Official Title	A Phase II Randomized Study to Assess Outcomes with Treosulfan-based versus Clofarabine-based Conditioning in Patients with Myelodysplastic Syndromes with Excess Blasts (MDS-EB), or Acute Myeloid Leukemia (AML) undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)
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FRED HUTCHINSON CANCER CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Protocol 10598

Consent to Participate in a Research Study called: A Phase II Randomized Study to Assess Outcomes with Treosulfan-based versus Clofarabine-based Conditioning in Patients with Myelodysplastic Syndromes with Excess Blasts (MDS-EB), or Acute Myeloid Leukemia (AML) undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)

- **Who is in charge of this research study?**

Principal Investigator		**Phone**
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➢ Important things to know about this study

You are invited to participate in a research study. The purpose of this research is to compare two different reduced intensity conditioning regimens to determine if one regimen is better than the other at preventing relapse.

People who agree to join the study will be asked to receive blood stem cell transplantation in Seattle. You will be required to be in Seattle for roughly 3 and 1/2 months. Your stay may be longer if you have any complications that require treatment.

You do not have to join this study. You can choose to receive standard methods to treat your blood cancer instead of participating in this study. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

➢ Why have I been asked to take part in this research study, and who is conducting it?

You are being asked to take part in this study because you have a severe blood cancer that may be treatable with a blood stem cell transplant from a matched related or unrelated donor. Because of your age or underlying health, you may have a higher likelihood of experiencing harm from a conventional stem cell transplant, so a lower intensity blood stem cell transplant is being offered to you. Low-intensity stem cell transplants use lower doses of chemotherapy or radiation than conventional (high intensity) stem cell transplants. This research study looks at ways to prevent the recurrence (or relapse) of your leukemia. We do not guarantee or promise that the treatment or procedures described in this study will be effective in treating your medical condition. This study is being performed here at the Fred Hutchinson Cancer Center.The Investigators of this study want you to understand that patients in clinical trials include only those who are completely informed and choose to participate. Please take your time to make your decision about whether to participate. We encourage you to discuss your decision with your doctor, family and friends.

➢ Why is this research study being done?

This study is being done because at the present time, stem cell transplantation is the only known cure for your leukemia. However, relapse still occurs in a proportion of patients. Because of your age or underlying health you may have a higher likelihood of experiencing harm with currently used stem cell transplant protocols. Therefore, you are invited to participate in this clinical trial using two different reduced intensity conditioning regimens. The purpose is to determine if one regimen is better than the other at preventing relapse. In regimen A (arm A), we are adding the drug treosulfan to a widely used combination of Fludarabine and low dose total body irradiation (TBI). Treosulfan has been used to treat patients with various blood disorders. Previous and ongoing studies suggest that this combination of drugs and TBI is well tolerated, and effective in terms of disease control. In regimen B (arm B), we are replacing the drug fludarabine with a newer, but similar chemotherapy drug clofarabine, which in previous studies had similar effects on the immune system as did fludarabine, but had stronger anti-leukemia effects.

In this trial a computer will randomly choose which conditioning regimen you will receive.

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

Up to 80 patients will take part in the study.

➢ **What tests, procedures, and treatments are part of this study?**

Standard procedures that will be done as part of pretransplant evaluation:
First we will need to find out whether you can be enrolled in this study. You will be asked to give information about your medical history and undergo exams and tests that may include the following, depending on your underlying disease:

- Bone marrow biopsy
- Creatinine clearance
  (Evaluates kidney function)
- Blood tests
- Chest x-rays and pulmonary function tests or 6-minute walk tests.
  (Evaluates lung function)
- Electrocardiogram and MUGA scan or echocardiogram
  (Evaluates heart function)
- CT-scan
  (Method used to obtain X-ray images lymph nodes and organs)
- Age-appropriate cancer screening

These exams and tests are not experimental. They are standard good medical care even if you do not join the study. If you do join, some of these procedures may be done more often than if you were not taking part in the study. The tests may be done on an outpatient basis at your doctor's office or clinic, or in a hospital.

Standard procedures that will be done as part of the transplantation:

Stem cell transplantation: Peripheral blood stem cells will be used in this study. They will be collected from the blood of the donor after treatment with a growth factor.These cells are then infused into your blood and travel to you marrow where they will begin to produce new blood cells.

Immunosuppression: a combination of drugs (other than the conditioning regimen) will be given before and after stem cell transplantation to suppress your immune system. This will allow the donor's stem cells to be accepted by your body, and they will also reduce the risk of graft-versus-host disease (GVHD).

GVHD is one of the main complications following transplantation. GVHD occurs because donor cells react against cells of your body causing inflammation that can involve the skin, liver and gut. GVHD can occur early after the transplant (*acute* GVHD) or late after transplant (*chronic* GVHD). GVHD is associated with a greater risk of dying from complications after the transplant.

The immune suppressing drugs cyclosporine and mycophenolate mofetil (MMF) will be used if you have a matched related donor. If you have a mismatched unrelated donor, another drug, sirolimus, will be added.

Blood and Bone Marrow Tests

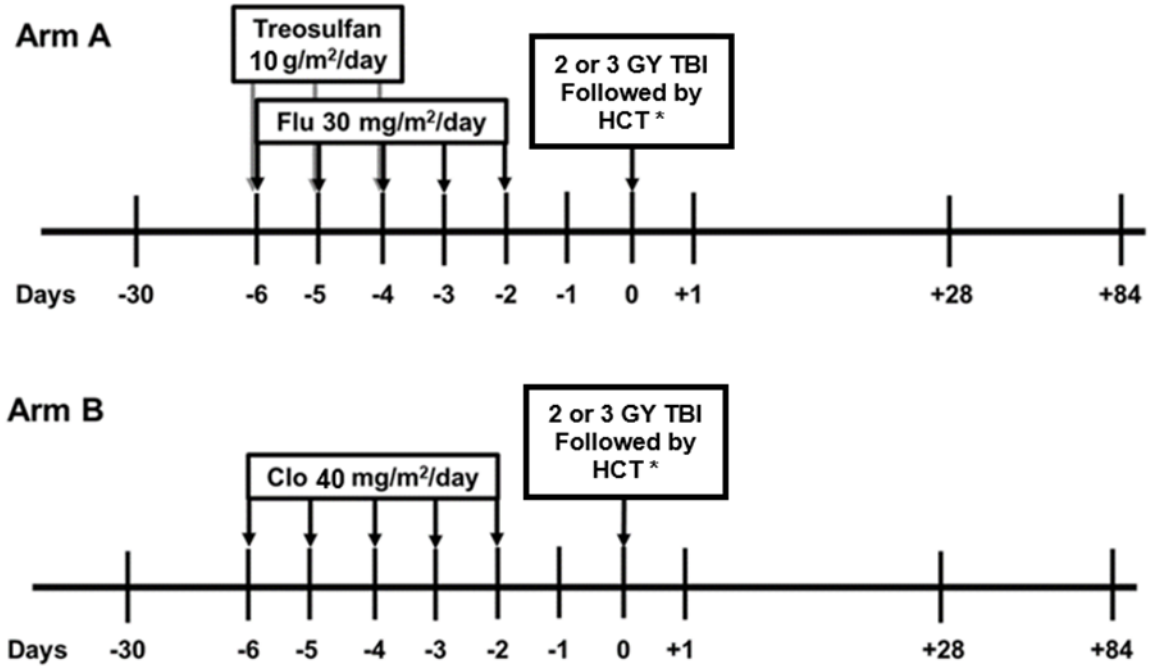
You will have blood tests at least three times a week to check kidney function and blood cell counts early after the transplant. Other blood tests will be done periodically to check your liver function and electrolytes. A bone marrow aspirate may also be required at a few time points to check for the presence of donor cells and cancer.

Molecular Test of Disease Response: Certain blood cancers can be monitored by special tests. One of these tests detects DNA of the tumor cells. This test is highly sensitive and may be used for monitoring the response of your cancer to the transplant. This test will be performed on blood and bone marrow samples. It will not add to the frequency of standard blood or bone marrow tests scheduled to monitor the response of the leukemia to the transplant, unless there is a clinical reason to do additional tests.

Molecular Test of Donor Engraftment: The percentage of donor cells in your blood and marrow can be monitored by special tests that detect the DNA of the donor cells. These tests, referred to as chimerism tests, evaluate the degree of donor engraftment after the blood stem cell transplant. This test will be performed using peripheral blood and bone marrow samples. This test will not add to the frequency of standard blood or bone marrow tests.

Research procedures in the study:

Schedules of conditioning regimens



Arm A: Conditioning for Stem Cell Transplantation Using Treosulfan:

- Patients with a related donor

Day Number	*-6*	*-5*	*-4*	*-3*	*-2*	*-1*	*0*	*+1*	*+ 30*	*+96*	*+150*
Fludarabine 30 mg/m^2/day	**x**	**x**	**x**	**x**	***x***						
Treosulfan *10*g/m^2/day	**x**	**x**	**x**								
*TBI**							2 or 3 Gy				
Stem cells							Infusion				
Cyclosporine				START	→	→	→	→	→	TAPER	STOP
Mycophenolate Mofetil							START	2 x day	STOP		

*TBI can be given on day -1 or day 0

- Patients with a unrelated donor

Day Number	*-6*	*-5*	*-4*	*-3*	*-2*	*-1*	*0*	*+1*	*+ 30*	*+40*	*+96*	*+150*	*+180*
Fludarabine 30 mg/m^2/day	**x**	**x**	**x**	**x**	***x***								
Treosulfan 10g/m^2/day	**x**	**x**	**x**										
*TBI**							2 or 3 Gy						
Stem cells							Infusion						
Cyclosporine				START	→	→	→	→	→	→	TAPER	STOP	
Sirolimus				START	→	→	→	→	→	→	→	TAPER	STOP
Mycophenolate Mofetil							START	3 x day	2 x day	STOP			

*TBI can be given on day -1 or day 0

Arm B: Conditioning for Stem Cell Transplantation Using Clofarabine:

- Patients with a related donor

Day Number	*-6*	*-5*	*-4*	*-3*	*-2*	*-1*	*0*	*+1*	*+ 30*	*+96*	*+150*
Clofarabine 40 mg/m^2/day	**x**	**x**	**x**	**x**	***x***						
*TBI**							2 or 3 Gy				
Stem cells							Infusion				
Cyclosporine				START	→	→	→	→	→	TAPER	STOP
Mycophenolate Mofetil							START	2 x day	STOP		

*TBI can be given on day -1 or day 0

- Patients with a unrelated donor

Day Number	*-6*	*-5*	*-4*	*-3*	*-2*	*-1*	*0*	*+1*	*+ 30*	*+40*	*+96*	*+150*	*+180*
Clofarabine 40 mg/m^2/day	**x**	**x**	**x**	**x**	***x***								
*TBI**							2 or 3 Gy						
Stem cells							Infusion						
Cyclosporine				START	→	→	→	→	→	→	TAPER	STOP	
Sirolimus				START	→	→	→	→	→	→	→	TAPER	STOP
Mycophenolate Mofetil							START	3 x day	2 x day	STOP			

*TBI can be given on day -1 or day 0

➢ **How long will I be in the study?**

Your treatment at the Fred Hutchinson Cancer Center will last approximately 3 and 1/2 months, but could be longer. You may be asked to return for follow up at 6 months and at one year in order to help manage any complications of the transplant that may have developed.

We would like to keep track of your medical condition for the rest of your life to fully understand the long-term effects of transplantation and of this study in particular. However, you may be taken off the protocol and followed less frequently if one of the following happens:

- The study treatment does not work for your cancer;
- You develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications;
- Your health gets worse;
- You are unable to meet the requirements of the study (for example, you cannot take the medicine as prescribed or you refuse follow-up);
- You start other treatments for your cancer;
- Other treatments for your cancer become available;
- By your request.

Your decision to participate in this study is completely voluntary. You may decide not to participate in this study at any time, for any reason, without notice. If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information cannot be removed from the study records. Prior to discontinuing the study, we request that you discuss your decision with your primary doctor and, if you wish, the research physician for this study.

➢ **We would like to follow you long-term**

Long-term follow-up means keeping track of someone's medical condition for a long time, and if you agree, for the rest of your life. This would help us learn about the long-term effects of the treatment. If you join this study, we would ask that you return for follow-up at 1 year after your transplant to see how you are doing. In addition, your transplant physician may invite you to come back each year to monitor your health if you can afford it. We ask that you have annual checkups with your doctor or doctors for the rest of your life. We will ask your doctor or doctors to send us a copy of your medical records.

➢ **What are the risks of the study?**

There may be side effects. Most of these are listed below, but they will vary from person to person.

If the side effects are caused by medications, they often go away shortly after the drugs are stopped. Please talk with your study doctor about these side effects. If you want to read more about the side effects from study drugs, please ask your doctor or pharmacist for more information.

Side effects that we know about are described in the table. Side effects are categorized into:

- **Likely side effects:** Occurring in 10% or more of patients (this means that 10 or more patients out of 100 might get this). Certain side-effects in this category could occur in virtually all patients.
- **Less likely side effects:** Occurring in 3-9% of patients (this means that 3 to 9 patients out of 100 might get this).

- **Rare side effects:** Not occurring very often, maybe less than 3% of patients (this means that 1 or 2 patients out of 100 might get this).

With any new drug or combination of drugs, there may be complications or side effects that we do not know about.

Likely Side Effects	*Less Likely Side Effects*	*Rare Side Effects*
Graft-versus-host disease	Allergic reaction (including itching, hives, flushing, hypersensitivity, shortness of breath, wheezing, chest tightness, skin rashes, fever, chills, muscle stiffening, severe breathing problems)	Sores in mouth and/or throat
Nausea	Jaundice (yellowish discoloration of sclera)	Hair loss
Vomiting	Rejection/graft failure(when the body rejects the transplanted donor cells)	Skin or nail discoloration
Diarrhea	Fluid retention (bloating or swelling)	Nail changes
Loss of appetite	Weakness	Painful burning on the skin of the hands and feet
Fever	Fatigue	Irregular menses or stopping of menses
Lowered white blood cell counts (may lead to infection)	Seizure	Infertility (inability to have children) in women or Sterility for men
Lowered platelet counts (may lead to bleeding)	Tremor	Failure of heart function
Lowered red blood cell counts (may lead to anemia, fatigue, shortness of breath)	Muscle or joint pain	Bleeding or dysfunction of the central nervous system
Infection	Red blood cell destruction	Failure of brain function
Time away from work		Impairment or failure of kidney function
		Failure of lung function
		Failure of liver function

In addition to the above risks, there is the risk of organ failure, involving heart, kidney, lung, brain, liver or other body parts. This risk is increased in those patients who have already had significant chemotherapy and/or radiation therapy or abnormal organ function *before* transplantation.

Although the aim of this study is to reduce the risks of stem cell transplants, **there could still be severe effects, including the risk of death**. In addition, the cancer may recur even if the transplant is initially successful. There is also the possibility that this approach may be less successful at treating your cancer than other trials.

Total Body Irradiation (TBI):

Likely Side Effects	Less Likely Side Effects
• Nausea (feeling sick to stomach) • Fatigue (feeling tired) • Sterility, and major genetic damage to any children conceived after transplantation	• Temporary hair loss • Vomiting (throwing up) • Diarrhea (loose stools) • Painful swelling of the parotid gland (a gland under the chin) for a few days • Cataracts (an opacity or whitening of the lens) may develop in the eye • Secondary cancers • Lung Damage

TBI will also destroy normal bone marrow cells in addition to the malignant cells.

TBI may cause sterility; however, the risk of infertility in this study will be lower than the risk after transplantation using higher doses of TBI. Although TBI can theoretically cause abnormalities in children born to transplant survivors, the incidence does not appear to be greater than in the general population. However, birth control should be used for at least one year after the transplant to minimize risk of conceiving.

The dose of TBI used in this study is approximately one-sixth of that used in conventional transplant protocols, and no severe acute side effects are expected.

You will also undergo diagnostic exams (CT scans, chest x-rays, bone scan, etc) to help follow your progress. This will expose you to very small doses of radiation. They are not expected to increase your health risk.

The chemotherapy used in the conditioning regimens can cause side effects, including those listed below.

Fludarabine

Likely Side Effects (over 10%)	Less Likely Side Effects (3-9%)	Rare Side Effects (under 2 %)
• Low white blood cell count with an increased risk of infection (from bacteria, fungi or viruses) • Lower platelet count with and increased risk of bleeding • Anemia • Infections	• Nausea (feeling sick to your stomach) • Diarrhea (loose stools) • Fatigue	• Vomiting (throwing-up) • Trouble seeing or problems with your eyes • Numbness or tingling in your fingers or toes • Confusion or coma • Pneumonia

Treosulfan

Likely Side Effects (over 10%)	Less Likely Side Effects (3-9%)	Rare Side Effects (under 2 %)
• Nausea and vomiting • Painful inflammation./sores of the lips and/or lining of the mouth that may cause difficulties eating(mucositis/stomatitis) • Low white blood cell count and increased risk of infection • Low platelet count and increased risk of bleeding • Low red blood cell count (anemia) and increased need for red cell transfusions • Infections • Fever (often associated with very low white blood count) • Rash • Weakness • Fatigue • Abnormal liver tests	• Fever, chills • Headache • Muscle or limb pain • Abnormal creatinine (kidney function test) • High blood pressure • Loss of appetite • Weight gain or loss • Constipation • Insomnia • Edema (swelling due to retention to fluids) • Dizziness • Back and bone pain • Chest pain • Veno-occlusive disease • Low blood pressure • Low potassium in blood • Low sodium in blood • High blood sugar • Pruritus (itching of the skin) • Flushing of face or neck • Indigestion/reflux • Difficulty swallowing • Pneumonia • Sepsis (severe infection) • Hypersensitivity • Palpitations, rapid or irregular heartbeat, atrial fibrillation • Shortness of breath • Petechiae (red spots on skin from bleeding) • Bleeding in lungs • Vaginal bleeding • Bladder irritation, blood in urine • Frequent urination	• Allergic reactions • Heart failure • Severe loss of kidney function requiring hemodialysis • Hepatorenal syndrome (a form of impaired kidney function) • Lung failure or pneumonia requiring oxygen therapy or mechanical ventilation • Seizures • Secondary cancers • Arthritis (joint problems) • Pericardial effusion/Pericarditis • Confusion • Lack of muscle coordination • Rectal inflammation • Neck pain • Pleural effusion (fluid in the lungs) • Cerebral hemorrhage (bleeding in the brain) • Peripheral neuropathy (pain, tingling and numbness in hands and feet) • Hair loss • Severe skin reaction • Skin peeling or changes in skin color or increased sensitivity or burning. • Hand foot syndrome • Gastritis • Low blood sugar • High potassium in blood • Abdominal fullness • Acidosis (too much acid in the body) • Dry eyes • Dry mouth • Pain in throat

Likely Side Effects (over 10%)	Less Likely Side Effects (3-9%)	Rare Side Effects (under 2 %)
		• Hiccups • Stuffy or runny nose • Encephalopathy (brain disease that can include temporary or permanent damage) • Ileus (temporary lack of the normal muscle contractions of the intestines) • Gastric hemorrhage

Clofarabine

Likely Side Effects (over 10%)	Less Likely Side Effects (3-9%)	Rare Side Effects (under 2 %)
• Low white blood cell count with an increased risk of infection (from bacteria, fungi or viruses) • Lower platelet count with and increased risk of bleeding especially after an injury • Anemia (lower red cell count in the blood) • Infections • Transient liver toxicity that resolves after clofarabine is stopped • Nausea (feeling sick to your stomach) • Vomiting (throwing up) • Diarrhea (loose stools) • Mild kidney function disturbance (when the kidneys fail to adequately filter waste products from the blood) • Fatigue • Low blood pressure (transient) • Tachycardia (increased heart rate - transient)	• Sepsis/Septic shock (overwhelming infection) • Abdominal pain	• Severe allergic reactions (with skin rash, low blood pressure) • Severe inflammatory reaction (an inflammatory state affecting the whole body, that can result in malfunction of various organs) • Kidney failure • Confusion or coma • Pneumonia (inflammation of one or both lungs) • Arrhythmia (disturbances of heart rhythm)

***Stem Cell Transplant*:** The infusion of donor stem cells should have no or only minimal side effects, just like a blood transfusion. Supportive care with red blood cell and platelet transfusions and antibiotic therapy may be necessary until the infused donor cells produce new blood cells.

Likely Side Effects	Less Likely Side Effects
• Low blood counts • Fever • Chills • Nausea • Infections	• Bleeding • Failure of the donor stem cells to grow • Shortness of breath

For patients receiving unrelated transplants there is the unlikely risk that for reasons beyond our control either (i) your unrelated donor will be unable to donate stem cells or (ii) the donation will result in a product that cannot be infused safely. If either of these extremely unlikely events were to occur after you receive the conditioning regimen, there is a chance that your own marrow cells will not recover. If your own marrow cells do not recover, the only way to prevent to protect you would be to find a replacement donor. Finding a replacement donor very quickly may be challenging, and the transplant using a replacement donor might not be successful. Additional rescue measures would be considered.

***Central Venous Catheter*:** A central venous catheter is a small hollow tube that is placed in a large vein, typically just behind your collar bone while using a local numbing medication. It is used to infuse the donor cells, to give intravenous medicine and to withdraw blood for lab tests.

Less Likely Side Effects	Rare Side Effects
• Clotting of blood (treated with a medicine that dissolves clots) • Bleeding around the catheter • Infection in the tissues around the catheter or in the bloodstream • Skin redness at the catheter exit site, which may require treatment with an antibiotic.	• A small chance of a puncture to the lung during placement of the catheter • A blood clot can form on the tip of the catheter, break off, and go into the lungs (pulmonary embolus), which could cause shortness of breath and pain and potentially death.

Graft-versus-host disease (GVHD): GVHD is a known potential complication of stem cell transplantation that occurs in 50 - 70% of patients on similar protocols. GVHD may be mild or severe and may require prolonged treatment with immune suppressive drugs. Severe GVHD and associated complications can result in death.

Early or Acute GVHD:	
• Skin rash • Lack of appetite, stomach cramps, diarrhea (loose stools) or "full" feeling in stomach • Problems of the liver (such as jaundice)	• Problems of the stomach, including intestinal bleeding • Nausea (feeling sick to stomach) • Vomiting (throwing up)

Chronic GVHD may occur after transplantation and may involve any of the above, plus:	
• Problems of the eyes • Problems of the skin • Problems of the liver • Problems of the joints	• Problems of the mouth, lips, and throat • Dry Mouth and/or Eyes • Lung Damage • Hair Loss

Cyclosporine (CSP), mycophenolate mofetil (MMF), and sirolimus are used in different combinations in this study to prevent GVHD. The side effects of these drugs are listed below.

Mycophenolate Mofetil (MMF): MMF is a drug used for suppressing the immune system for stem cell transplantation. The drug is well tolerated. Some patients who were given MMF after solid organ transplants (e.g. a kidney) experience a reversible fall in red cell or white cell counts. A few cases of Pure Red Cell Aplasia (PRCA), a condition in which the bone marrow stops producing red blood cells, have been reported. Generally PRCA can be reversed by reducing or stopping MMF. Your blood counts will be monitored closely and if significant decrease is noted, dose adjustments or stopping your MMF may be indicated.

A few cases of so-called progressive multifocal leukoencephalopathy (PML), a rare disorder of the central nervous system (weakness on one side of the body, lack of emotion, confusion, cognitive difficulties, and loss of coordination), have occurred after MMF. PML can be triggered when the polyomavirus (or JC virus) is activated. You should notify your doctor immediately if you develop any of the above symptoms.

FOR WOMEN WHO COULD BECOME PREGNANT: Birth defects could occur if you take MMF while you are pregnant. As discussed above, you must use 2 effective forms of contraception if you are fertile and sexually active. You should talk to your doctor to find out which methods of birth control would be most effective for you. You must notify your doctor and the coordinating center for the study immediately if you become pregnant while you are taking MMF. You should not breast feed while you are taking MMF.

Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
• Nausea (feeling sick to stomach)	• Vomiting (throwing up) • Diarrhea (loose stools) and abdominal discomfort • Lower red blood cell count that is reversible • Lower white blood cell count with increased risk of infection	• Stomach and bowel bleeding (blood in stools) • Secondary cancers

Cyclosporine (CSP): Cyclosporine is a drug used for suppressing the immune system.

Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
• Nausea (oral administration)	• Headache	• Patients have had seizures, but it is unclear whether cyclosporine, other

• Vomiting (oral administration) • High blood pressure (hypertension) • Shaking of hands (tremor) • Increased hair growth • Effect on mental function • Loss of magnesium, calcium, potassium	• Painful sensation in hands or feet which went away with the improvement of the GVHD or when the cyclosporine was switched from the intravenous to the oral form. • Change in liver or kidney function • Changes in how clearly one can think • Increases in cholesterol and triglyceride	drugs, or a combination of drugs were responsible. • Kidney damage severe enough to require the use of IV fluids or an artificial kidney machine (dialysis) • Destruction of red blood cells (hemolysis) may result in withholding cyclosporine or discontinuing it's use • Bleeding of the brain (relation to cyclosporine unknown)

If your kidney function is poor prior to transplant, there is an increased risk that you may develop kidney failure and even require hemodialysis (artificial kidney) for a while. There is also a risk that you may develop a new (secondary cancer), a risk about twice as high as in the healthy population.

The side effects of cyclosporine are generally reversible after decreasing the dose or stopping the drug.

Sirolimus (rapamycin):

Likely Side Effects	**Less Likely Side Effects**
• Increase in blood pressure • Headache, or tremors • Altered levels of magnesium and potassium in the blood. • Decreased kidney function • If blood lipids (triglycerides and cholesterol) are increased the use of drugs to correct this problem may be necessary • Destruction of red blood cells (hemolysis) can occur with sirolimus	• Seizures • Breakdown of muscle (rhabdomyolysis) • Some patients have had seizures, but it is unclear whether sirolimus, other drugs, or a combination of drugs were responsible • Loss of kidney function • Low white blood cell count with an increased risk of infection (from bacteria, fungi or viruses) • Lower platelet count with and increased risk of bleeding • Anemia • Infections • Blurry vision

These effects are generally reversible upon decreasing the dose or stopping the drug.

Risk to the Unborn: You should ***not*** become pregnant or father a child while on this study. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant or men who have the potential of fathering a child must use two

forms of effective birth control for one year after transplant. Effective birth control would be defined as the following: 1) refraining from all acts of vaginal intercourse (ABSTINENCE); 2) consistent use of birth control pills; 3) injectable birth control methods (Depo-Provera); 4) tubal sterilization or male partner who has undergone a vasectomy; 5) placement of an IUD (intrauterine device); and, 6) use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.

Sterility and Future Childbearing Potential for Men and Women: Chemotherapy and/or irradiation may affect fertility. Male patients may become sterile (unable to produce sperm). Female patients may find that their menstrual cycle becomes irregular or stops permanently. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT OR FATHER A CHILD, and you must use some effective method of birth control for at least one year after the transplant. Damage to reproductive tissue may result in birth defects or permanent inability to have a child or become pregnant. You should discuss these risks and options in detail with your doctor before entering this study.

➢ **Are there benefits to taking part in this study?**

We are testing two different reduced-intensity conditioning regimens to determine if one regimen is better than the other at preventing relapse of your type of blood cancer. Based on what we know, we anticipate that the regimens used here are better tolerated and may have a lower relapse frequency than other conditioning regimens currently in use. We hope the information from this study will help other people with blood cancers in the future.

➢ **What if new information is learned while I am in this study that might affect my health?**

If we learn any new information that might affect your health, welfare, safety, or willingness to stay in the research study, your doctor (physician) will tell you. You may be asked to sign another consent form if you wish to stay in the research study at that time.

➢ **You have other choices besides this study.**

You do not have to join this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no".

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Instead of being in this study, you can decide to have:

- Chemotherapy with other drugs known to be effective for your underlying cancer.
- A stem cell transplant on another protocol or treatment plan.
- No treatment.

Enrollment in this study may exclude you from other research studies.

➢ **Protecting Privacy as an Individual and the Confidentiality of Personal Information**

Some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study

- Fred Hutchinson Cancer Center (Fred Hutch)
- University of Washington (UW)
- Medexus Pharma Inc., the funder of the study
- medac GmbH, the provider of Treosulfan
- The Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- U.S. Office for Human Research Protections (OHRP)
- Institutional Review Board (IRB), including the Fred Hutchinson Cancer Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- National Marrow Donor Program

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they would see a copy of this consent form.

➢ Would we pay you if you join this study?

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

➢ What are the costs?

Treosulfan is provided free of charge by medac GmbH. Tests or procedures performed only for the study will be provided without cost to you. You or your insurance company would have to pay for the costs of standard treatment in this study. You may want to talk with your insurance company about its payment policy for standard medical care given during a research study and the frequency of testing that is allowed. If your insurance company does not pay, you may be billed for those charges. If you have any questions concerning your costs, financial responsibilities, and/or medical insurance coverage for this activity, please ask your physician or contact the Patient Financial Services Department at (206) 606-6226.

➢ What if you get sick or hurt after you join this study?

For a life threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is resolved or as soon as you can.
For all other medical problems or illness related to this research, immediately contact the emergency number at 206-598-8902. They will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

➢ **What will my information and/or tissue samples be used for?**

Your information and samples will be used for the purposes of this study. Your samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

During this study, we do not expect any research test results that would affect your care, so we do not plan to return results to you.

➢ **Will my information and/or tissue samples ever be use for future research?**

Your information and tissue samples (even if made anonymous) will not be used for any research other than this study.

➢ **Do I have to be part of the study?**

You do *not* have to participate in this study. Your decision to participate is voluntary and should only be made when you have a complete understanding of all treatment options and of the risks involved in participating in this study.

If you have questions about the study, please talk with your physician or one of the investigators listed at the beginning of the consent. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers. You may also wish to discuss this matter with a relative, or friend.

➢ **What are my rights as a study participant?**

- You do not have to join this study. You are free to say "yes" or "no".
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.

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.

➢ Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of study visits and procedures.
- Take study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

➢ Who can I call if I have questions or problems?

For Questions About	Please Contact
This study and what it involves	Your doctor (physician) or one of the investigators listed at the beginning of the consent
Your rights as a participant in a research study	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Center)
Your bills and health insurance coverage	Fred Hutchinson Cancer Center, Patient Financial Services at 206-606-6226
Research related injury	Your physician or one of the investigators listed at the beginning of this consent
Emergency care	**Emergency (24 hour) phone**: UWMC (206) 598-8902;
Medical records	Contact the Fred Hutchinson Cancer Center Director of Health Information Management at 206-606-2174.

➢ Where can I get more information about cancer and its treatment?

You can call the Cancer Information Service at 1-800-4-CANCER or visit the National Cancer Institute's Clinical Trials Web Site at http://cancertrials.nci.nih.gov.

You can also visit the NCI's Web sites…cancernet™: comprehensive clinical trials information http://cancernet.nci.nih.gov.

If you would like additional information about the drugs used in this trial and their side effects, you should ask your doctor or pharmacist. You can also get information at any time from the doctor in charge of your medical care in this study or one of the study investigators.

You will get a copy of this form. You may also request a copy of the protocol.

CONSENT TO PARTICIPATE IN THE RESEARCH STUDY

I have carefully read this consent form. This study has been explained to me. I understand that it is my choice whether or not to take part in this study. I am aware of the possible risks and

benefits of taking part in this study. I have had the chance to ask questions about it, and all questions were answered to my satisfaction. I now agree to take part in this research study.

I also give permission to the people and organizations connected with this research study to review and copy my research records, both during the research and the long-term follow-up.

_____

Research Participant / Printed Name, Signature, and Date

If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

_____

Witness or Interpreter / Printed Name, Signature, and Date

MEDICAL STAFF PERSON'S STATEMENT

I have discussed the above research study, including the study purpose, procedures, risks and benefits, and possible alternatives, with the person signing above. All the elements of informed consent were reviewed and discussed with the subject. Special concerns that the participant expressed were noted and appropriately addressed. I encouraged questions and have answered all questions to the best of my ability. The participant is aware that he/she has a choice in taking part in this study. A signed copy of the consent form will be given to the participant.

_____

Medical Staff Person's Signature / Printed Name, Signature, and Date

_____

Signature of Any Additional Staff Person Present During Consent Process (if present)

Current Version: 08/20/2024
Previous Version: 12/15/2022
Copies to: Patient, Medical Records, Research File

Signed Consent <u>MUST</u> be sent to Data Management – Mail Stop LF-229
Fred Hutch, 1100 Fairview Ave N, Seattle, WA 98109-1024