloudiness of the eye, visual disturbances • Glaucoma • Infection • Non-healing wound • Diabetes • Damage to the bone which may cause joint pain and loss of motion • Kidney stones • Heartburn

RARE, AND SERIOUS In 100 people receiving Prednisone, 3 or fewer may have:
• Bleeding from sores in the stomach • Broken bones

Rasburicase side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rasburicase, more than 20 and up to 100 may have:
• Swelling of the body

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rasburicase, more than 20 and up to 100 may have:
• Fever • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rasburicase, from 4 to 20 may have:
• Rash • Allergic reaction

RARE, AND SERIOUS In 100 people receiving Rasburicase, 3 or fewer may have:
• Difficulty breathing • Destruction of red blood cells in blood

Rituximab side effects may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab (MoAb C2B8 anti CD20, chimeric), more than 20 and up to 100 may have:
• Nausea • Chills, fever • Reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Numbness and tingling of the arms and legs • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab (MoAb C2B8 anti CD20, chimeric), from 4 to 20 may have:
• Anemia which may require blood transfusions • Bruising, bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Heart stops beating • Sores in eye • A tear or a hole in the stomach that may require surgery

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab (MoAb C2B8 anti CD20, chimeric), from 4 to 20 may have:
• Diarrhea, vomiting • Pain • Swelling of the body • Hepatitis which may cause yellow eyes and skin • Dizziness, headache • Kidney damage which may require dialysis • Cough • Scarring of the lungs • Stuffy nose • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Rituximab (MoAb C2B8 anti CD20, chimeric), 3 or fewer may have:
• Damage to the brain which may cause changes in thinking

Reproductive risks:

You should not become pregnant, breastfeed, or father a baby while on this study and for at least 3 months after protocol therapy has ended. The drugs in this study could be very damaging to an unborn baby.

It is important that you understand that you need to either practice "abstinence" (that is avoiding sexual activity) or use birth control while on this study.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must be willing to use 2 highly effective forms of contraception throughout protocol therapy and for at least an additional 3 months after the last dose of protocol therapy. Also, men who have a pregnant partner must be willing to use a condom during sexual activity throughout protocol therapy and for 3 months after the last dose of protocol therapy.

If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as

well as other unknown effects on the developing unborn baby. If a woman becomes pregnant while on this study or within 4 weeks after the last dose of study drug, she will be asked information concerning the outcome of her pregnancy. If a female partner of a male patient becomes pregnant while the male patient is on the study or within 4 weeks after the last dose of study drug, the male patient must notify the investigator.

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 addition of the drug blinatumomab 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 blinatumomab 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 may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **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?

The ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. 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 proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. 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 privacy.

You should also understand that your doctor and ECOG-ACRIN may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, 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**
- **ECOG-ACRIN Cancer Research Group (ECOG-ACRIN)**
- **National Cancer Institute (NCI)**
- **Food and Drug Administration (FDA)**
- **Other regulatory agencies and/or their designated representatives**
- **Drug manufacturers and/or their representatives**
- **Central laboratories, banks and/or reviewers**
- **Amgen**
- **American College of Radiology Imaging Network (ACRIN)**

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

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 Division of Cancer Treatment and Diagnosis, NCI, will provide you with the investigational agent, blinatumomab, free of charge to all participants. If blinatumomab becomes commercially available for this indication, there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should this situation arise.

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://www.cancer.gov/clinicaltrials/learningabout/payingfor in the informed consent.

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?

It is important that you tell your doctor if you feel that you have been injured because of taking part in this study. Contact information for your study doctor is listed on the consent cover page.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

No funds have been set aside to compensate you in the event of injury.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your doctor about any questions or concerns you have about this study. Contact information for your study doctor is listed on the consent cover page.

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.

Please note: This 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. 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.

About Providing Samples (Specimens) for Research

Please read this form and ask about anything that is not clear to you. This is part of the **informed consent** process for research. This is to inform you of the possible risks, benefits, and limits of giving your samples for research.

You are being asked to give some of your samples (called **specimens**) and related information to be used for research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for research is up to you. No matter what you decide, it will not affect your medical care.

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 samples requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your samples will be used only for the projects in which you agree to participate.

What are samples and where are they stored?

A sample is any material taken from your body such as tissue, blood, urine and other fluids.

If you agree, your samples will be sent to laboratories to be used in research or will be stored for research in a Cooperative Group bank supported by the National Cancer Institute. A Cooperative Group bank contains samples and information. Your samples are kept along with those from other people in this bank. Researchers then ask for samples from the bank to study them.

What information will be collected?

When your samples are sent from the institution treating you to a research laboratory or Cooperative Group bank, some personal identifying information (such as your initials) will be sent with the samples. Any personal identifying information sent with the samples is <u>not</u> given to other researchers. The personal identifying information is used only by the laboratory or bank to make sure they have the right samples. Your privacy will be protected

to the fullest extent possible. This will be discussed later in the section "How will information related to my samples be protected?"

Other information that might be used for research includes:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments

What will happen to my samples if I agree to give them for research?

If you agree to provide samples for the planned laboratory research studies, your samples will be sent to researchers who will study them to find answers to specific questions. These researchers may receive some personal identifying information but it will be used only to make sure they have the right samples.

If you agree to let your samples be kept for future research, your samples will be stored in a Cooperative Group bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. This information will not be put into your health record. Results may be used for future research.

You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Some of the coded research information may be sent to a central database. The information will continue to be made available for approved research. Your name or contact information will not be put in the database.

What kind of research will be done with my samples?

Many types of research use normal or diseased (**cancerous**) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called **genetic research**.

Your samples may be looked at**:**

- To see if a trait is passed down in families from one generation to the next (**inherited**). This type of research may help to explain why some cancers run in families or why some people have side effects from treatment while others do not. This is often studied through blood cells and DNA (**genes**).
- To learn about changes in the body that happen after you were born (**non-inherited**). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

Will it help me if I give my samples for research?

Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

What are the risks of giving my samples for research?

- There can be side effects when samples for research are collected. Side effects from the collection of the samples for research, if this occurs, are described in the projects below.
- There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives.
- Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.
- Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Some states have laws to protect against genetic discrimination. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please ask the study staff or check the Internet.

The chance that your information could be misused is very small. We have many protections in place to lower this risk. See the next section, "How will the information related to your samples be protected?" Your privacy will be protected to the fullest extent possible.

How will information related to my samples be protected?

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

1. Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) can match you to the code on your samples 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 restricted access to freezers or rooms that contain samples.
3. Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.
4. Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.
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 Cooperative Group 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 legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.

Making your choice

The choice to take part is up to you. You may choose not to let us store and use your samples. If you decide not to let us store and use your samples, it will not affect your care and you may still participate in the main part of this clinical trial. You may also take part in other research studies.

To learn more, ask the study staff for the booklet called “Providing Your Tissue for Research: What You Need to Know" and it can be found at https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P067. The web version of the information is located at: http://www.cancer.gov/clinicaltrials/learningabout/providingtissue. You may want to read the section “Why do people do research with tissue?”

If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff and let them know that you do not want your samples used for research. Contact information for your study doctor is listed on the consent cover page. Then, any sample that remains in the bank will no longer be used. Samples that have already been given to or used by researchers cannot be returned or destroyed.

Thank you for considering whether to allow your samples to be banked for future research. Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. **If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at 888-657-3711.**

Laboratory research studies

This study includes one or more laboratory tests that will analyze small samples of blood and bone marrow. 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. The bone marrow samples will be from aspirates

used to diagnose and monitor your disease, collected at the time points outlined above in the main consent. The blood samples will be collected at the same time blood is being collected for tests to monitor your health. In most cases an additional needle stick will not be required to collect the blood samples. The blood samples will be collected by using a needle to draw some blood from a vein in your arm. Additional tubes of blood (approximately six (6) to eight (8) teaspoons per time point) will be collected, at the end of cycles one (1) and two (2) of induction chemotherapy, prior to randomization (at the end of intensification), at the end of the first two (2) cycles of blinatumomab or at the end of cycle (2) of consolidation, and if your cancer gets worse (relapse). There can be mild pain, or some bleeding and bruising when the blood is drawn. Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but should only last a few minutes after the blood is drawn.

The specimens will be sent to laboratories where tests will be performed. Researchers will perform these tests to study the biology of your leukemic cells in order to understand the differences in the way the body handles certain drugs and how your disease responds to the treatments. These studies may help explain why some people respond to treatment and why others do not.

Please 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 samples (specimens) for future research

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

This means any samples left over after the central review and the laboratory research studies will be stored for future research studies.

We would like to collect additional blood and some cheek cells for banking for future research. Approximately three (3) to four (4) teaspoons of blood will be collected before you begin treatment, at the end of cycles one (1) and two (2) of induction chemotherapy, prior to randomization (at the end of intensification), at the end of the first two (2) cycles of blinatumomab or at the end of cycle two (2) of consolidation, and if your cancer gets worse (relapse). The cheek cells will be collected before you begin treatment (or any other time point during the study) by gently scraping the inside of your mouth with a cotton swab or rinsing your mouth with Scope or salt water.

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

Please read the questions below carefully and circle "Yes" or "No".

May we have some additional blood and some cells from your cheek for future research about cancer?

I agree to provide additional specimens for research.

Yes No

May we keep any samples left over after the central review and laboratory research studies for research about cancer?

My coded samples and related coded information may be kept for use in research to learn about, prevent, find, or treat cancer? This may also include research on inherited traits (genes passed on in families).

Yes No

May we keep any samples submitted for research about other diseases?

My coded samples and related coded information may be kept for use in research to learn about, prevent, find, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).

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 my hospital or the ECOG-ACRIN Cancer Research Group 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 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)