Informed Consent to Participate in Research

BMT CTN 2203

A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate/Ruxolitinib versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

Your Name: _____

Principal Investigator:

Insert local PI information

Sponsor: This study is sponsored by Incyte Corporation and the National Institutes of Health, through the Blood and Marrow Transplant Clinical Trials Network

The ethics of this study have been reviewed and approved by the National Marrow Donor Program Institutional Review Board.

Your study doctor or nurse will review this **Consent Form** with you, including:

- ✓ The purpose of the research
- ✓ Possible risks and benefits
- ✓ Other options available to you
- ✓ Your rights if you join the study

1. Study Overview

We invite you to join this clinical trial, also known as a research study. We're doing this study to see if the drug ruxolitinib with the drugs tacrolimus and methotrexate given before and following a peripheral blood stem cell transplant will prevent graft-versus-host disease (GVHD), a serious complication of a stem cell transplant, better than the drugs post-transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil.

The drug being studied in this clinical trial, ruxolitinib, is manufactured by a pharmaceutical company called Incyte Corporation. Incyte will provide ruxolitinib to patients free of charge for this study.

You're being asked to join because you have a blood cancer that can be treated with a transplant.

An allogeneic transplant uses healthy blood forming cells donated by someone else matched to you, and those cells are used to replace the unhealthy ones you have.

An allogeneic transplant is a treatment option for you because you have a blood cancer. First, you will receive chemotherapy and possibly radiation. Then, on the day of transplant you'll receive the donated blood-forming cells from your donor through your central venous catheter. You will also receive drugs to help prevent side effects and complications.

If you join, you will:

- Be in the study for up to two years.
- Receive three medicines (either a combination of ruxolitinib, tacrolimus, and methotrexate, referred to as the investigational arm; or a combination of post-transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil, referred to as the standard arm) to try to prevent GVHD after your transplant.
- Receive a transplant (blood-forming stem cells from a donor).

Some possible risks and benefits of joining the study include:

Possible Risks: You may have side effects from the drugs, including ruxolitinib. If you are randomized to take ruxolitinib, your doctor will closely monitor your blood levels for signs of graft failure or in case you need a blood transfusion. While doctors have not seen evidence of this with prior use of ruxolitinib it will be monitored closely during this study. Other possible risks of taking ruxolitinib are described later in this consent form. There are many potential risks of having a transplant as listed later in this consent regardless of enrollment on this research study.

Possible Benefits: You may have less severe complications after transplant than if treated with standard drugs, not including ruxolitinib.

If you do **not** join the study, you have other treatment options, such as:

- A transplant using different medicines to try to prevent GVHD
- Joining another clinical trial, if available (check with your doctor)
- Treating symptoms of the blood cancer

- While ruxolitinib is not approved for this indication, a physician could provide this treatment off study
- No treatment

Key points:

- Being in any research study is your choice.
- You may or may not benefit from being in the study. Knowledge gained from this study may help others.
- If you join the study, you can quit at any time. If you decide to quit the study, it will not affect your care at [name of facility or institution].
- Ask the study staff questions about anything you do not understand, or if you would like more information. You can ask questions now or any time.
- Take time to talk about the study with your doctor, study staff, and your family and friends. It is **your** choice to be in the study. If you decide to join, please sign the end of this Consent Form. You'll get a copy to keep. No one can force you to join this study.

2. Study Purpose

We're doing this study to find out if the investigational drug ruxolitinib, given with the drugs tacrolimus and methotrexate before and following peripheral blood stem cell transplant will prevent graft-versus-host disease (GVHD), a serious complication of a stem cell transplant, better than the standard drugs post-transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil.

A blood stem cell transplant is a typical treatment for high-risk forms of blood cancers, which can include acute and chronic leukemias, lymphoma and myelodysplastic disorders. It replaces the abnormal (or diseased) blood cells with healthy cells from a donor. It requires a close tissue match between you and the donor. Your donor could be a family member, or it could be an unrelated person. The chemotherapy and radiation you get to destroy the abnormal cells and prepare your body for transplant is called the conditioning regimen. When lower doses of chemotherapy and radiation than usual are given, it's called a reduced-intensity conditioning regimen.

A common problem that may occur after a blood stem cell transplant is a condition known as Graft-Versus-Host Disease (GVHD). The "graft" is the donor blood cells that you will get during your transplant. The "host" is the person (in this case, you) receiving the cells. GVHD is when the donor graft attacks and damages some of your (the transplant recipient's) tissues.

- There are two forms of GVHD. One form, called acute GVHD, occurs early after transplant. The second form, called chronic GVHD, can develop months or years after transplant.
- Acute GVHD can cause skin rash, stomach or intestinal problems such as nausea, vomiting, or diarrhea. It may also damage your liver and cause hepatitis or jaundice (yellowing of the skin).

- Chronic GVHD can cause the same effects as acute GVHD as well as dry eyes, thickening or tightening of the skin, or difficulty swallowing or breathing.
- GVHD may also increase your risk of infection.

Ruxolitinib is a type of drug called a Janus kinase inhibitor which works by decreasing the immune response of cells in the body. Early studies have shown that ruxolitinib may help to prevent the donor's cells transplanted in a transplant from attacking the cells in your body and may prevent GVHD when given with tacrolimus and methotrexate. Tacrolimus and methotrexate are FDA approved and standard medications given to patients after peripheral blood stem cell transplant.

Ruxolitinib has been approved by the U.S. Food and Drug Administration (FDA) as a ***treatment*** for GVHD but has not been approved by any regulatory authorities to ***prevent*** GVHD. This research study is registered with the FDA, and they will monitor it. Ruxolitinib has been approved by the FDA to treat steroid-refractory acute GVHD and steroid-refractory chronic GVHD. Ongoing phase 2 clinical trials to look at how well the drug works have demonstrated that when transplant recipients take ruxolitinib in the first year of transplant, the risk of developing GVHD is low. However, more clinical trial results are needed to determine whether it is safe and effective in preventing GVHD after transplant.

This is a phase 3 study. Studies in this phase test to see if a new treatment is better than current standard treatment, including medicines already approved by the FDA. Phase 3 studies are conducted after the dose of the drug and the side effects have already been studied in phase 1 and 2 trials. This trial is an open-label study which means that you and your doctor will both know which treatment arm you are assigned to.

Dose Finding Run-in

The first 50 participants to join this trial will be a part of the dose finding run-in portion of the study that will take place prior to the randomized phase 3 portion. This is being done to find the best dose to use for the phase 3 and closely monitor the safety of ruxolitinib for the participants in this trial. If you are one of the first 50 participants to join this trial, you will be randomized to one of two doses of ruxolitinib.

Once 50 participants have been enrolled in the dose finding run-in and completed the Day 100 study visit, their safety data will be analyzed, and if there are no concerns, enrollment in the phase 3 portion of the study will begin. The best dose of ruxolitinib will also be selected to use in the phase 3 portion.

Phase 3

If you are not one of the first 50 participants, you will be randomized to receive one of the two regimens outlined in Table 1. Approximately 261 participants will be enrolled in each of these groups:

- Group A (investigational): Ruxolitinib (dose determined by run-in portion), tacrolimus, and methotrexate.
- Group B (standard): Tacrolimus, mycophenolate mofetil, and cyclophosphamide.

If you are one of the 50 participants in the dose finding run-in, you will continue on ruxolitinib, and tacrolimus in the same way as patients in the phase 3 portion of the study.

The cells you get during your transplant are called a graft. Graft failure happens when the new cells don't make the new healthy blood cells as expected. Although prior studies have not shown evidence of graft failure with use of ruxolitinib, your doctor and study team will monitor you closely for any signs of it while taking the study drug.

3. Study Treatment and Tests

You will have exams and tests performed as part of the routine care for a peripheral blood cell transplant. Your doctor will discuss any needed routine exams, tests, and procedures with you and address any questions you may have. These tests and procedures are also outlined in Appendix A at the end of this document. If there are any tests below or in Appendix A that you don't feel you've had done or are worried about, please let your doctor know before agreeing to join this study.

Being on this study may require more visits than you would have with only a routine transplant, and your doctor will discuss these differences with you. Your doctor and study team will make every effort to perform assessments via remote telemedicine visits when possible if you do not live near your transplant center.

The following describes the **research procedures** that will be performed if you decide to join this study:

Before the Transplant:

- Patient Reported Outcome (PRO) survey
- Research blood tests (approximately 2.5 tablespoons)

Study Enrollment:

- Randomization: We will use a computer to randomly assign you to 1 of 2 treatment groups. You will have an equal chance of being in either group, similar to flipping a coin. You or your doctor will not choose your group. Once you're assigned a group, you or your doctor can not change your group.

During the Transplant:

- Blood (approximately 2.5 tablespoons) and urine samples for research will be taken prior to your transplant and shortly after your transplant.
- All other parts of the transplant day will be routine.

After the Transplant:

- Study treatment: You will receive one of two possible drug combinations to prevent GVHD. Doctors want to know which combination (investigational or standard) is better, or if they give the same results. The study will help doctors decide which treatment is best at preventing GVHD for future transplant patients. These combinations are listed in Table 1 below.
- Research tests and procedures: Patient Reported Outcome (PRO) surveys, urine tests, and research blood tests (approximately 2.5 tablespoons per visit, for 10 visits after your transplant). Blood will be drawn and urine obtained for research tests whenever possible at

the same time as routine tests. Some research blood samples may be stored for future research. An electrocardiogram (EKG) test will be done on Day 7 and Day 21 after the transplant.

- Blood samples for pharmacokinetics: If you are one of the 200 participants to receive ruxolitinib, following transplant, blood samples will be taken to understand how your body interacts with ruxolitinib. Approximately 4ml (less than 1 tablespoon) of blood will be collected up to 5 times after your transplant.
- Blood samples for immune reconstitution: If you are one of the 250 participants in the Phase 3 portion, blood samples will be taken to understand how the cells in your body recover after transplant. Approximately 5ml (less than 1 tablespoon) of blood will be collected once before your transplant and 7 times after your transplant.

Table 1: Study Treatment Arms

Group A (investigational): Ruxolitinib, tacrolimus, and methotrexate	**Group B (standard): Tacrolimus, mycophenolate mofetil, and cyclophosphamide**
• Ruxolitinib: given initially twice a day as a pill by mouth beginning the day before your transplant. The dose given will be determined by the run-in phase. You will continue taking this drug for 12 months after your transplant. After 12 months, your doctor will slowly decrease the amount of drug given to you and eventually stop. • Tacrolimus: given initially daily as a pill by mouth at a dose of 0.05-0.06 mg/kg/day or intravenously (IV) through your vein at a dose of 0.02-0.03 mg/kg/day, beginning 3 days before your transplant. Your doctor will slowly decrease the amount of drug given to you and eventually stop. This process occurs over several months. • Methotrexate: given intravenously (IV) through your vein at a dose of 5 mg/m^2 on 3 different days (Day 1, 3, and 6) after your transplant.	• Tacrolimus: given initially daily as a pill by mouth at a dose of 0.05-0.06 mg/kg/day or intravenously (IV) through your vein at a dose of 0.02-0.03 mg/kg/day, beginning on Day 5 after your transplant. Your doctor will slowly decrease the amount of drug given to you and eventually stop. This process occurs over several months. • Mycophenolate mofetil: The starting dose will be 15mg/kg given daily intravenously (IV) through your vein or as a pill by mouth 3 times a day, beginning on Day 5 after your transplant, and will continue for 30 days. Your doctor may decide to continue this drug if you still have GVHD. • Cyclophosphamide: given intravenously (IV) through your vein at a dose of 50 mg/kg, over 1-2 hours, on Day 3 and Day 4 after your transplant.

If you decide to join this study, you will take surveys. These surveys are not part of routine transplant care and are being done for research only. We will ask you to complete surveys with questions about your physical and emotional well-being similar to 'are you able to run errands and shop?' These surveys will help us learn about a patient's life after a transplant. Everyone will take the surveys. You can choose to do the surveys online, on paper, or by phone. You can skip any questions you do not want to answer.

You will complete the first two surveys at your hospital - before you start transplant treatment, and one month after transplant. The Survey Research Group (SRG) team from the Center for Blood and Marrow Transplant Research (CIBMTR) will contact you to give you the surveys after transplant. The SRG is part of the study team working with your study doctor.

You will be asked to complete surveys a total of seven (7) times during the two years you are in the study. Each survey will take between 10 and 25 minutes to complete. The surveys will be prior to transplant then 1 month, 3 months, 6 months, 12 months (1 year), 18 months, and 24 months (2 years) after transplant.

You can also choose how to take the surveys:

- **Online:** SRG will send you a link to the survey. The link will not have any information that could identify you.
- **On paper**: SRG will send you the survey in the mail, with a stamped and addressed envelope, to return the survey.
- **By phone:** SRG will call you and ask each survey question over the phone.

If we send you a survey, but don't receive it back, the SRG may contact you by phone, email, or mail to make sure you got the survey and remind you to complete it. You can tell us how you would like to be contacted, and we will document your preference in a study form within our secure database.

The SRG's contact information is listed below. They will always contact you from these addresses or phone numbers. In addition, team members will always say they are contacting you about this study and are from the Survey Research Group with CIBMTR.

Phone: 1-888-298-6714

Email: PROGRESS-IV-Surveys@nmdp.org

Mailing Address: 500 N 5th Street, Minneapolis, MN, 55401-1206

We will share your contact information with the SRG so they can reach you for study surveys. If your contact information changes (for example, emails to you cannot be delivered), they may ask your study doctor or search online for updated contact information. It might be necessary to use an internet-based search service (such as Accurint®) to find you. By choosing to participate in this study, you are giving the SRG permission to use such a service to search public and non-public information to attempt to locate you.

Your survey answers will only be used for this study and will not be shared with your study doctor. We will not look at your answers to check for health issues. If you have any serious health issues or other concerns, immediately talk with your doctor or nurse.

For your time, you will be reimbursed $20 for each completed survey. The SRG will mail $20 Visa gift cards within a month after receiving each completed survey (a total of up to $140 if all surveys are completed).

A complete table of both standard and research exams and procedures is included in Table 2 below.

Stopping Treatment

Treatment will stopped if:

- You tell your doctor you do not want to take the treatment anymore; or
- Your doctor decides the treatment, or any study procedures may be harmful to you; or
- You become pregnant; or

- The sponsor closes the study; or
- The study is closed by any local health authorities or the committees responsible for the review of this study.

Seeing your Research Results

Your doctor may share with you your research results. Your doctor will share any results with you if they show that you need new treatment or need to change your treatment. If you'd like to see specific results, tell your doctor.

Timeline and Participants

This study will take you about 2 years to complete. The total study will take almost 6 years to complete and will include approximately 572 people.

Table 2: Schedule for Health Evaluations

	Screen-ing	**Pre-Trans-plant**	**Day 0** (day of transplant	**Day 3** (-1 day)	**Day 7** (± 3 days)	**Day 14** (± 3 days)	**Day 21** (± 3 days)	**Day 28** (± 3 days)	**Day 35** (± 3 days)	**Day 42** (± 3 days)	**Day 49** (± 3 days)	**Day 56** (± 3 days)	**Day 63** (± 3 days)	**Day 70** (± 3 days)	**Day 77** (± 3 days)	**Day 84** (± 3 days)
Medical history, physical exam, and weight	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Blood tests	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Complete GVHD assessment					X	X	X	X	X	X	X	X	X	X	X	X
Infection assessment	X		X			X		X		X		X		X		X
Disease evaluation	X															
Electrocardiogram (EKG)	X				X*		X*									
Patient Reported Outcome surveys	X*							X*								
Pregnancy testing (if applicable)	X							X				X				X
Blood samples for research		X*			X*	X*	X*	X*				X*				
Urine samples for research		X*			X*	X*	X*	X*				X*				

*Indicates exams and procedures done for research purposes which would not be done with a routine transplant.

Table 2: Schedule for Health Evaluations (continued)

	Day 99 (± 7 days)	**Day 112** (± 7 days)	**Day 140** (± 14 days)	**Day 196** (6 months post-BMT) (± 14 days)	**Day 252** (± 14 days)	**Day 280** (± 14 days)	**Day 308** (± 14 days)	**Day 364** (1-year post-BMT) (± 14 days)	**Day 392** (± 14 days)	**Day 420** (± 14 days)	**Day 532** (18 months post-BMT) (± 28 days)	**Day 730** (2 years post-BMT) (± 60 days)	**End of Treatment**
Medical history, physical exam, and weight	X			X				X			X	X	
Blood tests	X		X	X	X	X	X	X			X	X	
Complete GVHD assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection assessment	X	X		X		X		X	X	X	X	X	X
Disease evaluation	X							X			X	X	
Electrocardiogram (EKG)													
Patient Reported Outcome surveys	X*			X*				X*			X*	X*	
Pregnancy testing (if applicable)		X*		X*		X*		X*	X*	X*			X*
Blood samples for future research	X*			X*		X*		X*				X*	

Urine samples for future research	X*			X*									

*Indicates exams and procedures done for research purposes which would not be done with a routine transplant.

4. Risks and Benefits

Possible Benefits

Taking part in this study may or may not make your health better. If it works for you, you may have less severe complications after transplant. The information from this study could help future patients with similar disorders also have less severe complications after transplant. The information from this study could help doctors learn more about medications used to prevent GVHD.

Possible Risks

You may have side effects during the study. Side effects can range from mild to severe. Your health care team may give you medicine to help with certain side effects, like an upset stomach. In some cases, side effects can last a long time or may never go away. The following are possible risks you may encounter if you decide to join this study.

Risks of Medicines

The following information outlines the risks of ruxolitinib, the medication being studied in this trial. If you are randomized to take ruxolitinib, your doctor will closely monitor your blood levels for signs of graft failure or in case you need a blood transfusion. While doctors have not seen evidence of this with prior use of ruxolitinib it will be monitored closely during this study. Appendix A outlines the risks of other medications given as part of a routine transplant.

Table 3: Ruxolitinib

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• High cholesterol levels in the blood • Increased liver enzyme levels in the blood • Low platelet levels, which may cause bruising, bleeding • Low red blood cell counts, which may cause tiredness or may require blood transfusions	• Diarrhea, constipation, nausea, passing gas • Difficult or labored breathing • Dizziness • Headache • High blood pressure • High triglyceride levels in the blood • Infection, which may cause fever and chills • Low white blood cells, which may cause increased infections and slower wound healing • Muscle spasms • Problems sleeping • Weight gain	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Inflammation of the brain in a syndrome that can cause confusion, weakness, trouble speaking, sadness or personality changes, trouble with memory, balance problems, and/or changes in vision. • Skin cancers

Other Treatments or Medicines

Some medicines react with each other, so it's important to tell the study doctor or staff about any other drugs, treatments, or medicines you're taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It's also important that you tell the study staff about any changes to your medicines while you're in the study.

Reproductive Risks

The treatments in this study have not been proven to be safe at any stage of pregnancy and could affect the health of infants exposed to them via mother's milk. Therefore, if you are pregnant or nursing, you are not eligible for this study. If you can get you pregnant must use effective birth control while receiving chemotherapy, total body irradiation (TBI), and drugs to prevent GVHD, and for 15 months after transplant. Effective birth control is defined in the following sections.

The drugs used in this research study may damage your reproductive organs, affect your ability to have children or possibly cause birth defects if you take them while you are pregnant. It is important that you are not pregnant or breast-feeding and do not become pregnant during the course of the study.

It is important that both women who can become pregnant and their male partners use birth control for 15 months after transplant while on this study.

If you can become pregnant:

If you can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use an effective method of birth control during your transplant and continue until you are finished with your GVHD prevention treatment. You may want to talk with your doctor about ova banking before having a transplant.

Effective birth control is defined as the following:

1. Not have any vaginal sex (abstinence)
2. Consistently use birth control pills or patch
3. Use injectable birth control (for example, Depo-Provera [medroxyprogesterone] injection or Nexplanon [etonogestrel] implant))
4. Have tubal sterilization (tied tubes)
5. Have placement of an IUD (intrauterine device)
6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have vaginal sex.

Tell your doctor right away if you become pregnant during the study. Your doctor will discuss the risks to your unborn child and options with you and will watch you closely if you become pregnant.

If you're male:

Your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant. Please check with your doctor to understand more about these risks.

You must use one of the following birth control methods:

1. Not have any vaginal sex (abstinence)
2. Vasectomy
3. Use of condoms with contraceptive foam every time you have sex.

Or your partner must:

1. Consistently use birth control pills or patch
2. Use injectable birth control (for example, Depo-Provera [medroxyprogesterone] injection or Nexplanon [etonogestrel] implant)))
3. Have placement of an IUD (intrauterine device)
4. Use a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have vaginal sex.
5. Have had a tubal ligation (tubes tied)

Tell your doctor right away if your partner becomes pregnant during the study. Your doctor will discuss the risks to your unborn child and your options.

Additional Information about Mycophenolate Mofetil (MMF):

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
- MMF can make birth control pills not work well. So, you have a **higher** risk of becoming pregnant while you are taking it.
- If you could become pregnant, you **must** use 2 effective forms of birth control for 4 weeks before starting MMF, during treatment, and for 15 months after transplant.

If you think you might be pregnant or could become pregnant prior to enrollment, you should **not** join this study.

Surveys

There are very few risks with taking the study surveys. The main risk is that your confidentiality could be lost. The study team will do everything it can to keep your answers confidential.

Also, some of the questions or topics may upset you. If this happens, your doctor can connect you with a counselor or trained support specialist, if needed.

Your doctor will not be able to see your answers on the surveys. The answers will not be shared with anyone until after the study is done and you will not be able to be identified.

Unforeseen Risks

Other new risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. There may be some unknown or unanticipated side effects from this treatment. The study team will do everything they can to keep you safe and lower your risk of side effects.

There may be unknown risks with stopping ruxolitinib abruptly. You should speak with your doctor before you stop taking your study medication.

Previous studies have not shown an increased risk for relapse from taking ruxolitinib. Part of the purpose of this study is to find out whether the risk of relapse, GVHD or death is different with the investigational treatment.

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

5. Your Rights to Withdraw, Ask Questions, and Seek Other Treatment

Being in this study is your choice. You can choose **not** to be in this study or leave this study at any time. If you choose to not join or leave this study, it won't affect your regular medical care in any way. If at any time you are considering leaving the study, talk to your study doctor about your health and safety.

You have the right to ask questions about the study at any time. If you have questions about the study, please contact:

[Insert contact details for Principal Investigator or study team]

If you want to talk with someone not directly involved in the study, or have any complaints or questions about your rights as a research participant, you may contact:

NMDP Institutional Review Board Administrator at: 800-526-7809

You must tell [insert name of Principal Investigator] if you decide to leave the study.

If you choose not to join, other options are available. Your study doctor will talk with you about your options. If you decide not to join this study, your medical care will not be affected in any way. If you join this study, you cannot be in another clinical trial at the same time.

Your other choices may include:

- A transplant using different medicines to prepare your body for transplant
- Joining another clinical trial, if available (check with your doctor)
- Treatment of blood cancer symptoms
- While ruxolitinib is not approved for this indication, a physician could provide this treatment off study
- No treatment

Every treatment option has benefits and risks. Talk with your doctor about your choices before you decide if you will be in this study.

6. New Information Available During the Study

During this study, the study doctors may learn new information about the study drug or the risks and benefits of taking part in the study. If they learn new information, they'll tell you as soon as it's available.

The new information may mean that you can no longer participate in the study, or you may not want to continue. If this happens, the study doctor will stop your participation and offer you all available care to meet your health care needs.

7. Privacy, Confidentiality, and Use of Information

Your privacy is very important to us. The study doctors, study sponsor, and other groups with access to your study-related medical information will do everything they can to protect it. The study doctors can protect your records if there is a court case. However, some of your medical information may be shared if required by law. If this happens, the study doctors will do their best to make sure that any information that goes out to others will **not** identify you.

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept confidential (private). However, we cannot promise total privacy.

To make sure the study is running ethically, some government agencies or other groups may need to access part of your medical records. For this study, those groups include:

- Blood and Marrow Transplant Clinical Trials Network Data and Coordinating Center (BMT CTN DCC), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP)/Be The Match registry and The Emmes Company, who are coordinating the studies of the BMT CTN
- The Food and Drug Administration (FDA) and National Institutes of Health (NIH), which includes the National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Office of Human Research Protections (OHRP)
- Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for reviewing this study
- Incyte Corporation, the drug company that makes ruxolitinib and provides it for this study

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Study information may also be used for research in the future. These projects could be related to your disease or similar diseases, or development of the study drug.

We might use information from this study to get approval from the government, like the Food and Drug Administration (FDA).

Private information, blood, or tissue taken during the study may be used for future research. If the study team does this, the information, blood, or tissue will not be attached to you or your name in any way and results of the research done with it will not be given to you. To learn more, read section 8 on Blood Samples for Future Research.

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 website will include a summary of the results. You can search this website at any time.

You will **not** be able to access your study results before the study is done. This helps keep the study results accurate and trustworthy.

When the study is complete, you can ask your study doctor for your health information from the study. **By signing this Consent Form, you agree to ask for your results only after the study is done.** You will still have access to your regular medical records.

Data about your health, including follow-up after two years may be obtained by the BMT CTN from the CIBMTR, which captures information on all US transplants.

8. Leaving the Study

You can choose to leave the study at any time.

You may also be told to leave the study for reasons such as:

- You don't meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You're having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

Even if you leave the study, the information and research samples already collected from you will be included in the study evaluation. If you don't want your information or samples to be used, you **must** let your study doctor know.

9. Cost and Reimbursement

You will not be paid for joining this study. You will not be paid or reimbursed for any extra expenses (such as travel or meals) from your participation in this study.

A new drug or product may be developed from this study. Incyte Corporation will not pay you if a commercial product is developed from blood or tissue taken from you during this study.

You will receive pre-paid visa gift cards valued at $20 when you complete the surveys at each visit (a total of up to $140 if all surveys are completed). This survey compensation may be taxable.

Most of the visits for this study are standard medical care for patients undergoing a transplant and will be billed to your health insurance company. You and/or your health insurance company will need to pay for some or all of the costs of standard medical treatment in this study.

Some health insurance plans will not pay for costs of care when you take part in a research study. Check with your health plan or insurance company to find out if they will pay.

You or your health insurance company will not be charged for extra tests or research costs for this study.

For questions about your costs, financial responsibilities, and/or health insurance coverage for this study, please contact [Center/ Financial Counselor] at: [Number].

Physical Injury as a Result of Participation

Tell your study doctor or staff if you think you've been hurt because of being in this study.

You'll get medical treatment if you're hurt as a result of this study. The study sponsor will pay for medical treatment as a result of unintended injury.

In case of injury resulting from this study, you don't lose any of your legal rights to seek payment by signing this form.

10. Statement of Consent

TITLE: BMT CTN 2203: A Randomized, Multicenter, Phase III Trial of Tacrolimus/ Methotrexate/ Ruxolitinib versus Post-Transplant Cyclophosphamide/ Tacrolimus/ Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

- I have read and understood this Consent Form. The purpose and description of the research study has been explained to me.
- I have had the chance to ask questions and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I have had the chance to discuss my participation in this research study with a family member or friend if I choose.
- I understand that…
  - I may not directly benefit from taking part in the study.
  - My name and personal information will not be identified even if information gained during the study is published.
  - I can leave this study at any time and doing so will not affect my current care or prevent me from receiving future treatment.
  - I will be given a copy of this signed consent form.
  - I do not give up any legal rights by signing this form.

_____

Participant Name (or Legally Authorized Representative)

_____ _____

Participant Signature (or Legally Authorized Representative) Date (MM/DD/YYYY)

Physician Certification

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____
Counseling Physician Name

_____ _____
Counseling Physician Signature Date (MM/DD/YYYY)

Interpreter Certification (if needed)

I certify that I have provided an accurate interpretation of this consent form. I believe the participant has understood the information provided.

_____
Interpreter Name

_____ _____
Interpreter Signature Date (MM/DD/YYYY)

Use of a Witness: Complete if the subject is unable to read and/or write but can otherwise communicate and/or comprehend English (e.g. blind, physically unable to write, etc.) or when an interpreter was used but is not physically present (e.g. a language line is used):

Declaration of witness:
By signing below, I confirm I was present for the entire consent process. The method used for communication with the subject was

_____.

_____

Witness Signature: _____

Printed Witness Name: _____

Date (DD/MM/YYYY): _____

11. Optional Samples for Future Research

This section of the Consent Form is about the collection of optional samples for future research studies from people who are taking part in the study. You can choose to give samples for future research studies if you want to. You can still be a part of the main study even if you say "no" to giving optional samples for these studies. Please mark your choice at the end of this section.

If you agree to provide optional samples, here is what will happen:

- Blood and/or urine samples will be collected at 12 time points: during screening, before conditioning for transplant, and at 7 days, 14 days, 21 days, 28 days, 56 days, 99 days, 196 days, 280 days, 364 days, and 730 days post-transplant. Approximately 34.5ml of blood (about 2.5 tablespoons) will be drawn each visit for a total of 414ml blood (about 30 tablespoons) over the course of the study.
- In addition to the 12 time points noted above, additional samples will be collected at the time of certain events like GVHD, relapse, and a change in your treatment. No more than 4 additional samples will be collected. Approximately 34.5ml of blood (about 2.5 tablespoons) will be drawn at those times for a maximum of 138ml blood (about 9 tablespoons) for these additional samples.
    - Your samples will not be attached to you or your name in any way (deidentified). Results of the research done with this sample will **not** be given to you.
    - Your samples will be sent to the BMT CTN designated Biorepository for processing and initial storage.
    - Your samples may be stored in a repository designated by the BMT CTN and may be used for approved research studies by investigators in the broader scientific community. A repository is a place that protects, stores, and sends out samples for approved research studies. These deidentified samples will remain in a repository even if you withdraw consent.
    - Your name will be removed from the research sample and given a bar code. This bar code helps link your sample to de-identified data and other samples collected on this study by the Data and Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC). Only the research team at your hospital will be able to link you to the research sample.
    - Samples will be stored until they are used up or until it is determined that they are not likely to be used in future research, at which time they will be destroyed.

Genome-Wide Association (GWA) Studies

- Your blood and cells have genetic information, called DNA. DNA from your stored samples and your health information might be used in GWA studies for a future project either done or supported by the National Institutes of Health. GWA studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may raise a person's risk of developing a certain disease
- If your genetic information is used in a GWA study, the researcher will add the DNA test results and non-identifying information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you or link you to your information or research samples. The CIBMTR restricts the use of the data to studies of BMT and cellular therapy.
- Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is small but may grow in the future. Researchers must protect your privacy and keep your information confidential.
- A federal law called the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request the genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding your health insurance. This federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits

The research that may be done with your blood samples is not designed specifically to help you. The benefits of research using blood samples include learning more about what causes GVHD, SAA, cancer, and other diseases, how to prevent them, and how to treat them.

Risks

There is a small risk of an infection or fainting from the blood draw. There are no major risks to collecting your urine samples.

A possible risk is the loss of confidentiality about your medical information. We will do our best to make sure that your personal information is kept private. The chance that this information will

be given to someone else is very small.

Some general things to think about when letting us store your blood samples for research are:

- The choice to let us collect and/or store blood samples for future research is up to you. No matter what you decide to do, it will not affect your care.
- If you decide now that your blood samples can be collected and stored for research, you can change your mind at any time. Just contact your study doctor in writing and let them know that you do not want us to continue storing your blood samples. Their mailing address is on the first page of this form. Then, any unused blood samples that remain will no longer be stored for research. However, samples and information that have already been shared with researchers cannot be taken back or destroyed.
- In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

  Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, you will not be told of the results and the results will not be put in your health records.
- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.
- Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not affect your care.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please mark your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at [telephone number].

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

You can change your mind at any time about allowing us to use your samples and health information for research. However, samples and information that have already been shared with researchers cannot be taken back or destroyed.

If you withdraw consent for research use of your samples, there is no penalty or loss of benefits to which you are otherwise entitled. Data and samples that have not been shared will be withdrawn from any repository, if possible, but data already distributed for research use will not be retrieved.

Statement of Consent for Optional Samples for Trial-Related and Future Research Studies

The purpose of collecting and storing optional samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep. I understand that I do not have to allow the collection and storage of my samples for study-specific and future research studies. If I decide to **not** let you store research samples now or in the future, it will not affect my medical care in any way.

If I agree, I understand that optional samples may be collected and that my samples and related information can be stored indefinitely by the BMT CTN designated Biorepository for research to learn about, prevent, or treat GVHD, cancer, or other health problems. I also understand that my DNA and health information may or may not be used in GWA studies.

Future Research Studies

❑ I freely agree to give samples for future research and genomic studies.

❑ I do **not** agree to give samples for future research and genomic studies.

_____
Participant Name (or Legally Authorized Representative)

_____ _____
Participant Signature (or Legally Authorized Representative) Date (MM/DD/YYYY)

12. Appendix A: Standard Transplant Information and Risks

Routine Tests and Procedures

Before the Transplant:

You'll need to have several tests to see if you can be in the study and undergo transplant. Many of these tests are part of your regular care. The following tests would be done even if you decide not to join this study:

- Medical history
- Physical exam, including height and weight
- Blood tests, including HLA typing
- Bone marrow biopsy
- Chest X-ray or CT scan
- EKG or Electrocardiogram
- ECHO or Echocardiogram (Heart ultrasound)
- Liver scan if you've had a lot of red blood cell transfusions
- Lung function tests
- Kidney function tests
- Pregnancy test, if you can get pregnant
- Urine test

HLA (Human Leukocyte Antigen) are markers found on most cells in your body which your immune system uses to recognize which cells belong in your body and which do not. HLA typing is used to match patients receiving a peripheral blood cell transplant with an appropriate donor and requires taking a sample of your blood.

Before your transplant, your doctor will choose a conditioning regimen. The conditioning regimen prepares your body for transplant. It uses chemotherapy and/or radiation to destroy the cancer cells and the cells that make up your immune system. The conditioning regimen also helps the donor cells engraft. "Engraft" means that the cells start to grow and make new cells and show up in your blood. Your doctor will decide which regimen you will receive before you are assigned to 1 of the 2 study treatment groups, if you decide to join this study.

Standard of Care Conditioning Regimens

All of the immune suppressive and conditioning regimen drugs listed below are commonly used in blood stem cell transplant. The tables below describe all conditioning regimens that are allowed to be used in this study. The regimen you will receive depends on your doctor's choice.

Table 1: Conditioning Regimens

Reduced Intensity Conditioning	Nonmyeloablative Conditioning
Fludarabine/Busulfan (Flu/Bu) • Fludarabine (120-180 mg/m^2 total dose) • Busulfan (less than or equal to 8 mg/kg PO or 6.4 mg/kg IV total dose)	**Fludarabine/Cyclophosphamide (Flu/Cy)** • Fludarabine (90-120 mg/m^2 total dose) • Cyclophosphamide (120 mg/kg or 2250 mg/m^2 total dose)
Fludarabine/Melphalan (Flu/Mel) • Fludarabine (120-180 mg/m^2 total dose) • Melphalan (100 - 140 mg/m^2 total dose)	**Fludarabine/ Cyclophosphamide/TBI (Flu/Cy/TBI)** • Fludarabine (150 mg/m^2 total dose) • TBI (200-400 cGy total dose) • Cyclophosphamide (29-50 mg/kg total dose)

During and After the Transplant:

Even if you decide not to join this study, the following events and tests would still take place.

On your transplant day (Day 0), the stem cells will be given to you through your central line, like a blood transfusion. The cells will travel through your bloodstream to your bone marrow where they will start to make healthy, new blood cells after several weeks.

Your doctor may decide to give you other medicines throughout your treatment to help with any side effects or discomfort.

You will also need several tests after transplant to see how your body is doing with the treatment. These tests are part of regular care for patients who have had a transplant. They would be done even if you were not part of this study.

- Blood tests
- Bone marrow tests
- Liver tests
- Physical exam

You will receive standard drugs to help prevent a complication called graft-versus-host disease, or GVHD. These are given even if you do not join the study. GVHD occurs when the donor cells see your body as foreign (or different) and attack it. It can be a very serious life-threatening side effect of transplant.

Potential Risks and Side Effects of the Transplant

There are many potential risks of having a peripheral blood stem cell transplant as listed below regardless of enrollment on this research study.

- **Damage to the organs in your body.** This could affect any organ in your body such as your heart, lungs, liver, gut, kidneys, bladder, and brain. Although many patients recover, these complications may result in organ failure, permanent damage or even death.

- **Serious infections.** It can take your immune system many months to recover from transplant. During this time, you have a higher risk of infections. You will take medicines to lower your risk, however these don't always work. If you have an infection, you may have to stay in the hospital. Although most infections can be treated, some may cause death.
- **Disease comes back.** Your disease may not go away with transplant, or it may come back even if the transplant works at first.
- **Graft failure.** The blood-forming cells from your donor (the "graft") may not grow inside your body. The risk of this happening is up to 15%. Graft failure may cause low blood counts for a long time. If this happens, you may need another transplant. Graft failure can cause death.
- **Cancer.** You could develop a blood cancer, such as myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or other cancers. If this happens, it's usually 2-10 years after transplant but can develop any time after transplant. With chemotherapy drugs that have been used for transplant, the risk is less than 10%. If cancer develops, you may need more treatment with chemotherapy or another transplant. Some patients have developed cytogenetic abnormalities (abnormal chromosomes) in bone marrow cells following transplant that may be a result of the chemotherapy medicines. The long-term risks are not completely understood. One potential risk is the development of MDS or a leukemia.
- **Damage to your thyroid or other endocrine glands.** This can affect the thyroid function and patients may require medication.
- **Serious bleeding.** Your red blood cells, white blood cells, and platelets can be slow to recover after transplant. This means you'll be at risk for bleeding and infections. Until your blood counts recover, you'll need blood and platelet transfusions and antibiotics to prevent infections from occurring.
- **Non-physical risks.** Patients who have a transplant may experience non-physical risks including that you may not be able to attend school or work.
- **Risks of blood draws.** There are no major risks with blood draws. A blood draw can hurt a little and may cause a bruise. On rare occasions, people feel lightheaded or faint. Only trained people will draw your blood.
- **Graft-versus-host disease (GVHD).** GVHD happens when the donated cells see your body as foreign and attack it. GVHD can be treated, but treatment can take months to years. Sometimes GVHD is severe and may lead to death. You'll be watched closely for this complication and given drugs to prevent and/or treat it. GVHD is treated with drugs that weaken the immune system so you may be more likely to get serious infections while you're taking them. GVHD can develop in the early weeks or months after transplant. This is often called acute GVHD. GVHD can also develop months or years after transplant. This is often called chronic GVHD.

Acute GVHD Symptoms:

- Skin rash, discoloration, and/or tightness of skin
- Lack of appetite, stomach cramps or abdominal pain, nausea, vomiting, diarrhea or "full" feeling in stomach, weight loss

- Liver problems, which can make the skin yellow

Chronic GVHD Symptoms:

- Dry eyes, problems with vision
- Hair loss
- Liver problems
- Mouth problems, including dry mouth, mouth sores, dry and sore lips or throat, problems swallowing
- Skin rash or thickening (scleroderma)
- Difficulty moving joints
- Shortness of breath
- Muscle cramps, pain, or weakness

Risks of Medicines

The following tables outline the risks of medicines you may receive as part of your routine transplant. Your doctor will decide which medicines are best for you.

Table 2: Methotrexate

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Increased risk of sunburn or rash • Nausea, vomiting, loss of appetite • Sores in mouth which may cause difficulty swallowing	• Anemia from low red blood cell count which may cause tiredness, or may require transfusion • Blood clots which may cause swelling, pain, shortness of breath • Bruising, bleeding from low platelet count • Diarrhea, sores in the gastrointestinal tract • Fluid around the heart • Hair loss • Hepatitis or liver damage which may cause yellowing of eyes and skin, generalized swelling • Infection, especially when white blood cell count is low • Kidney damage	• A new cancer • Damage to brain, which may cause seizure • Internal bleeding which may cause belly pain, black tarry stool, blood in vomit • Scarring of the lungs which may cause shortness of breath, confusion • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Table 3: Tacrolimus (FK506, Prograf®)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Abnormal body movement, including tremors • Abnormal levels of sugar, fat, or minerals (like sodium or potassium) in your blood • Constipation, diarrhea, nausea, vomiting, reflux, lack of desire to eat • Difficulty sleeping • Dizziness • Feeling of "pins and needles" in arms and legs • Headache • High blood pressure which may cause dizziness, chest pain • Itching, rash • Kidney damage which may cause swelling, may require dialysis • Low red blood cell counts, which may cause tiredness, or may require blood transfusions • Low platelet levels, which may cause bruising, bleeding • Low white blood cell counts, which may lead to infection • Liver damage • Swelling of the body	• A new cancer • A tear or a hole in your bowels which may cause belly pain and may require surgery • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Change in the heart rhythm, abnormal heartbeat, or heart stops beating • Damage to brain, which may cause headache, seizure, blindness • Damage to lungs, which may cause shortness of breath, fluid around lungs • Heart attack or heart failure which may cause chest pain, swelling of ankles, and tiredness	• Damage to small blood vessels with resulting small blood clots and possible organ damage

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, Sundrop,* and *Sunny Delight*.

Table 4: Mycophenolate Mofetil (MMF, Cellcept®)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Birth control may not work as well • Damage to unborn baby if you become pregnant while taking this medicine • Difficulty breathing, cough • Headache • High blood pressure • Low white blood cell count with increased risk of infection • Nausea, vomiting, diarrhea, stomach pain • Swelling of the hands, feet, ankles, or legs • Tremors	• Anemia (low red blood cell count) • Change in the levels of salts in the blood • Decreased platelet count, may cause blood loss into stool or vomit, increased bruising • Difficulty falling asleep or staying asleep • Dizziness • Low blood pressure • Pain in joints or muscles • Rash	• A new cancer • Change in vision • Encephalopathy or brain dysfunction that can lead to death • Excessive tiredness • Fast heartbeat • Progressive Multifocal Leukoencephalopathy – This is caused by a virus that damages the protective covering in the brain • Severe difficulty breathing • Weakness

Table 5: Cyclophosphamide (Cytoxan®)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Absence of menstrual cycles which may decrease the ability to have children • Feeling tired • Hair loss, skin changes, rash, change in nails • Infection, especially when white blood cell count is low • Nausea, vomiting, diarrhea, loss of appetite, pain in belly • Sores in mouth • Swelling of the bladder which may cause cramps, pain, and bleeding	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Decrease in platelets which may cause bleeding • Decrease in red blood cells, which may require blood transfusions • Loss or absence of sperm which may lead to an inability to father children	• A new cancer • Damage to the heart or heart failure which may cause shortness of breath, swelling, cough or tiredness • Scarring of the lungs which may cause shortness of breath, fluid arounds the lungs • Swelling of the brain which may cause dizziness, confusion

Table 6: Busulfan

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Abnormal or fast heartbeat • Abnormal salt and/or vitamin levels that may require IV fluids • Anemia (low red blood cells) which may require blood transfusions • Chills, fever • Constipation, diarrhea, heartburn, nausea, vomiting, loss of appetite, stomach pain • Cough, stuffy nose • Damage to the liver or kidneys • Difficulty sleeping • Dizziness, headache • Feeling tired • High blood pressure • Infection, especially when white blood cell count is low • Low platelet counts which may cause bruising or bleeding • Pain • Rash • Sadness, worry • Sores in mouth which may cause difficulty swallowing • Swelling of the body	• Blood in the urine • Coughing up blood • Damage to or scarring of the lungs • Loss or absence of sperm • Menopause • Seizure • Visual disturbances	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Fluid around the heart • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Low blood pressure which may cause feeling faint

Table 7: Fludarabine

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Anemia (low red blood cells) which may require blood transfusions • Cough • Feeling tired or irritable • Infection, especially when white blood cell count is low • Low platelet counts, which may cause bruising or bleeding • Pain	• Chills • Confusion • Damage to brain, lungs, or other organs. This may cause tiredness, changes in thinking or shortness of breath • Feeling of "pins and needles" in arms and legs • Nausea, vomiting, loss of appetite • Sores in mouth which may cause difficulty swallowing	• Blood in urine • Changes in vision • Kidney damage which may require dialysis • Liver damage • Seizures

Table 8: Melphalan

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Anemia (low red blood cells) which may require blood transfusions • Diarrhea • Feeling tired • Infection, especially when white blood cell count is low • Nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Swelling of the body	• Inflammation of blood vessels • Kidney problems which may require dialysis • Liver problems which may cause yellow eyes or skin • Low platelet counts, which may cause bruising or bleeding • Scarring of the lungs which may cause shortness of breath	• A new cancer • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness

Table 9: Low Dose Total Body Irradiation (TBI)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Anemia (low red blood cells) which may require blood transfusions • Infection, especially when white blood cell count is low • Low platelet counts, which may cause bruising or bleeding • Mouth sores • Nausea, vomiting, stomach pain, diarrhea	• Eye cloudiness • Hair loss • Inability to have children • Painful swelling of the salivary glands under the ears for a few days • Redness of the skin	• A new cancer • Back pain • Difficulty swallowing • Hormone problems (such as thyroid disease or diabetes) • Kidney problems • Learning problems • Liver problems • Lung inflammation • Slow growth (for example, height)