Northside Hospital Informed Consent

A Phase II Trial of Nonmyeloablative Haploidentical Peripheral Blood Stem Cell Transplantation Followed By Maintenance Therapy With the Novel Oral Proteasome Inhibitor, MLN9708, in Patients with High-risk Hematologic Malignancies

Principal Investigator: Scott Solomon, M.D.

Associate Investigators: Lawrence Morris, M.D.
Kent Holland, M.D.
Asad Bashey, M.D., PhD
Melhem Solh, MD

Blood and Marrow Transplant Group of Georgia
(BMTGA)
5670 Peachtree Dunwoody Road, Ste 1000
Atlanta, GA 30342
404-255-1930

WHAT IS THE PURPOSE OF THE STUDY?

You are being asked to take part in a research study because you have a blood cancer or blood disorder that may be treatable with a stem cell transplant (SCT) from a relative or an unrelated donor (allogeneic transplant). However, you do not have a brother or sister or an unrelated donor who is a complete tissue match. Tissue typing shows that you do have a family member who is a partial match (haploidentical donor). A complete tissue match is when another person has the exact same HLA makeup that you, as the transplant recipient do. HLA stands for Human Leukocyte Antigen. HLA are proteins (markers) found on most cells in your body. Your immune system uses these markers to recognize which cells belong in your body and which do not. When a person is said to be a complete match, their HLA markers look identical to your markers and the risks of complications following bone marrow or stem cell transplant may be decreased. When HLA markers do not match completely, they are said to be a partial match or mismatch.

Two of the major complications of SCT are graft-versus-host disease (GVHD) and graft rejection. GVHD occurs when cells of the donor's immune system injure your normal tissues.

Initials _____

GVHD can cause rash, diarrhea, or liver damage, and can be severe enough to cause death. Acute GVHD usually occurs within the first 100 days post transplant and most often affects the liver, skin and gut. Chronic GVHD usually occurs after 100 days post transplant and can affect the liver, skin and gut as well as any other organ such as the eyes, mouth or lungs. However, cells of the donor's immune system can also attack cancer cells and prevent the cancer from coming back. Graft rejection occurs when your immune system destroys all the cells of your donor's bone marrow.

Previous studies from this institution have shown that using cyclophosphamide (a type of chemotherapy) both before and after a transplant from a partially matched (haploidentical) family donor can reduce your risk of developing complications after transplant including graft rejection and GVHD. Using this approach, our group and others have shown that the risk of complications following haploidentical transplantation is no higher than what is seen following transplants from a fully matched donor.

However, another important risk of an allogeneic stem cell transplant is that your disease may come back (relapse). We are conducting this research study to find out whether an investigational drug called MLN9708 (ixazomib citrate) can be used safely and effectively as part of your transplant process to prevent your disease from relapsing. MLN9708 is a type of targeted drug known as a proteasome inhibitor. It is a once-weekly oral version of a currently available drug called bortezomib (Velcade®), which is FDA approved for the treatment of multiple myeloma and mantle cell lymphoma. In addition to its ease of use, being an oral drug, MLN9708 may also be more effective and better tolerated than Velcade®, and clinical trials are currently being performed in patients with multiple myeloma. In this trial, we are using MLN9708 to help improve the results of haploidentical transplantation. Many of the risks and benefits of transplant are related to effects of the donor's immune system: either against your normal tissues (GVHD) or against the cancer cells, the so called graft-versus-malignancy (GVM) effect. Natural killer (NK) cells have been shown to be an important part of the donor immune system and the GVM effect – they can directly kill cancer cells and help to prevent relapse. Drugs like MLN9708 and Velcade® have been shown to improve the cancer killing ability of NK cells. These drugs have also been shown in animal models to decrease the risk of GVHD. It is hoped, in this protocol, that MLN9708 will decrease your chance of relapse by improving the GVM effect, while minimizing your risk of GVHD.

Initials _____

The word "investigational" means that MLN9708 is not approved by the U.S. Food and Drug Administration (FDA). The FDA is allowing the use of MLN9708 in this study. The chemotherapy and other drugs used in this study are FDA approved for use in SCT.

This is an investigator-initiated study. The principal investigator, Scott R. Solomon, MD (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

This consent form will provide you with information about this research study. Before you decide to take part, you should understand enough about the risks and benefits of participating to make an informed decision. This process is known as informed consent. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision. You will be asked to sign this form if you wish to participate.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study will be conducted only at the Blood and Marrow Transplant Program at Northside Hospital. We anticipate enrolling 25 patients over the course of 2 years.

HOW LONG WILL I BE IN THIS STUDY?

You have an opportunity to receive MLN9708 for up to 12 months after your transplant. Once you have received your first dose of study treatment, you will be followed throughout your treatment plan and will continue for 30 days after your last dose of treatment to monitor your health for any adverse reactions. You will continue to follow up with either BMTGA or your referring physician as part of routine transplant follow up indefinitely. The follow up obtained after transplant is to determine disease free survival, presence of graft-versus-host disease, engraftment (if donor cells are functioning appropriately in your bone marrow) and quality of life after the transplant. These are standard evaluations for transplant recipients.

WHAT WILL HAPPEN TO ME ON THIS STUDY?

If you agree to be in this study, you will be evaluated at Northside Hospital and the Blood and Marrow Transplant Group of GA (BMTGA). This evaluation may include the following tests and/or procedures:

- Medical history and physical examination
- Bone marrow biopsy and aspiration - A bone marrow aspiration is a procedure in which an area of the hip bone is numbed, and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through a needle.
- Various blood tests including a complete blood count (CBC) and chemistry panel to see how well your organs are functioning. Approximately 6.5 tablespoons of blood are taken for all blood tests.
- Additional blood tests called infectious disease markers (IDMs) that test for HIV (human immunodeficiency virus, the virus that causes AIDS [Acquired Immune Deficiency Syndrome]), hepatitis and other transmittable diseases. State law requires that the results of positive tests for HIV (Human Immunodeficiency Virus) and hepatitis be reported to a local health agency.
- Electrocardiogram or ECG (tracing of the electric activity of the heart)
- CT/PET (Computed tomography/Positron emission tomography) scans to determine the extent of your disease if you have Non-Hodgkin's Lymphoma or Hodgkin's Disease
- ECHO (echocardiogram) or MUGA (multi-gated acquisition scan) which is a test to see how well your heart is functioning
- Pulmonary Function Tests (PFTs) to determine how well your lungs are working
- Serum Pregnancy test for women of child bearing potential
- Approximately two ounces of extra blood will be drawn at six separate times (pre-transplant, one, two, three, six and twelve months post-transplant) to determine how the investigational drug, MLN9708, affects the recovery of your immune system following transplant. These research samples are optional and you may choose not to allow us to collect these samples but still participate in this research study. You will be asked about your willingness to provide these extra samples toward the end of this consent form. You will be able to agree or disagree to provide these samples.

All of these tests, with the exception of the additional blood samples for research, are considered routine and would be done prior to transplant whether or not you participate in this study.

If you are found to be eligible, and you choose to join this study, a central venous catheter will be placed under your collarbone, if you do not already have one. This catheter will be used for many things during the transplant including chemotherapy, fluids, antibiotics and other medications, blood transfusions, and intravenous feeding (if necessary).

Initials _____

You will be given Fludarabine for 5 consecutive days prior to your stem cell infusion by IV (intravenous) infusion. These days will be considered day -6 to day -2 of the study. You will receive 2 doses of cyclophosphamide on days -6 and -5. You will then receive Total Body Irradiation (TBI) on day -1.

Your stem cell infusion day will be considered Day 0. Your donor's stem cells will be collected by apheresis. Apheresis is a process which removes the donor's blood, pulls out the stem cells that will be given to you and returns the blood back to the donor's body. After the stem cells are processed, they will be given to you through your catheter on the inpatient bone marrow unit.

You will then receive Cyclophosphamide on days 3 and 4 after your transplant and begin a drug called tacrolimus on Day 5 that will aid in the prevention of graft rejection and GVHD. On day 5 you will also start weekly treatments of MLN9708. MLN9708 will be given orally in 28-day cycles. You will receive a weekly dose of MLN9708 for 3 weeks and then rest for one week. That is considered one cycle. You may be able to receive up to 12 cycles of MLN9708 after your transplant.

Days –6, -5 Fludarabine 30 mg/M^2 IV qd
Cyclophosphamide (CTX) 14.5 mg/kg IV qd*
Mesna 11.6 mg/kg IVqd

↓

Days –4→ -2 Fludarabine 30 mg/M^2 IV qd

↓

Day –1 TBI (Total Body Irradiation) 200 cGy

↓

Day 0 Infuse unmanipulated PBSCs
(peripheral blood stem cells)

↓

Days 3, 4 CTX 50 mg/kg IV q d

↓

Day 5 Begin Tacrolimus and
MLN9708 4mg weekly x 3doses every 28days, up to 12 monthly cycles

↓

Day 30, 60, 90 Assess Chimerism in peripheral blood

↓

Day 180 Discontinue Tacrolimus

Initials _____

During your treatment and follow-up, samples of blood, bone marrow, urine, and body fluids may be taken. Standard of care practice will require your blood to be drawn from your catheter almost everyday you come into the clinic and everyday when you are in the hospital. If your blood counts are low, you will be given red blood cells (cells that help your body carry oxygen to your organs) and platelets (cells that help the blood to clot) transfusions. You will also be given antibiotics to prevent and treat any infections.

You must agree to use a reliable form of birth control while on this study. Some of these treatments may seriously harm or kill a fetus. If you are a woman capable of having children, you will be given a pregnancy test before you begin the study. You may not join this study if you are pregnant or breast-feeding. If you become pregnant, you must notify the doctor listed on this form immediately. The treatment will be stopped and you will be taken off the study.

You will need to come back to the BMTGA clinic for daily evaluations for at least 100 days after your transplant. Usually around 100 days after your transplant you may be discharged back to the care of your referring physician. All test results will be shared with you and your local physician. Periodically personnel from the BMTGA clinic will be contacting you to see how you are doing and will also request pertinent records from your referring physician related to your status. You will need to have follow-up visits at BMTGA at 6, 12, 18, 24 and 36 months for purposes of this study. Additional, more frequent visits may be required if your physician feels it is necessary.

WHAT ARE THE RISKS OF THE STUDY?

POSSIBLE DISCOMFORTS AND RISKS OF MLN9708

There are risks to taking part in any research study. During the study, you may have problems or discomforts and risks from MLN9708, MLN9708 and other drug combinations, and/or study procedures. The more commonly occurring discomforts and risks are listed below, as are the rare but serious discomforts and risks. You should discuss these with your study doctor. There is always the possibility that unknown risks may occur, however your doctor will watch closely for problems or discomforts and risks. Many discomforts and risks go away shortly after treatment is stopped or with treatment for the discomforts and risks, but in some cases discomforts and risks may be serious, long-lasting or permanent and may even result in hospitalizationor death.

If any discomforts and risks occur, you must tell your study doctor or study staff, even if you do not think they are related to the study drug.

Initials _____

MLN9708

Based on studies of MLN9708, it is possible to predict some of the discomforts and risks. However, it is possible that MLN9708 may cause risks that have not yet been observed in patients. The following risks might be seen based on previous experience:

- Low platelet count which may increase the chance of bleeding (33%)
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body (45%)
- Feeling tired or weak (48%)
- Nausea (41%)
- Vomiting (30%)
- Diarrhea (39%)
- Numbness or tingling or pain feelings in hands and feet (21%)
- Constipation (21%)
- Lowered red cells or anemia which may make you feel tired (22%)
- Lowered white blood cells called neutrophils that may increase your risk of infection (19%) and may be associated with fever (<1%)

- Other discomforts and risks reported in studies with MLN9708, which may have been due to the patient's disease, MLN9708, other medications, or some combination of these include:
  - Not feeling like eating (13%)
  - Electrolyte imbalance [blood chemical imbalance] (18%)
  - Loss of water from the body (dehydration) because of vomiting and/or loose stools (11%)
  - High blood creatinine and renal failure, which means your kidneys are having trouble working well.Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney [dialysis] (3%)
  - Flu-like symptoms and other upper respiratory tract infections (17%)
  - Lung infections including pneumonia or pneumonitis (7%)
  - Cough (12%)Chills (6%)

Initials _____

- Pain in the abdomen (11%) or back (15%)
- Swelling or fluid build-up in the arms or legs (20%)
- Lowered blood pressure (12%) that can commonly cause you to feel light-headed, faint or pass out when you stand up (4%)
- Lowered white blood cells called lymphocytes (10%)
- Pain (muscular) in extremities (10%)

Some discomforts and risks that occur with lesser frequency (<1%) than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience, we do not know if MLN9708 causes such problems. Stevens Johnson's Syndrome, a severe, life-threatening or deadly condition that may involve rash, skin peeling and mouth sores has been reported in ongoing MLN9708 studies. Stevens Johnson Syndrome is a disorder of the immune system, which differs from a regular skin rash.

In addition, posterior reversible encephalopathy syndrome has also been reported with MLN9708 with lesser frequency (<1%). This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible.

Transverse myelitis, also a rare condition (<1%), is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving MLN9708. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether MLN9708 causes transverse myelitis, however, as it happened to a patient receiving MLN9708, we are not able to exclude the possibility that MLN9708 may have contributed to transverse myelitis.

Progressive multifocal leukoencephalopathy (PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1%) in patients taking MLN9708. It is not known whether MLN9708 may contribute to the development of PML.

Additionally, it is worth noting that:

- MLN9708 is similar to the drug known as VELCADE ® (bortezomib) for Injections, which is approved for the treatment of multiple myeloma (a cancer of the plasma cell), as well as mantle cell lymphoma (a cancer of the lymph nodes) in patients who have received at least one prior therapy.
- MLN9708, like Velcade, should not be taken if you have ever had an allergic reaction to boron or boron containing products. Allergic reactions may be possible.

- The following side effects have been reported with VELCADE use and therefore may also be a risk with MLN9708:
    - Reactivation of the herpes virus infection such as herpes zoster (shingles) that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time; and
    - Rapid death of cancer cells that may let large amounts of the cells into the blood that injure organs, such as kidneys (this is referred to as tumor lysis syndrome). Your study doctor can talk with you about other common side effects with VELCADE use.

- The more severe but rare side effects seen with VELCADE include, but are not limited to, worsening of your heart function (congestive heart failure), disorders that could affect the function of your lung that could be serious enough to result in death, and liver failure. Your doctor can talk to you further about the risks of VELCADE.

- Other drugs and supplements may affect the way MLN9708 works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

RISK TO THE UNBORN CHILD (MEN AND WOMEN)

Female subjects: We do not know if the study drug MLN9708 will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study.

You must have a negative pregnancy test prior to enrolling in the study.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal),

you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see examples below).

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex or non-latex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

You must use birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male subjects: We do not know if using MLN9708 will affect sperm. Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period (including interruptions in treatment). Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non-latex condom with a spermicidal agent) during the entire study drug treatment period, and for 90 days after completing study drug treatment. Or, you should completely avoid having heterosexual intercourse.

Highly effective methods	**Other effective methods (barrier methods)**
Vasectomy	Latex or non-latex condom with or without a spermicidal agent
	Diaphragm with spermicide; Cervical cap with spermicide; Sponge with spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

Initials _____

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

Graft Versus Host Disease (GVHD): A major risk of the allogeneic transplant is the risk of developing GVHD. GVHD occurs when cells of the donor's immune system, which are present in the bone marrow, attack your normal tissues. GVHD can cause rash, diarrhea, or liver damage, and can be severe enough to cause death.

GVHD can be classified as either acute or chronic. Acute GVHD, if it occurs, usually appears within the first 100 days after transplantation. It can affect the skin, liver and the intestinal tract. The chance of having all three areas affected is possible. The affect on these areas can be at different stages of severity. The possible signs/ symptoms for acute GVHD of the skin, liver and intestinal tracts are as follows:

- GVHD of the skin: Elevated red rash, rash with blisters or dry, peeling skin
- GVHD of the liver: Liver function tests above normal range or liver failure
- GVHD of the intestinal tract (gut): Diarrhea greater than 500 ml/day or several liters of diarrhea a day with severe abdominal pain

Chronic GVHD is a multi-system disease that can affect almost any organ in the body. The mostly commonly involved organs are the skin, mouth, liver and eyes. This form of GVHD usually occurs more than 100 days after your transplant. The possible signs/symptoms of chronic GVHD include the following:

- GVHD of the skin: Red rash or thick, dry skin over some or most of your body
- GVHD of the mouth: Dry and/or sore mouth
- GVHD of the liver: Liver function tests above normal range or liver failure
- GVHD of the eyes: Dry eyes or corneal erosion/ conjunctivitis (infection)

Graft rejection: Another risk of allogeneic transplant is that the donor's stem cells will not grow. If this happens, your own bone marrow is unlikely to come back given the intensity of pre-transplant therapy. Graft rejection is life-threatening and usually fatal without performing a second transplant procedure. You will have routine blood tests about day 30, day 60, day 180 and yearly to see how many donor cells are in your bone marrow.

Hemorrhagic cystitis: This complication is seen more frequently following mismatched allogeneic transplants. About 1-2 months after transplant, patients may develop painful and often bloody urination that is usually related to a viral infection of the bladder. Although not usually life-threatening, this complication may require patients to need additional hospitalization for pain control or bladder irrigation.

Veno-Occlusive Disease (VOD): The pre-transplant treatment with drugs and/or radiation can damage the liver. This complication is called VOD. VOD may develop within the first month after the stem cell transplant and causes pain and enlargement of the liver, a buildup of fluid in the abdomen and sometimes around the lungs, and jaundice (yellowing of the skin/eyes). There is no proven treatment for VOD. VOD may get worse and cause fatal liver damage.

Infections: Patients receiving allogeneic transplants have weakened immune systems for many months following the transplant and are at risk for multiple potentially life-threatening infections from viruses, bacteria, fungi, and parasites. You will receive preventative antibiotics to help reduce the risk of infection, and will be monitored closely for signs of fever and infection.

You will be given chemotherapy during your transplant process. Risks associated with these drugs include:

Fludarabine: low white blood cells (which could lead to an increased risk of infection), low red blood cells (which can cause you to feel tired, short of breath or weak), low platelets (which can increase your risk of bleeding), weakness, agitation, confusion, numbness and/or tingling in the fingers and/or toes, changes in vision, nausea, vomiting, diarrhea, soreness in the mouth, decreased appetite, difficulty breathing, cough or bleeding in the urine.

Cyclophosphamide: abdominal pain, diarrhea, painful sores on/in the mouth or stomach, loss of appetite, nausea and/or vomiting. There may be temporary and total hair loss affecting not only the scalp but also underarms, beard, eyelashes and pubic area. The hair usually does grow back

when drug treatment is stopped. Cyclophosphamide will decrease the blood cells produced in bone marrow including low white blood cells (which could lead to an increased risk of infection), low red blood cells (which can cause you to feel tired, short of breath or weak) and low platelets (which can increase your risk of bleeding). Breakdown products of cyclophosphamide can cause bladder irritation and bleeding. This can cause pain and the appearance of blood in the urine and scarring of the bladder. You will be given a medicine (Mesna) and extra fluid hydration in an effort to prevent this. At very high doses, cyclophosphamide can cause severe heart muscle injury or death.

Taking cyclophosphamide can damage the male (testes) or female (ovaries) sex glands. Women, who are still menstruating may have irregular periods or stop having periods. The ability to have children will likely be permanently impaired.

Very rarely after getting cyclophosphamide there can be scarring of the lungs which could cause you to experience coughing spells and shortness of breath. There is also a small chance after taking cyclophosphamide of getting a second cancer (i.e. leukemia or solid tumor).

TBI Decrease in blood counts (white blood cell and platelet), fatigue, hair loss, skin changes included redness, irritation, swollen or blistered, "sunburned" or "tanned", dry, flaky or peeling skin, itchiness. There may be an increased risk of secondary cancer from the use of radiation.

Tacrolimus (FK-506): constipation, diarrhea, nausea, vomiting, headache, insomnia, tremor, localized skin burning, pruritus (itching), skin erythema (redness), and reduced kidney function.

Other risks associated with stem cell transplant

Drawing blood from your arm may cause pain, bruising, lightheadedness, and, on rare occasions, infections. We will make every attempt to use your central venous catheter for drawing blood when possible.

Central venous catheter placement risks include bleeding, infection and lung puncture causing collapse of the lung. In rare cases, surgery is needed to correct these problems. After the catheter has been inserted, there may be problems with infection or blood clots. The risk for these problems increases with the length of time that the catheter is in place. Treatment may include antibiotics and "blood thinners" to dissolve the clot. Sometimes, the catheter needs to be removed. Very rarely, there is irreversible swelling of an arm or the neck.

Initials _____

Psychological risks: It is possible that in addition to the physical risks, there are also psychological and emotional risks to the relationship you may have with your donor if the donor changes his/her mind during the treatment and decides not to donate stem cells. The Blood and Marrow Transplant Program at Northside Hospital has a Health Psychologist on staff to help you with any psychological or emotional needs that you may have during the transplant process.

Unknown Risks: There is always the risk that unexpected side effects will occur. Your doctor will check you closely to see if any side effects are occurring and routine blood tests will be done to monitor the effects of treatment. For more information about risks and side effects, ask the researcher or study doctor at your institution.

BENEFITS

There is no guarantee that your condition will improve as a result of participation in this study. However, SCT does offer a potential cure of your blood disease. In addition, MLN9708 may improve your outcome by decreasing the chance of relapse following transplant. There is also a possibility that the treatment will have no effect on your disease or that it may even be harmful to you. Future patients with similar blood diseases or disorders may benefit from what is learned from this study.

ALTERNATIVE TREATMENT

Other options may be available, including other research studies or standard of care therapy including transplant at BMTGA or other institutions. It is possible that if you choose not to participate in this study and still go on to transplant, you may receive any or all of the commercially available drugs being used in this study. If you do not go on study, you will not be able to receive MLN9708. You may also choose not to receive treatment for your blood disease or disorder and receive comfort care only, where treatments are directed only at reducing symptoms, relieving suffering, and maximizing comfort. This type of care does not treat your disease directly, but instead tries to improve how you feel.
Should you choose not to participate in this study, your ability to received medical care at BMTGA or Northside Hospital will not be affected.

During your participation in this study, you will be informed in a timely manner of any significant new information that may affect your willingness to stay in this study.

COSTS

You will not be compensated or receive payment for participating in this study. MLN9708 will be provided to you free of charge. The other drugs used in this study are commercially available and will be charged to you and your insurance provider. You and your insurance company will be responsible for all costs related to the study treatment that are considered standard of care. Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company may not pay for routine costs of treatment because you are taking part in a research study. We will help you determine the extent of your insurance coverage before you are enrolled on this study.

Your participation in this research study may contribute to the development of commercial products from which Millennium Pharmaceuticals, Inc. or others, may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit. Millennium Pharmaceuticals, Inc. is providing MLN9708 for this study free of charge. The company is also providing some financial support for the Blood and Marrow Transplant Program at Northside Hospital to conduct this study.

COMPENSATION FOR INJURY

If you suffer an injury directly related to your participation in this project, Northside Hospital will provide the medical and ancillary services ordered by the doctors at the established charges for these services. Neither Northside Hospital nor Blood and Marrow Transplant Group of Georgia will provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. Northside Hospital and BMTGA will charge your insurance carrier, you, or any other party responsible for your treatment costs.

STATEMENT OF NON-WAIVER

By signing this consent form, you have not waived any of your legal rights or released any party from liability for negligence.

WILL MY RECORDS BE CONFIDENTIAL?

Efforts will be made to keep your personal information confidential. Absolute confidentiality cannot be guaranteed; however, confidentiality will be maintained to the extent permitted by local, state, and federal law.

Your personal health information will be used and disclosed to others for this research study. A

decision to participate in this study means that you agree to the use and disclosure of your personal health information for the purposes explained in this consent form.

During the course of this study the research team may use the following health information: Results of tests, exams or procedures conducted for this study, information in the research record, results of physical exams, blood tests, x-rays and other medical procedures, and other information in your medical record pertaining to your care.

The following individuals or entities will have access to your personal health information as necessary to conduct this research study:

- BMTGA clinical research team and clinical staff (involved in patient care)
- The Northside Hospital Blood and Marrow Transplant Program research and clinical staff (involved in patient care)
- Northside Hospital healthcare professional team (e.g., nurses or radiologists involved in patient care)

Your personal health information may also be disclosed to:

- The Food and Drug Administration (FDA), a group that regulates research
- Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMDP), groups that maintain Registry databases that include all patients who receive blood and marrow transplants
- The Northside Hospital Institutional Review Board (a board that oversees research done by the Blood and Marrow Transplant Program at Northside Hospital to ensure that the rights of human subjects are protected.)
- Millennium Pharmaceuticals, the company who is responsible for supplying the study drug, its collaborators and designees

There is the potential of further disclosure of your personal health information by these individuals or entities such that your information is no longer subject to protection under federal regulations governing the privacy of health information. Information connected to research and treatment offered may result in scientific presentations and publications, but precautions will be taken to make sure you cannot be identified in any way.

By signing this consent form, you authorize the use of your personal health information. This authorization has no expiration date. You have the right to revoke your authorization to use your

personal health information.

The revocation must be in writing and sent to the Director of the Central Research Office at Northside Hospital at 1000 Johnson Ferry Rd. NE, Atlanta, Georgia 30342. If you revoke your authorization it will not apply to prior uses or disclosures of your personal health information made in accordance with the purposes explained in this consent form.

If you refuse to provide authorization to use and disclose your personal health information for this study, the investigator may refuse to include you as a participant in this study.

If you are treated as part of a research study your right to access the health information used and disclosed for the study may be restricted during the course of the research study; however, your right to access will be reinstated, upon completion of the research study. You have the right to review the results of any testing done on you during the course of evaluation and treatment.

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.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate in this study. If you do participate, you may freely withdraw from the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. Your decision will not change your ability to receive medical care at Northside Hospital and BMTGA.

Your participation in this study may be stopped at any time by the study doctor without your consent due to:

- Unacceptable toxicity (side effects) from study treatment;
- Inability to follow study procedures as outlined in the protocol as described in this consent form;
- Unforeseen events which make continuing on treatment against medical judgment;
- Serious adverse event that requires you to end your study participation;
- The study is closed early for safety or efficacy (effectiveness) reasons;
- You withdraw your consent to participate;
- For any other reason that your physician feels is necessary.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?

If at any time you would like to ask questions about this research study, please call Dr. Lawrence Morris, Dr. Scott Solomon, Dr. Asad Bashey, Dr. Melhem Solh or Dr. Kent Holland at (404) 255-1930.

The Institutional Review Board at Northside Hospital has reviewed this study in the context of certain federal regulations relating to experimentation involving human subjects. Approval of this study by the Northside Hospital Institutional Review Board is not an endorsement of this study or its outcome. If you have any questions or concerns about this study or your rights as a research subject, you should contact the Chairman of the Northside Hospital Institutional Review Board at (404) 851-6848.

WHERE CAN I GET MORE INFORMATION?

There are many places to obtain additional information about cancer treatment and cancer research. Some suggested sources of information are detailed below:

You may call the National Cancer Institute's (NCI) Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

Visit the NCI's Web site at: http://www.nci.nih.gov/cancerinfo/

You will be given a signed copy of this consent form.

OPTIONAL RESEARCH SAMPLES

This study is collecting additional research samples to determine how the investigational drug, MLN9708, affects the recovery of your immune system following transplant. You are able to decline these research samples and still participate in this study.

_____ I AGREE to allow additional blood to be collected for research purposes only.

Initials

_____ I DO NOT AGREE to allow additional blood to be collected for research purposes only.

Initials

STATEMENT OF CONSENT

My signature on this informed consent form means that I understand the explanation and freely consent to participate. I will be given a signed copy of this consent form. I also certify that I have been allowed to ask questions and that I have received answers to these questions.

I understand that by consenting to participate in this study, I am responsible for carrying out instructions and that I must report to my doctors, nurses, or other personnel any information that might be pertinent to this study such as any side effects of the treatment. Any reluctance that I might have to continue must also be reported. I have been informed that any new information that might affect my willingness to continue my participation in this study will be told to me in an appropriate way. I further authorize the use and disclosure of my personal health information for the purposes described in this consent form.

Printed Name/Signature of Recipient or Legal Representative Date Time

Representative's Authority to Sign

Printed Name/Signature of Person Obtaining Consent Date Time

INVESTIGATOR STATEMENT

It has been explained to the person named above the nature of the treatment plan described above. To the best of my knowledge the person signing this consent form understands the nature, demands, benefits and risks involved in participating in this treatment plan.

Signature of Physician Date Time