Study Title for Study Participants: Testing the addition of inotuzumab to the usual chemotherapy treatment for adolescent young adults with acute lymphoblastic leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A041501 – A Phase III Trial to Evaluate the Efficacy of the Addition of Inotuzumab Ozogamicin (a Conjugated Anti-CD22 Monoclonal Antibody) to Frontline Therapy in Young Adults (Ages 18-39 Years) with Newly Diagnosed Precursor B-Cell ALL

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

What is the usual approach to my acute lymphoblastic leukemia?

You are being asked to take part in this study because you have acute lymphoblastic leukemia (ALL). People who are not in a study are usually treated with multiple chemotherapy drugs as part of a regimen that is FDA approved. There are two different approaches that are used, one for adults (40 and older) and one for adolescent young adults, or AYAs (age 18-39). The 18-39 age range for study participants was chosen because the AYA regimen used in the study has been shown to be safe and more effective than adult regimens in this age group. The usual treatment for AYAs consists of five courses that include Course I (Remission Induction), Course II (Remission Consolidation), Course III (Interim Maintenance), Course IV (Delayed Intensification) and Course V (Maintenance). Each course uses a different combination of chemotherapy drugs. The goal of Course I is to eliminate the leukemia cells from your body and allow normal blood cells to return. The goal of Courses II-V is to destroy any remaining leukemia cells and help prevent your leukemia from returning. Course I is 4-6 weeks, and you may spend some or much of this time in the hospital to minimize complications from infections. Almost all of this treatment after the first course can be given on an out-patient basis for most patients. For patients who receive the usual approach for this cancer, about 70 out of 100 are free of cancer at five years.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- you may choose not to be treated for cancer and may want to receive comfort care to relieve symptoms.

Why is this study being done?

The first purpose of this study is to test the safety of the addition of a new drug called inotuzumab along with the usual chemotherapy drugs used for adolescent young adults. Inotuzumab is investigational and is not FDA-approved. There will be about 6 to 12 patients taking part in this first portion of the study.

The second purpose of this study is to compare any good and bad effects of using inotuzumab along with the usual chemotherapy treatment for your cancer to using the usual treatment alone. The addition of inotuzumab to the usual treatment could prevent the cancer from returning or getting worse but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. There will be about 341 people taking part in this study.

What are the study groups?

This study has two study groups.

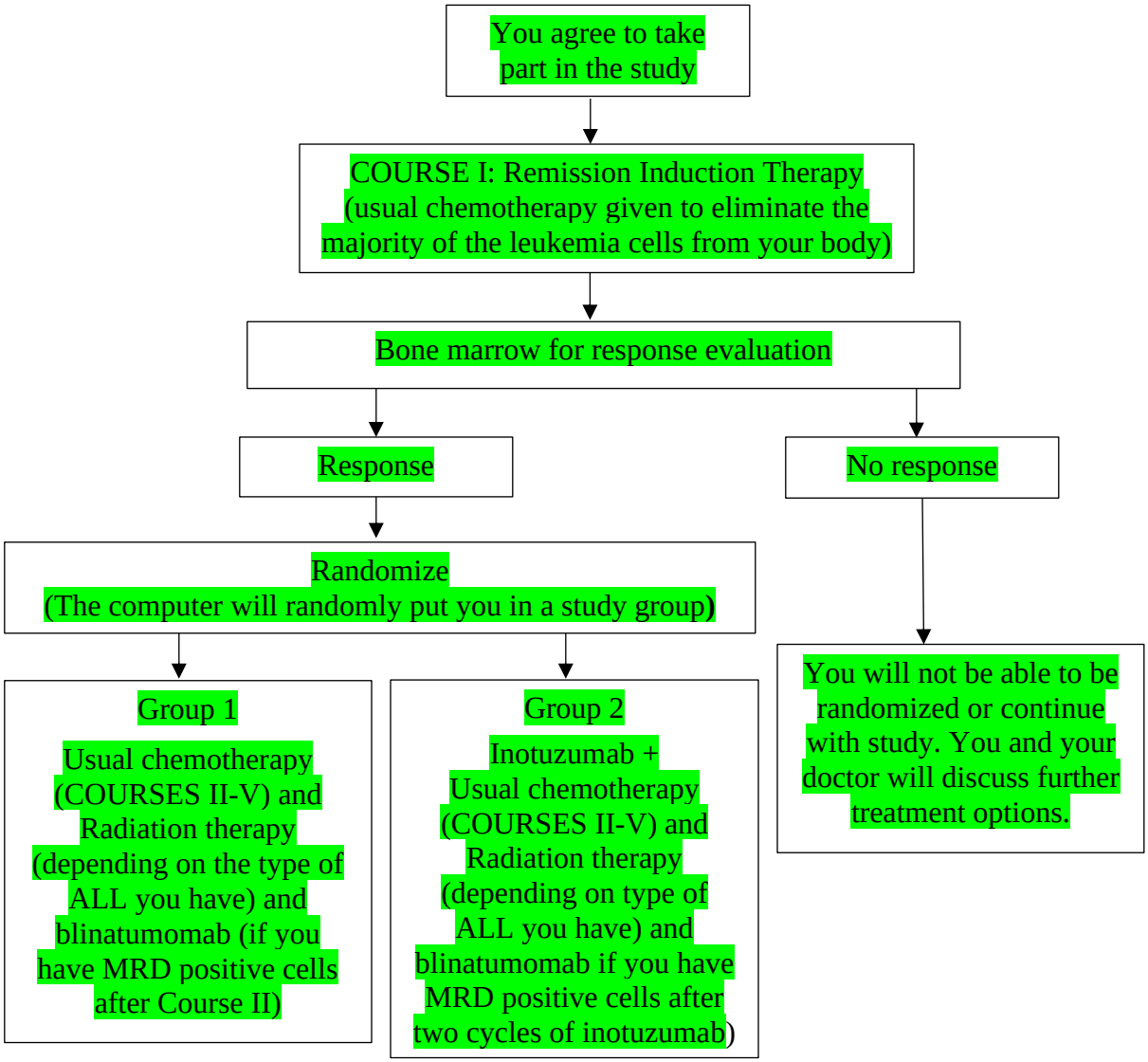
- **Group 1** will get the usual series of leukemia treatments that are divided into five courses of different combinations of chemotherapy drugs. These drugs include cytarabine, cyclophosphamide, dexamethasone, doxorubicin, daunorubicin, mercaptopurine, methotrexate, pegaspargase, thioguanine, vincristine, and maybe rituximab (depending on if you have a certain type of ALL called CD20+). Depending on the type of your ALL, you may also need to be treated with radiation. If you have Minimal Residual Disease (MRD) positive cells present in your bone marrow after Course II, you may be given blinatumomab.
- **Group 2** will get the usual chemotherapy drugs used for this type of cancer (cytarabine, cyclophosphamide, dexamethasone, doxorubicin, daunorubicin, mercaptopurine, methotrexate, pegaspargase, thioguanine, vincristine, and maybe rituximab) **plus a study drug called inotuzumab** in between Course I and Course II. Inotuzumab will be given through a vein in 3 doses over a 28-day period called a cycle, for a total of two cycles. If you have a certain type of ALL, you may also need to be treated with radiation. If you have Minimal Residual Disease (MRD) positive cells present in your bone marrow after two cycles of inotuzumab, you may be given blinatumomab.

Additional information on the standard treatment for ALL is attached at the end of this document in Appendix I.

In order to make sure that adding inotuzumab is safe, the first six to twelve patients who enroll on the study will be automatically assigned to Group 2 and closely watched for any side effects.

Once it is confirmed that the addition of inotuzumab is safe, then a computer will by chance assign you to treatment groups in the study. This is called randomization. This means that a computer will by chance assign you to either Group 1 or Group 2. This is done by chance because no one knows if one study group is better or worse than the other.

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



How long will I be in this study?

You will receive five courses of therapy that are part of the usual chemotherapy treatment. These five courses of therapy will last for about 3 years and 3 months if you are a male, or 2 years and 3 months if you are a female. If you are assigned to Group 2, you will also receive a drug called inotuzumab for a little less than 2 months after you are randomized. After you finish the study treatment, your doctor will continue to watch you for side effects and follow your condition for seven to eight years. You will be followed by clinic visit every 2 months for two years, then every 3 months for two years, then every 6 months for up to 10 years since you started the study. After

you finish seeing your doctor, we will collect the results of any of the usual blood or bone marrow tests you have done in the subsequent 5 years to see if your DNA has changed.

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests and procedures to make sure it is safe for you to participate. If you join the study, there will be exams, tests and/or procedures that will be done to closely monitor your safety and health. Most of these are included in the usual care you would receive even if you were not in a study.

Listed below are those exams, tests, and procedures that may not be needed with the usual approach, but are needed more frequently if you are in the study. The purpose of these procedures is to ensure your safety. We will use them to carefully monitor the effects of the study treatment, including preventing and managing side effects. The insurance coverage information for the tests and other parts of the study is listed in a later section, "What are the Costs."

- A bone marrow aspirate (removal of a sample of bone marrow fluid) and biopsy will be done before you begin the study, at the end of Course I, the end of Course II, the end of Course IV, and the end of Course V to monitor your disease, and if you were to progress or relapse. About 1 tablespoon of bone marrow aspirate will need to be taken for the study at these times. These samples are required and will be collected at the same time as other bone marrow samples that are part of the usual treatment for leukemia.
- About 2 tablespoons of blood will need to be taken for the study before you begin treatment, three times during Course I, two times during Course II, at the end of Course IV, at the end of Course V, and if you were to progress or relapse. These samples are required and will be collected at the same time as other blood samples that are part of the usual treatment for leukemia.
- **If you are in Group 2,** a bone marrow aspirate and blood tests will be done at the end of cycles 1 and 2 of inotuzumab. About 1 tablespoon of bone marrow aspirate and about 2 tablespoons of blood will need to be taken for the study at these times.

These samples are required in order for you to take part in this study because the research on the sample is an important part of the study. Samples taken for the study are collected in a similar way to samples collected for the usual treatment. These blood and bone marrow aspirate samples will be used to help investigators determine who will be most likely to respond to this treatment in the future. Given that there is currently no information that would affect your clinical care that is being tested, these results will not be available to you or to your study doctor. However, at the completion of the trial, overall study findings will be shared with study participants and their doctors.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are those exams, tests and procedures that will be done for research purposes only.

- Before you begin the study, about 1 teaspoon of bone marrow aspirate will be collected and sent to University of New Mexico for a genetic test to find out if you have a certain

subtype of ALL (BCR-ABL1-like). The results of this test will be used to help ensure that an equal number of patients with this subtype are assigned to each treatment group. This sample will be collected at the same time that a bone marrow procedure is performed as part of the usual treatment for leukemia and is collected in a similar way to samples collected for diagnosis. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. The results will not be shared with you or your doctor. However, if at any point you cannot continue on with the study because your leukemia is not responding to the treatment in the study, then the results will be shared with your doctor for consideration of other treatment options.

If any additional blood or bone marrow aspirate is left over after the tests are performed, then the remaining sample will be stored for future use in a "biobank." Biobanking will be discussed in the "ADDITIONAL STUDIES" section. The remaining sample will only be saved for future use if you provide your consent by circling "yes" under question #4.

What possible risks can I expect from taking part in this 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 study drugs may not be better, and could possibly be worse, than the usual approach for your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. (For non-U.S. participants, please verify the existence of such laws before including the following sentence.) There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

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

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

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.

- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

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

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

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

<u>Study GROUP 1 and GROUP 2</u> – **Possible side effects of COURSE I-V treatment (the usual approach for this type of cancer)**

Possible side effects of **COURSE I** treatment (Daunorubicin, Dexamethasone, Vincristine, Cytarabine, IT Methotrexate, Pegaspargase):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine (ara-c), Dexamethasone, Daunorubicin, IT Methotrexate, Pegaspargase, Vincristine, more than 20 and up to 100 may have:
• Blood clot • Rash, hives • Swelling in the rectum which may cause rectal pain • Diarrhea, constipation, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Anemia which may cause tiredness, or may require blood transfusions • Fever, chills • Hair loss • Pink or red colored urine, sweat, or saliva • Pain, swelling and 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 the body, tiredness, bruising • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • High blood pressure which may cause headaches, dizziness • Skin changes, acne • Weight gain in belly, face, back and shoulders • In children and adolescents: decreased height • Infection, especially when white blood cell count is low • 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 Cytarabine (ara-c), Daunorubicin, Dexamethasone, IT Methotrexate, Pegaspargase, Vincristine, from 4 to 20 may have:

- Bruising, bleeding
- Numbness and tingling of the arms and legs
- Severe blood infection
- Liver damage which may cause yellowing of skin or eyes
- Swelling and redness of the eye, drooping eyelids
- Damage to the heart which may cause shortness of breath, tiredness
- Abnormal heart beat
- Chest pain
- Dark discoloration of the nail, skin
- Loss of nails
- Cloudiness of the eye, visual disturbances
- Redness and pain at the site of previous radiation
- Cancer of the bone marrow (leukemia) cause by chemotherapy
- Hoarseness
- Night sweats
- Non-healing wound
- Heartburn
- Kidney stones
- Swelling of the brain which may cause blurred vision and/or confusion
- Damage to the brain which may cause changes in thinking
- Confusion, dizziness

RARE, AND SERIOUS

In 100 people receiving Cytarabine (ara-c), Daunorubicin, Dexamethasone, IT Methotrexate, Pegaspargase, Vincristine, 3 or fewer may have:

- Seizure
- Bleeding from sores in the stomach
- Broken bones
- Damage to the pancreas
- Blurred vision
- Broken bones

- Paralysis, weakness
- Bleeding into the space of the spine at the site of injection

Possible side effects of **COURSE II** treatment (Cyclophosphamide, Cytarabine, IT Methotrexate, Mercaptopurine, Vincristine, Pegaspargase):

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Cyclophosphamide, Cytarabine IV or SQ; IT Methotrexate, Mercaptopurine (MP), Vincristine, and Pegaspargase e, more than 20 and up to 100 may have:

- Hair loss
- Diarrhea, constipation, nausea, vomiting, loss of appetite
- Infection, especially when white blood cell count is low
- Absence of menstrual period which may decrease the ability to have children
- Blood in urine
- Blood clot
- Swelling and sores in the rectum which may cause rectal pain
- Sores in mouth which may cause difficulty swallowing
- Anemia which may cause tiredness, or may require blood transfusions
- Fever
- Damage to the liver which may cause belly pain, bleeding, yellowing of skin or eyes
- Fatigue
- 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
- Chills
- Pain
- Swelling of the body
- Blockage of the airway which may cause cough, wheezing
- Hives, rash

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Cyclophosphamide, Cytarabine IV or SQ; IT Methotrexate, Mercaptopurine (MP), Vincristine, and Pegaspargase, 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
- 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
- Chest pain
- Swelling and redness of the eye
- Drooping eyelids
- Sores in stomach
- Hoarseness
- Abnormal heart beat
- Night sweats
- Swelling of the brain which may cause blurred vision, and/or confusion
- Damage to the brain which may cause changes in thinking
- Confusion, dizziness

RARE, AND SERIOUS

In 100 people receiving Cyclophosphamide, Cytarabine IV or SQ; IT Methotrexate, Mercaptopurine (MP), Vincristine, and Pegaspargase, 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
- A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy
- Swelling of the body including the brain which may cause dizziness, confusion
- Damage to the pancreas causing abdominal pain
- Damage or scarring of the lungs which may result in shortness of breath
- Seizure
- Paralysis, weakness
- Bleeding into the space of the spine at the site of injection

Possible side effects of **COURSE III** treatment (Vincristine, IV Methotrexate, Pegaspargase, IT Methotrexate):

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Vincristine, IV Methotrexate, Pegaspargase, and IT Methotrexate, 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
- 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
- Diabetes
- Increased risk of sunburn, rash

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Vincristine, IV Methotrexate, Pegaspargase and IT Methotrexate, 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
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Drooping eyelids
- Hoarseness
- Swelling of the brain which may cause blurred vision and/or confusion
- Damage to the brain which may cause changes in thinking
- Confusion, dizziness
- Nausea, vomiting, diarrhea
- Rash
- Tiredness
- Pain
- 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
- Sores in mouth which may cause yellowing of eyes and skin
- Scarring of the liver
- Hepatitis
- Hair loss
- A new cancer resulting from treatment of earlier cancer
- 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
- Damage to the brain which may cause changes in thinking

RARE, AND SERIOUS In 100 people receiving Vincristine, IV Methotrexate, Pegaspargase, and IT Methotrexate, 3 or fewer may have:
• Blood clot • Damage to the pancreas • Seizure • Bleeding in the brain • Paralysis, weakness • Bleeding into the space of the spine at the site of injection

Possible side effects of **COURSE IV** treatment (Cyclophosphamide, Cytarabine, Dexamethasone, Doxorubicin, Pegaspargase, Thioguanine, IT Methotrexate, and Vincristine):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Cytarabine, Dexamethasone, Doxorubicin, Pegaspargase, Thioguanine, IT Methotrexate, and Vincristine, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness • Skin changes, rash, acne, hives • Swelling of the body, tiredness, bruising, bleeding or rectal pain • Weight gain in belly, face, back and shoulders • In children and adolescents: decreased height • Pain, belly pain • Infection, especially when white blood cell count is low • 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 • Hair loss • Nausea, vomiting, constipation, loss of appetite • Absence of menstrual period which may decrease the ability to have children • Blood in urine • Sores in mouth, throat or stomach which may cause difficulty swallowing • Red colored urine, saliva, or sweat • Chills, fever • Blockage of the airway which may cause cough, wheezing • Pain or redness at the site of injection • Numbness and tingling of fingers, arms, legs or toes • Headache, jaw pain and/or muscle pain • Weakness and difficulty walking

- Swelling of lower legs
- Blood clot
- Anemia which may cause tiredness, or may require blood transfusions

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Cyclophosphamide, Cytarabine, Dexamethasone, Doxorubicin, Pegaspargase, Thioguanine, IT Methotrexate, and Vincristine, from 4 to 20 may have:

- Cloudiness of the eye, visual disturbances
- Non-healing wound
- Heartburn
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusion
- Loss or absence of sperm which may lead to an inability to father children
- Stuffy nose
- Fluid around the heart
- Damage to the heart or heart failure which may cause shortness of breath, abnormal heart beat, swelling of ankles, cough or tiredness
- Chest pain
- Hepatitis or liver damage which may cause yellowing of eyes and skin
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Cancer of the bone marrow (leukemia) caused by chemotherapy
- Damage to organs which may cause infection, bleeding, may require transfusions
- Darkening of the nail beds or skin or hands and feet
- Loss of nails
- Swelling of the brain which may cause dizziness, confusion, shortness of breath
- Night sweats
- Drooping eyelids
- Swelling and redness of the eye
- Hoarseness
- Abnormal opening in or damage to the stomach which may cause belly pain
- Numbness and tingling of the arms and legs
- Severe blood infection
- Kidney stones or kidney damage which may cause swelling, may require dialysis
- Damage to the brain which may cause changes in thinking
- Confusion, dizziness

RARE, AND SERIOUS

In 100 people receiving Cyclophosphamide, Cytarabine, Dexamethasone, Doxorubicin, Pegaspargase, Thioguanine, IT Methotrexate, and Vincristine, 3 or fewer may have:

- Blurred vision
- Bleeding from sores in stomach
- Broken bones

- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body
- Scarring of the lungs
- Damage to the pancreas
- Seizure
- Paralysis, weakness
- Bleeding into the space of the spine at the site of the injection

Possible side effects of **COURSE V** treatment (Vincristine, Dexamethasone, Mercaptopurine, IT Methotrexate, and Methotrexate PO):

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Mercaptopurine PO, Methotrexate PO, IT Methotrexate, Dexamethasone, Vincristine, more than 20 and up to 100 may have:

- Damage to the liver which may cause belly pain, bleeding
- Loss of appetite
- In children and adolescents: decreased height
- Mood swings
- Swelling of the body, tiredness, bruising
- High blood pressure which may cause headaches, dizziness, blurred vision
- Belly pain
- Increased appetite and weight gain
- Weight gain in the belly, face, back and shoulders
- 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
- Skin changes, rash, acne
- Bleeding of the eye
- Difficulty sleeping
- Loss of bone tissue

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Mercaptopurine PO, Methotrexate PO, IT Methotrexate, Dexamethasone, Vincristine, 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
- 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
- Hepatitis, liver damage, or scarring of the liver which may cause yellowing of eyes and skin
- Increased risk of sunburn, rash, skin changes, acne
- A new cancer resulting from treatment of earlier cancer
- Confusion
- Seizure
- 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
- Cloudiness of the eye, visual disturbances
- Glaucoma
- Non-healing wound
- Diabetes
- Damage to the bone which may cause joint pain and loss of motion
- Kidney stones
- Heartburn
- Drooping eyelids
- Hoarseness
- Loss of bone tissue
- Swelling of the brain which may cause blurred vision, and/or confusion
- Damage to the brain which may cause changes in thinking

RARE, AND SERIOUS

In 100 people receiving Mercaptopurine PO, Methotrexate PO, IT Methotrexate, Dexamethasone, Vincristine, 3 or fewer may have:

- Damage to the pancreas causing abdominal pain
- Damage to the lungs which may result in shortness of breath
- Bleeding from sores in the stomach
- Broken bones
- Blurred vision
- Paralysis, weakness
- Bleeding into the space of the spine at the site of injection

Study GROUP 2 ONLY – Patients who are in Group 2 will be given the **study drug inotuzumab** between Course I and Course II. In addition to side effects outlined above, people who are in **Group 2** may also experience the possible side effects of inotuzumab listed below.

Possible side effects of Inotuzumab:

COMMON, SOME MAY BE SERIOUS In 100 people receiving inotuzumab ozogamicin (PF-05208773), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Belly pain • Nausea • Tiredness, fever • Bruising, bleeding • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving inotuzumab ozogamicin (PF-05208773), from 4 to 20 may have:
• Bloating, constipation, diarrhea, vomiting • Fluid in the belly which may cause swelling • Sores in the mouth which may cause difficulty swallowing • Chills • Damage to the liver which may cause yellowing of eyes and skin • Loss of appetite

RARE, AND SERIOUS In 100 people receiving inotuzumab ozogamicin (PF-05208773), 3 or fewer may have:
• Reaction during or following a drug infusion which may cause rash, low blood pressure • Change in the heart rhythm • Kidney damage which may require dialysis

If you have a certain type of leukemia (CD20+), you will be given **rituximab** in courses II, III and IV along with the other drugs listed. **This is the usual approach for this type of leukemia.** In addition to side effects outlined above, people who receive rituximab may also experience the possible side effects listed below.

Possible Side Effects of Rituximab:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, 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
- Anemia which may require blood transfusions
- Numbness and tingling of the arms and legs
- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Rituximab, from 4 to 20 may have:

- Bruising, bleeding
- Abnormal heartbeat
- Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Sores in eye
- A tear or a hole in the stomach that may require surgery
- Diarrhea, vomiting
- Pain
- Swelling of the body
- Hepatitis, or liver damage 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, 3 or fewer may have:

- Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability. This is called progressive multifocal leukoencephalopathy (PML).
- Heart stops beating

If you have MRD positive cells present in your bone marrow after Course II (if you are in Group 1) or after 2 cycles of Inotuzumab (if you are in Group 2), you may be given **blinatumomab**. **This is the usual approach for this type of leukemia.** In addition to side effects outlined above, people who receive blinatumomab may also experience the possible side effects listed below.

Possible Side Effects of Blinatumomab

COMMON, SOME MAY BE SERIOUS In 100 people receiving blinatumomab (AMG 103), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • 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 (AMG 103), from 4 to 20 may have:
• Blood clot which may cause swelling, pain, shortness of breath • Abnormal heartbeat • Pain • Constipation, diarrhea, vomiting • 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 • 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 • Cough, shortness of breath • Nose bleed • 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 (AMG 103), 3 or fewer may have:
• Damage to the bone marrow which may cause infection, bleeding, may require transfusions • Internal bleeding which may cause black tarry stool, blood in vomit • Air trapped in internal organs that may cause discomfort or pain • Bleeding of the mouth • Kidney damage which may require dialysis • Bleeding in the brain • Damage to organs (brain, lungs) which may cause shortness of breath • Damage to the brain or nerves • 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" • Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles

Radiation Therapy

If your leukemia has affected other parts of your body or if doctors think that it may affect other parts of your body, then you will need to receive radiation. **This is the usual approach for this type of leukemia.** In addition to side effects outlined above, people who receive radiation may also experience the side effects listed below.

Possible Side Effects of Radiation Therapy:

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• Reddening, tanning, or peeling of the skin • Mild pain • Hair loss • Tiredness • Diarrhea, nausea • Anemia, which may require transfusion • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Thickening and numbness of the skin • Sores or ulcers on the skin or near the cancer location

- Permanent hair loss
- Bleeding from the skin
- Sores in mouth which may cause difficulty swallowing

RARE, AND SERIOUS
In 100 people receiving radiation therapy, 3 or fewer may have:

- Damage to internal organs
- Abnormal opening in internal organs which may cause pain and bleeding

Possible risks and side effects of sample collection:

Bone marrow sample: There may be some temporary pain or discomfort associated with bone marrow aspirations and biopsies 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.

Blood sample: Blood collection is usually a very low risk procedure. There is a small risk of bleeding, bruising, infection, inflammation, blood clot or discomfort at the site of the blood collection. Attention will be taken to apply pressure following the procedure to reduce bleeding. You may feel dizzy or faint when blood is being drawn. We will ask you to lie down for a few minutes until any dizziness passes.

Spinal tap risks: Intrathecal methotrexate will be given by lumbar puncture (spinal tap) at the times listed in Appendix I to prevent the cancer cells from entering the central nervous system. There may be some local discomfort and a headache afterwards associated with this routine outpatient procedure. Convulsions (seizures) have rarely occurred after central nervous system treatment.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. It is recommended that you not become pregnant or father a child for at least one year after permanently stopping all study treatment, however, these issues should be discussed carefully with your doctor. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

In addition to the risks identified above, patients should avoid alcohol and over-the-counter pain relievers while being treated on this study.

You will be provided with a clinical trial wallet card, which will inform other healthcare providers that you are participating in a clinical trial. You are to keep the wallet card with you at all times.

What possible benefits can I expect from taking part in this study?

This study may or may not help you. It is not possible to know at this time if the study drug is better than the usual approach. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

What are the costs of taking part in this study?

<u>Your Potential Costs:</u>

You and/or your health plan/insurance company will be responsible for:

- The infusion of the study drug inotuzumab (if you are in Group 2), non-study drugs and all premedications, fluids and procedures
- Exams, tests, and procedures that may be needed to manage side effects and to monitor your safety and may be needed more frequently while you are on the study.

You are responsible for all co-pays and deductibles according to your benefit plan with your insurance. It is important for you to speak to your insurance company/health plan to ensure that you understand your coverage and whether you might need approval to take part in a study. While most plans cover clinical trials, it is your responsibility to check with them.

Ask your doctor, nurse, case manager, or financial counselor/advisor if you are unsure which costs will be billed to your insurance/health plan. If you have other questions about what your plan

covers, you may also ask to speak to a hospital/clinic financial counselor/advisor or case manager at the hospital or clinic.

Costs Paid by the Study
Exams, tests, and procedures done for research purposes only will not be billed to you or your insurance plan. This includes the special genetic test done before you begin the study.

If you are in Group 2: The inotuzumab will be supplied at no charge while you take part in this study. The cost of getting the inotuzumab ready and giving it to you is not paid by the study sponsor, so you or your insurance company may have to pay for this. It is possible that the inotuzumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You will not be paid for taking part in this study. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.
If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

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

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- Montana Cancer Consortium
- The Alliance and other participating groups in the National Clinical Trials Network, such as ECOG-ACRIN, SWOG, and NRG
- Any drug company supporting the study

- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

Who can answer my questions about this study?

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

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Health Outcomes Study

If you choose to take part in this study, you will be asked during Maintenance Therapy (Course V), to track your medication, complete questionnaires, and use a special bottle cap (called a MEMS Cap) to track how often you're taking your medication. Researchers will use this information to help better understand experiences and difficulties of taking oral medication for leukemia.

The study will take place over 5-6 months at some point during Maintenance Therapy (Course V).

You will be asked to do the following if you choose to take part in the study:

- Use a special bottle cap for methotrexate (MTX) and mercaptopurine (6-MP) to count how many times you open the pill bottles, and return the bottles to your physician at the end of the Health Outcomes study. Please note that you must agree to use a medication bottle cap, and cannot use a pill box.
- Complete a questionnaire at the beginning of the Health Outcomes study that asks about your demographic information (race/ethnicity, occupation, etc.), your thoughts and feelings about your doctor, how often you are taking your mercaptopurine pills (6-MP) and methotrexate (MTX), and how you are feeling. This questionnaire will take about 30 minutes to complete.
- Complete a questionnaire mid-way through the Health Outcomes study (~ 3 months) and at the end of the Health Outcomes study (~6 months). The questionnaire will ask about things like taking your 6-MP and MTX, using the MEMS caps, your health and your thoughts about your doctor. This questionnaire will take about 15 minutes to complete.

You may feel uncomfortable answering some of the questions, and you can skip any you do not want to answer. The answers will be kept confidential and will not be shared with your doctor.

1. Please circle your answer: I choose to take part in the Health Outcomes study and will fill out the forms and use the caps to track my medication:
   YES NO

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your blood and saliva. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect samples of your saliva and blood to study why people respond differently to leukemia treatments. In addition, the left over bone marrow you have donated previously for this study will also be used for some of the same research.

The researchers will also ask your permission to store remaining samples collected during the trial and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for future medical research. The research that may be done is unknown at this time. Storing samples for future studies is called “biobanking”. The Biobank is being run by the Alliance and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) If you agree to provide saliva samples, then these samples will be taken before you start treatment. For the sample, we will ask you to swish a small amount of mouthwash (like Scope) in your mouth for 30-60 seconds, and then spit the mouthwash into a container. This will provide buccal cells, which are not involved with your disease.
2) If you agree to provide leftover bone marrow, then any leftover bone marrow sample that you have donated previously for this study will be used for the research described above. You will NOT have to repeat a bone marrow procedure for additional aspirate.
3) If you agree to provide blood samples, about 2 teaspoons of blood will be collected from a vein in your arm six times as follows: before you start course I, once during weeks two, three and four of Course I, the fifth week of Course II and the first week of Course III.
4) If you agree to have leftover samples sent to the Biobank, then all left over saliva, blood and bone marrow samples will be sent to the BioBank for future research.
5) Your sample and some related health information will be sent to a researcher for use in the study described above. Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
6) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
7) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
8) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also 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 study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Alliance staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom Alliance sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor who will let the researchers know. 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 and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR THE LABORATORY STUDIES:

2. I agree to have my saliva collected and I agree that my specimen samples (saliva and left over bone marrow) and related information may be used for the laboratory studies described above.

   YES NO

3. I agree to have my blood collected and I agree that my specimen samples and related information may be used for the laboratory studies described above.

   YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

4. My samples (saliva, blood, and bone marrow) and related information may be kept in a Biobank for use in future health research.

   YES NO

5. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

   YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

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

APPENDIX I

Information for Patients on the Standard Treatment for ALL

Thank you for your interest in the A041501 study, **"*Testing the addition of inotuzumab to the usual chemotherapy treatment for adolescent young adults with acute lymphoblastic leukemia*."** This information sheet describes the usual treatment for your ALL that is used in this study.

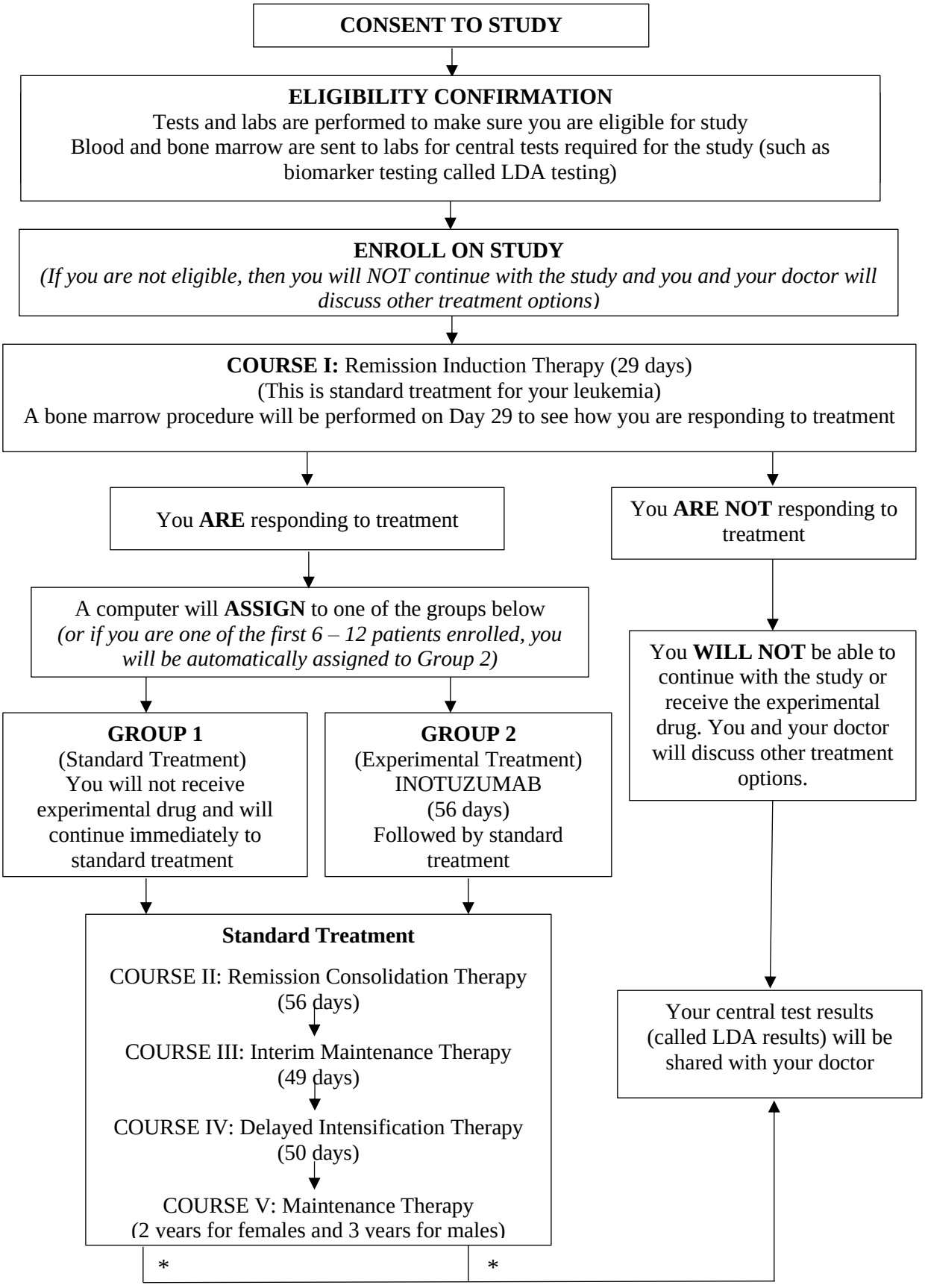
The usual treatment for your leukemia is a series of treatments that are divided into five courses of different combinations of chemotherapy drugs. **All patients who participate in this study will receive this usual treatment.** The five courses are:

- Course I (Remission Induction)
- Course II (Remission Consolidation)
- Course III (Interim Maintenance)
- Course IV (Delayed Intensification)
- Course V (Maintenance)

These courses and what will happen during each course are described below. If you are assigned to Group 2 of the study, you will get the usual treatment (Courses I-V) plus the study drug inotuzumab in between Course I and Course II.

The chart below shows what will happen if you participate in this study and when you will receive each course of the usual treatment.

Please let your doctor know if you have any questions about the study or the usual treatment.



* If at any time your leukemia gets worse in either Group 1 or Group 2, your central test results from LDA testing will be shared with your doctor.

Course I – Remission Induction Therapy

The goal of Course I is to eliminate the majority of the leukemia cells. The following chemotherapy drugs will be given over the course of four weeks during the first course of therapy:

Drug	Route	Days
Cytarabine (Ara-C)	IT injection	Day 1
Dexamethasone	Oral	Days 1-7 and 15-21
Daunorubicin	IV	Days 1, 8, 15, and 22
Vincristine	IV	Days 1, 8, 15, and 22
IT Methotrexate	IT injection	Days 8 and 29
Pegaspargase	IV	Day 4, 5, **or** 6

A **lumbar puncture** (also known as a "spinal tap") will be performed on **Days 1, 8 and 29** of this course to diagnose and treat any ALL cells that have entered into the central nervous system (CNS).

A **mandatory bone marrow aspirate and biopsy** will be obtained at the **end of Course I (on Day 29)** to monitor your disease. If your sample shows that your leukemia is responding to the treatment, then you will go on to be randomized to either Group 1 or Group 2. Additional samples may be necessary if your bone marrow is slow to recover to the number of normal cells required to proceed with treatment. If your sample continues to show that your leukemia is not responding to the treatment, then you will not be able to continue with the study (and will not be able to go on to be randomized to receive inotuzumab). Your physician may prescribe an alternative therapy for your disease.

Patients who go on and are randomized to Group 1 will go on to Courses II-V. Patients who go on and are randomized to Group 2 will receive inotuzumab before continuing on to Courses II-V.

Course II – Remission Consolidation Therapy

If you were assigned to Group 1, then you will start Course II after you finish Course I. If you were assigned to Group 2, then you will start Course II after you finish 2 cycles of inotuzumab therapy. All patients will go through this course of "Remission Consolidation" to try to prevent recurrence of your leukemia.

This treatment should begin immediately on Day 29 of the prior course or shortly afterwards. There should be no unnecessary delays. The following standard chemotherapy drugs will be given during the next 2 months of therapy:

Drug	Route	Days
Cyclophosphamide	IV	Days 1 and 29
Cytarabine (Ara-C)	IV or SC	Days 1-4, 8-11, 29-32, and 36-39
6-Mercaptopurine	Oral	Days 1-14 and 29-42
Vincristine	IV	Days 15, 22, 43, and 50

IT Methotrexate	IT injection	Days 1, 8, 15, and 22*
Pegaspargase	IV	Days 15 and 43
Rituximab**	IV	Days 1, 8, 29, 36

* Patients with leukemia cells in the spinal fluid will not have IT methotrexate given on days 15 and 22

** Rituximab is only given for patients who have a **certain type of ALL (CD20+)**

You should not take milk or citrus products with Mercaptopurine.

At the end of Course II, if your leukemia is not responding to the treatment in this study, you may be removed from further therapy on this study. Your physician may then prescribe an alternative therapy for your disease.

Course III – Interim Maintenance Therapy

If, after Course II, there is no clinical evidence of leukemia, you will receive a third course of treatment, referred to as "Interim Maintenance," to try to further prevent recurrence of your leukemia. This treatment is designed in part to decrease the risk of leukemia recurring in the brain and spinal cord (the central nervous system), known sites of recurrence in patients with ALL.

As soon as you have recovered sufficiently from Course II, the following standard chemotherapy drugs will be given without delay during the next cycle of therapy:

Drug	Route	Days
Vincristine	IV	Days 1, 11, 21, 31, and 41
Methotrexate	IV	Days 1, 11, 21, 31, and 41
IT Methotrexate	IT injection	Days 1 and 31
Pegaspargase	IV	Days 2 and 22
Rituximab*	IV	Days 1 and 11

***** Rituximab is only given for patients who have a **certain type of ALL (CD20+)**

Course IV – Delayed Intensification Therapy

If, after Course III, there has been a significant reduction of the number of leukemia cells in your bone marrow, that is, your bone marrow shows a response to therapy, you will receive the next course of treatment, referred to as "Delayed Intensification," to try to prevent recurrence of your leukemia. This treatment should be given without delay.

Drug	Route	Days
Doxorubicin	IV	Days 1, 8, and 15
Vincristine	IV	Days 1, 8, 15, 43, and 50
Dexamethasone	Oral or IV	Days 1-7 and 15-21

Pegaspargase	IV	Day 4, 5, **or** 6 AND Day 43
Cyclophosphamide	IV	Day 29
Cytarabine (Ara-C)	IV or SC	Days 29-32 and Days 36-39
6-Thioguanine (6-TG)	Oral	Days 29-42
IT Methotrexate	IT injection	Days 1, 29, and 36
Rituximab*	IV	Days 1 and 8

***** Rituximab is only given for patients who have a **certain type of ALL (CD20+)**

You should not take milk or citrus products with Thioguanine.

A **lumbar puncture** ("spinal tap") will be performed on **Days 1, 29 and 36** of this course to diagnose and treat any ALL cells that have entered into the central nervous system (CNS).

You will have a **bone marrow aspiration and biopsy** performed at **the end of this course** of treatment to allow the doctor to determine if the cancer has been destroyed in your bone marrow.

At the end of Course IV, if your leukemia is not responding to the treatment in this study, you may be removed from further therapy on this study. Your physician may then prescribe an alternative therapy for your disease.

Course V – Maintenance Therapy

If, after completing Course IV, you have recovered sufficiently from all the treatment courses, and there is no evidence of persistent leukemia in your bone marrow, that is, your bone marrow shows a remission from leukemia, you will receive a final prolonged course of treatment, referred to as "Maintenance Therapy."

Maintenance Therapy will consist of 12 week cycles of therapy and will continue to be administered to you for up to 24 months (2 years) if you are a woman or 36 months (3 years) if you are a man, from the time you began Course III. Each 12 week cycle will last 84 days. You will receive the following treatment during each cycle:

Drug	Route	Days
Vincristine	IV	Days 1, 29, and 57
Dexamethasone	Oral or IV	Days 1-5, 29-33 and 57-61
Mercaptopurine	Oral	Days 1-84
IT Methotrexate	IT injection	Day 1*
PO Methotrexate	Oral	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78**

* IT methotrexate is also given on Day 29 of the first 4 courses of maintenance therapy.

** PO methotrexate is held on Day 29 of the first 4 courses of maintenance therapy (when IT methotrexate is given).

You should not take milk or citrus products with Mercaptopurine.

A **bone marrow aspirate and biopsy** will be obtained **every six months** to monitor your disease. If a bone marrow aspirate and biopsy were to show that leukemia cells had returned to your bone marrow, this treatment will be discontinued.

Radiation Therapy (this is standard treatment)

In rare cases when leukemia cells invade the testes (testicles, gonads), 12 doses of radiation therapy (given Monday through Friday for a total of 12 treatments) are required for male patients (a total dose of 2400 cGy) during Consolidation Therapy (Course II). This treatment often results in skin redness and sterility (loss of fertility).

Patients who are known at diagnosis to have involvement of leukemia cells in their central nervous system (CNS) will receive radiation therapy over 10 doses (Monday through Friday) during the first cycle of Maintenance Therapy (Course V).

Central Nervous System Treatment (this is standard treatment)

Cancer cells have the ability to invade the central nervous system (the brain and spinal cord). Intrathecal methotrexate, which is used in Courses I, II, III, IV, and V will be given by lumbar puncture (spinal tap) into the central nervous system at the times indicated above to prevent the cancer cells from entering the central nervous system. A spinal tap involves inserting a needle into the spinal column and removing a small amount of spinal fluid. A local anesthetic will be given to numb the area prior to inserting the needle. The spinal tap will be done periodically to administer the drug and/or to assure that no cancer cells have spread to this area.

Blinatumomab Therapy (this is standard treatment)

If you are in complete remission, defined as having less than 5% lymphoblasts, but have a small amount of detectable disease (greater than 1 cancer cell in 1000 normal cells or 0.1%) this is referred to as MRD positive disease. If this is detected in your bone marrow after Course II (if you are in Group 1) or after 2 cycles of Inotuzumab (if you are in Group 2), you may be given blinatumomab. This is the standard approach for MRD positive acute lymphoblastic leukemia. Patients who receive blinatumomab for MRD positive disease are encouraged to undergo stem cell transplantation if a donor is available.