CONSENT FOR CANCER RESEARCH

Project Title: CASE 10Z17 A Phase II Study of Thiotepa added to Fludarabine and Melphalan as the Preparative Regime for Alternative Donor Transplantation

Sponsor: Case Comprehensive Cancer Center (Case CCC)

Principal Investigator(s): Leland Metheny, MD

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at University Hospitals (UH)

There may be some unfamiliar words used in this consent. There are several terms used throughout the consent document which are defined below.

- Hematologic malignancy means blood cancer. Diseases included in this study are: Acute Myelogenous Leukemia (AML), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Chronic Myelomoncytic Leukemia (CMML), Mixed Phenotype Leukemia or Biphasic leukemia (a mixture of leukemia types) Myelodysplastic syndrome (MDS), Myelofibrosis and Lymphoma
- Conditioning is the treatment that is given before a transplant. Conditioning helps your body get ready to accept the transplant (prevent graft rejection) and may also treat the underlying blood cancer (reduce tumor burden).
- Fludarabine, Thiotepa, Melphalan, cyclophosphamide, tacrolimus, , and Myclophelate Mofetil (MMF, Cellcept) are drugs that are used as part of the conditioning and considered standard of care. Fludarabine, Melphalan, cyclophosphamide, and Thiotepa are used to treat the cancer while tacrolimus, Myclophelate Mofetil (MMF, Cellcept) are used to prevent graft rejection.

What is the usual approach for my conditioning?
The usual approach of conditioning before your transplant is a combination of the drugs listed above.

What are my other choices if I do not take part in this study?
If you do not wish to take part in this research study, your study doctor will discuss alternate treatment options with you, including their benefits and risks. These may include:

- Getting treatment or conditioning without being in a study.
- Taking part in other investigational studies if they are available.
- Getting comfort care, also called palliative care, for your symptoms. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. Comfort care tries to keep you as active and comfortable as possible.
- Choosing not to participate in this study.

Talk to your study doctor about each of these choices before you decide if you will take part in this study. If you decide not to participate, withdraw your participation after starting the study, or are taken off the study, your study doctor will discuss all other treatment options with you.

Why Is This Research Being Done?
In this study, we are studying the drug thiotepa at a dose of 10mg/kg (or 5mg/kg if you are over the age of 60) in combination with a standard reduced intensity conditioning regimen for alternative donor transplant to see if it is safe and effective in patients with the hematologic malignancies listed on page 1 of this consent form.

There is a possibility that the investigators may become aware of new findings. These new findings may affect your willingness to continue participation. You will be informed of these new findings so that you may choose to stay or leave the study. It is your choice to join the study.

How Many People Will Take Part In This Study?
You will be one of 39 people joining this research study. This study will be done at Seidman Cancer Center in Ohio.

What are the study groups?
If you join this study, you will be asked to come to the Seidman Cancer Center for routine visits. All study participants will get the same study intervention, thiotepa, as part of their conditioning regimen which will include fludarabine and melphalan. Your full conditioning regimen will depend on the type of hematologic malignancy that you have, and the type of transplant you are undergoing. This will be explained to you during your regular visits as part of your regular care.

Before You Begin This Study:
You will need to have certain exams, tests or procedures before getting any study treatment. These are called screening tests. They are done to make sure you are eligible for the study. This is called the pretreatment "screening" period. You will be asked to sign this consent form before beginning any screening tests. Some of 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. If they were done too long ago they may need to be repeated. Your doctor/study team will discuss which, if any, tests need to be repeated. You will not receive any study treatment during this time.

Within *30* days before the first treatment, you will be asked to visit the clinic to have the following procedures done:

- Blood tests: Two tablespoons of blood will be withdrawn from a vein, usually in your arm. This blood will be sent to the lab to measure the function of your liver, kidneys, and bone marrow. This blood work will also test you for viruses, such as HIV or hepatitis. If you are a woman and able to have children a pregnancy test will be done.

- You will have a physical exam. The exam will check your health, height, weight, and a medication review. The medication review includes prescribed and over-the-counter medicines, and herbal supplements that you may be using.

- An evaluation of how well you are able to perform daily tasks and activities. This is also called performance status.

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 have the following tests and procedures done. Some of these may be done outpatient and some may be done in the hospital. Your care team will tell you the details about when you will be admitted for your transplant.

- 8 days before your transplant, you will receive the standard dose of melphalan over 30-60 minutes through an intravenous infusion through the central venous catheter (CVC) used for your transplant.
- 7 days before your transplant in addition to your regular care you will receive thiotepa at a dose of 10mg/kg (5mg/kg if you are older than age 60). Thiotepa is given over 30-60 minutes through an intravenous infusion through the CVC used for your transplant.
  6 days before your transplant through 3 days before your transplant, you will receive the standard dose of fludarabine in your arm over 30-60 minutes through an intravenous infusion through the CVC used for your transplant.
- Prior to your transplant you will be asked to sign the hospital consent form that explains the procedure.
- The study team will go over the criteria that you will need to meet before you can go home from the hospital but most patients are in the hospital for 20-30 days following the procedure.

How long will I be in the study?
You will stay in the study until any of the following happen:
- Your doctor has determined that your cancer has progressed,
- The study treatment becomes intolerable
- The completion of the study (12 months after your transplant)
- Termination of the study.
- Severe side effects occur,
- You or your physician wishes to discontinue treatment.

End of Study
You will be asked to continue all routine physician visits and blood work. Your participation in this study will last for up to 12 months after your transplant for safety follow-up.

You can decide to stop being in the study at any time. Tell the study doctor if you are thinking about stopping or decide to stop. It is important that you tell your doctor, so he or she can:

- tell you how to stop safely, since there are some times during the study when it would be very unsafe for you to withdraw.
- talk to you about what follow-up care and testing could be most helpful for you.

Risks

As with any experimental treatment, there may be adverse events or side effects that are currently unknown. Some of these unknown risks could be permanent, severe, or life-threatening. Your health care team may give you medicines to help lessen side effects. Side effects can be serious. Side effects can be long lasting. Side effects may never go away.

Thiotepa

Likely Side Effects (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
Lower white blood cell count with increased risk of infection Diarrhea (loose stools) Vomiting (throwing up) Liver damage Lower sperm production in men Hair loss Nausea (feeling sick to your stomach) Loss of appetite Missing or stopping menstrual cycle in women Mouth/throat sores Sterility (inability to have children)	Liver abnormalities Skin rash Change in skin coloring Risk of bleeding due to low platelet count	Confusion Disorientation

Melphalan

Likely Side Effects (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
Constipation Diarrhea Hair loss Mucositis Nausea and vomiting	Heart rhythm abnormalities Hepatitis Kidney failure	Allergic reaction Interstitial Pneumonia Seizure Lung fibrosis

Fludarabine

Likely Side Effects (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)

Diarrhea Mouth sores Nausea and vomiting Suppression of the immune system	Fever Numbness in the extremities Sleepiness Visual changes Weakness	Coma Cough Inflammation of the lung Interstitial Pneumonia Skin rash

Cyclophosphamide

Likely Side Effects (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
Sores in mouth or on lips Damage to male (tests) and female (ovaries) sex glands Diarrhea Fluid retention Hair loss Infertility Irregular or no menstrual cycles Loss of appetite Nausea, Vomiting Suppression of the immune system Decreased platelet count and increased risk of bleeding	Bleeding in the bladder Anemia (low red blood cell count) Damage to the fetus if you become pregnant while taking drug Stomach pain Skin rash	Allergic reaction Lung fibrosis (scarring of lung tissue with cough and shortness of breath) Serious skin rashes Severe heart muscle injury and death (at very high doses) Secondary (new) cancers

Tacrolimus (FK506, Prograf®)

Likely Side Effects (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
Kidney problems Loss of magnesium, calcium, potassium High blood pressure Tremors Increases in cholesterol and triglyceride Decreased platelet count with increased risk of bleeding Infections	Nausea Vomiting Liver problems Changes in how clearly one can think Insomnia Unwanted hair growth Confusion	Seizures Changes in vision Dizziness Red blood cell destruction

It is very important that you do not eat grapefruit or drink grapefruit juice while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study. Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

Mycophenolate Mofetil (MMF)

Likely Side Effects (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)

Infection Upset stomach, including nausea	Low blood counts Vomiting Diarrhea	Serious injury to your gut (digestive tract), including bloody stools and vomit Secondary cancers, such as lymphoproliferative disease or lymphoma Serious infections of the brain Risk to a baby in pregnancy Progressive Multifocal Leukoencephalopathy (PML-a rare and usually fatal viral disease that is characterized by progressive damage or inflammation of the white matter of the brain

Other risks

Your condition may not improve or may worsen while you are taking part in this study.

We cannot predict all risks or potential side effects.

Participation in this study may involve risks that are currently unforeseeable due to the nature of this research. However, if any new risks become known in the future, you will be informed of them.

Potential Risk or Discomfort from Procedures

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems. They may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Risks of Transplant

Risks of Transplant include fever, nausea and vomiting, fatigue, weakness, malaise, diarrhea, dark stools, sores in the mouth, headache, low blood counts, cough, swelling, rash, hives, allergic reaction, muscle pain, loss of appetite, painful urination, red urine, kidney damage, liver damage, serious infection, and death. Specific risks discussed below:

Graft rejection: Sometimes the cord blood or stem cells may not grow after they have been infused. This problem is termed graft rejection and is rare. The risk of developing graft rejection can be reduced by giving high-dose chemotherapy. The high-dose chemotherapy is not only given to get rid of the cancer cells, but it will get rid of the immune system and prevent graft rejection.

Graft-versus-host disease (GVHD): GVHD is the most common complication following allogeneic stem cell transplant. Development of GVHD can result in damage to the skin, intestine, liver, immune system, and occasionally bone marrow. Following an allogeneic stem cell transplant, the risk of GVHD is roughly between 20 and 30%. Methotrexate, and/or prednisone and/or mycophenolate mofetil, and/or cyclosporine/tacrolimus may be given to prevent the

development of GVHD. On the other hand, there is some benefit to the development of GVHD; the T-lymphocytes present in the cells obtained from an cord blood may kill any remaining cancer cells**,** a process called the graft-versus-tumor (GVT) effect. GVHD and GVT can occur despite the preventative medications. GVHD can be serious enough to cause death. Most common symptoms are skin rash diarrhea, yellowing of the skin, and also dry eyes, mouth sores and changes of the finger and toe nails. GVHD may also affect the lung, tendons and joints.

Veno-occlusive disease of the liver (VOD): VOD is damage to the blood vessels of the liver that can be caused by the chemotherapy given before stem cell transplant. In VOD the flow of blood into the liver is impaired. This causes a painful enlargement of the liver, an increase in body fluid and weight, and an increase in blood bilirubin. In severe cases the liver fails, which can result in death.

Damage to the kidneys: Kidney damage may occur due to medicines used as part of the transplant and to prevent GVHD. Kidney function will be monitored carefully during and after the transplant procedure.

Damage to the lungs: Lung damage may occur due to the chemotherapy used prior to stem cell transplant or as a result of the transplant itself. Lung inflammation that occurs early after transplant, in the absence of infection, is known as *idiopathic pneumonia syndrome or IPS*. IPS occurs in less than 10% of patients that received allogeneic stem cell transplant. However, if/when it occurs, IPS can be fatal. Prednisone will be given to reduce the inflammation should IPS occur. Other IPS treatment options may be used at the discretion of the treating physician.

Serious infections: Infections in the blood stream or other organs are more likely to occur because the immune system is weakened for a period of time by the stem cell transplant and the medicines used to prevent GVHD. These infections are sometimes fatal.
These side effects, alone or in combination with other problems, may be severe enough to cause death.

Reproductive Risks
Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women cannot be in the study. If you are a woman who is able to get pregnant you will have a pregnancy test. The pregnancy test must be negative before you can enter this study. If you are sexually active, you must agree to use appropriate contraceptive (birth control) measures during the study. Medically acceptable contraceptives include: (1) surgical sterilization, (2) approved hormonal contraceptives such as birth control pills, (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). If you do become pregnant during this study, you must inform your study physician immediately. You should continue to use birth control for at least 12 months after finishing the study.

The treatment used in this study could affect your sperm and could potentially harm a child that you may father while on this study. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study. Medically acceptable contraceptives include: (1) surgical sterilization, or a (2) condom used with a spermicide. You should continue to

use birth control for at least 12 months after finishing the study.

If you become pregnant while you are taking part in this study, you must notify one of the study doctors. The doctors will work with you so that management of the pregnancy and the possibility of stopping the study treatment can be discussed.

Benefits

There is no guarantee that you will receive any benefits from this study., Taking part in this study may or may not cause your health to improve. The potential benefit of this treatment is the possibility for better cancer control. In addition, others may benefit from the knowledge my doctors may gain from use of this therapy. This information may benefit other patients with cancer in the future.

Costs and Compensation

Your involvement in this research study is voluntary and you will not be paid for your participation.

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 (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). 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.

For more information on clinical trial and insurance coverage, you can visit the National Cancer Institute's (NCI) website at
http://cancer.gov/clinicaltrials/understanding/insurance-coverage

You can print a copy of the 'Clinical Trials and Insurance Coverage' information from this website. Another way to get information is to call 1-800-4-CANCER (1-800-422-6237) and ask NCI for a free copy.

Notice for Managed Care (Medicare Advantage Plan) Beneficiaries

Certain services provided to you as a participant in a clinical study are allowable to be billed to and paid by your medical insurance. These services are referred to as "covered" clinical study services. If you have a Medicare Advantage Plan as part of your medical insurance, the Centers for Medicare & Medicaid Services (CMS) require that traditional Medicare will be billed for those services. When this occurs, you will remain responsible for paying the coinsurance and deductibles according your Medicare Advantage Plan. Your Medicare Advantage Plan should cover any associated cost share related to Medicare. Please speak with a financial counselor to understand what the specific financial impact will be for you associated with participating in this clinical study.

Research-Related Injury

If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research-related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting University Hospitals Cleveland Medical Center's Research Subjects Rights at ([redacted].

Privacy and Confidentiality

A. Confidentiality

The medical and research information recorded about you will be used within University Hospitals and/or disclosed outside University Hospitals as part of this research. Some of the tests and procedures done solely for this research study also may be placed in your medical record so your other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in the medical chart.

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

This research study will involve the recording of current and/or future identifiable (pertaining to only you) medical information from your hospital and/or other health care provider (for example, your physician's office) records. This information that will be recorded will be limited to information concerning treatment of your cancer (for example, diagnostic information, lab and scan results, medications, medical history). This information will be used to determine your eligibility for this study and to follow your response once you are enrolled in the study.

Parts of your identifiable medical record information that pertain to your participation in this study may be sent to a central location for review (photocopied and mailed, or electronically transmitted, such as by fax or email). The organizations receiving your identifiable medical record information may not have the same obligations to protect your information and may further disclose it to groups not named here. Information released to these parties is no longer under the control of the study doctor and can no longer be protected by Federal Privacy Rules.

The purposes of disclosing your medical record information to the organizations are to collect the data necessary to complete the research, to properly monitor how this study is carried out, and to answer research questions related to this research study.

We will do our best to make sure that the personal information in your medical record will be kept

private. However, we cannot guarantee total privacy. To protect your privacy, the study staff will use your study number and initials rather than your name on any photocopies of your study records, and on any blood samples that are sent outside of the local research institution(s) for review or testing. If information from this study is published in scientific journals or presented at scientific meetings, your name and other personal information will not be used.

B. Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to [redacted] and the research staff at University Hospitals for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the University Hospitals Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Study sponsors and their agents;
- other staff from the Principal Investigator's medical practice group;
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to [redacted] Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, you can ask the Principal Investigator and/or research staff: [redacted], 11100 Euclid Avenue, Cleveland, OH 44106 [redacted].

Emergency and After-hours Contact Information
If you are a University Hospitals patient, and you need to contact study staff outside normal business hours, you may contact [redacted] at ([redacted]) and you will be transferred to the answering service, which can put you in contact with the oncologist (cancer doctor) on call.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects' issues, you may contact the University Hospitals Cleveland Medical Center's Research Subjects Rights Phone line at [redacted].

Where Can I Get More Information?
You may call the National Cancer Institute's Cancer Information Services at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615
You may also visit the NCI website 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 study doctor.

US National Institutes of Health (NIH) Clinical Trial Database

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.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Printed Name of Participant	Date	Time

Signature of Participant or Child's Signature if this form is used to obtain assent (for minors ages ≥14 years of age)

Printed Name of Parent or Legal Guardian	Date	Time

Signature of Parent or Legal Guardian	Relationship to Participant

Signature of Witness	Date	Time

Printed Name of Witness

Use for inclusion of illiterate individuals, blind individuals or individuals who cannot physically sign but are able to provide informed consent.

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____ _____ _____

Signature of Person Obtaining Consent Date Time

_____

Printed Name of Person Obtaining Consent

_____ _____

Printed Name of Legally Authorized Representative [LAR] Date Time

If Participant is a Legally Incompetent Adult

_____

Signature of Legally Authorized Representative [LAR]

I have discussed the information contained in this document with the LAR and it is my opinion that the LAR understands the risks, benefits, alternatives and procedures involved with this research study.

_____ _____ _____

Signature of Person Obtaining Consent Date Time

_____

Printed Name of Person Obtaining Consent