INSTITUTE: National Cancer Institute

STUDY NUMBER: 07-C-0195 PRINCIPAL INVESTIGATOR: Steven Pavletic, M.D.

STUDY TITLE: Phase II Trial of Targeted Immune-Depleting Chemotherapy and Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation Using 8/8 and 7/8 HLA-matched Unrelated Donors and Utilizing Two Graft-versus-Host Disease Prophylaxis Regimens for the Treatment of Leukemias, Lymphomas, and Pre-malignant Blood Disorders

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Standard

INTRODUCTION

We are asking you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

We are conducting a study of allogeneic stem cell transplantation from HLA-matched unrelated, volunteer donors for cancers of the blood and immune system. Because you have one of the cancers with which we are concerned, and an HLA-matched unrelated donor has been identified, we are inviting you to participate in this pilot trial of Targeted Immune-Depleting Chemotherapy and Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation (abbreviated RIST).

The cancers with which are concerned include non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, acute lymphocytic leukemia, NK cell neoplasms, and T-cell neoplasms (e.g. adult T-cell leukemia lymphoma, hepatosplenic T-cell lymphoma and enteropathy associated T-cell lymphoma). It also includes pre-cancerous blood conditions including myelodysplasia, idiopathic myelofibrosis, polycythemia vera, and chronic myelomonocytic leukemia.

Why are you being asked to take part in this study?

This research study is for patients who do not have an HLA-matched sibling and who have had a potential HLA-matched unrelated donor identified through one of the bone marrow donor registries such as the National Marrow Donor Program. To be eligible to participate on this study you must match on 8/8 or 7/8 HLA markers with your potential unrelated donor to enroll in the study.

How many people will take part in this study?

Up to 210 people (105 patients/105 donors) will take part in this research study.

Description of Research Study

About 5 to 10 tablespoons of blood will be drawn to check how closely you and your donor are genetically matched. Often this blood test has already been performed at your home medical office prior to a visit to the NIH or it will be performed at the NIH Clinical Center. In this study, we will accept patients 18 to 69 years of age.

Rarely, a volunteer donor may become unavailable or the donor apheresis center is unable to collect enough stem cells to perform the transplant. If this happens, you will be removed from the study before transplantation unless we are able to identify another suitable unrelated donor. If you have already received the conditioning chemotherapy, you will still be removed from the study, but we will continue to care for you.

"Stem cells" are immature blood cells, like seeds; they grow in the bone marrow and produce all of the cells needed for normal blood and immunity. When these stem cells are taken from one person (called the "donor") and given to another person (called the "recipient"), it is known as "allogeneic" stem cell transplantation (SCT). Originally, stem cells were collected for transplantation by taking samples of bone marrow from the donor. This was commonly called "bone marrow transplantation." Now, most allogeneic transplants use stem cells collected from the donor's blood.

Allogeneic stem cell transplantation (SCT) has been used successfully to treat, and sometimes cure, many kinds of cancer or pre-cancerous conditions that develop in blood or immune system cells. Large doses of chemotherapy drugs and/or radiation have been traditionally used to eliminate most of the cancerous or abnormal cells from the recipient's system, along with most

of his or her own stem cells and immune cells. Donor stem cells can then replace the recipient's stem cells in the bone marrow, restoring normal blood production and immunity; this process is called "engraftment". In this way, an allogeneic SCT provides not only new blood cells but an entire new immune system. Immune cells from the donor are important not only to protect the transplant recipient from infections; these transplanted cells can sometimes eliminate the abnormal cells that caused the patient's disease. This type of immune attack is called the "graft-versus-tumor" (GVT) effect, and it is thought to be the main reason that allogeneic SCT cures some patients of these conditions.

If the recipient's immune system remains strong enough after large doses of chemotherapy or radiation, it may attack and destroy the donor's cells after the transplant. This is called "graft rejection." When this happens, the transplant recipient's own stem cells may be so severely damaged after chemotherapy or radiation that they cannot produce blood cells, usually leading to death. Another serious complication can occur if donor immune cells recognize and attack the recipient's normal tissues, damaging the liver, intestinal tract, and skin. This type of immune attack is called "graft-versus-host disease", or GVHD.

Graft rejection or GVHD after allogeneic SCT are less likely when the transplant recipient and donor are very similar genetically. To measure how genetically similar a recipient and donor are, both persons are tested to identify protein markers on the surface of their blood cells and other body tissues. These markers are called "human leukocyte antigens", or HLA. A person inherits half of his or her HLA markers from each parent. Your immune system uses HLA proteins on your body's cells to tell the difference between normal, healthy tissues and foreign organisms like bacteria or viruses. Differences in HLA proteins between a donor and recipient make it more likely that one person's immune system will recognize the other person's cells as foreign, causing graft rejection or GVHD. A donor and recipient who share all 8 of their HLA markers are called "HLA-identical". A transplant from an HLA-identical sibling (brother or sister) has a lower chance of graft rejection or GVHD, compared with other donors for allogeneic SCT. Many people have cancers that could be treated with allogeneic SCT, but only 20-30% of people have HLA-identical sibling donors. For some people without HLA-identical sibling donors, an HLA-matched unrelated donor can be used, but the risk of graft rejection and GVHD is higher. Patients on this study with a partial genetic match (7/8 HLA genes) with their unrelated donor may have a modestly higher risk of complications compared to subjects with a full genetic match with their unrelated donor (8/8 HLA genes).

Severe GVHD is the leading cause of death in patients who receive an allogeneic SCT. Drugs can prevent GVHD after allogeneic SCT, but they do not work all the time.

We are trying to improve the results of allogeneic SCT from HLA-matched unrelated donors. The methods we are testing in this research study include:

- Immune-depleting chemotherapy (also known as chemotherapy that lowers your immune system) will be given to you to try to stabilize the cancer before your transplant, and to

lower the chance of graft rejection. Then you will receive reduced-intensity transplant chemotherapy (also called "conditioning regimen") this will help make the SCT less harmful for transplant recipients. All patients on this study will receive chemotherapy to weaken your immune system that matches the type of disease you have prior to the transplant.

- This study will use two different combinations of drugs to prevent GVHD. Both of these drug combinations have been successful in preventing GVHD, but they work in different ways and affect the rebuilding of the immune system after the transplant. The purpose of this study is to study differences in how the immune system is rebuilt after these two different combinations of drugs. The specific combination of drugs that you will receive to prevent GVHD is determined randomly (similar to flipping a coin) at the time you agree to participate in this study.

Each of these methods will be explained in the following pages.

Immune-Depleting Chemotherapy and Reduced-Intensity Allogeneic Stem Cell Transplantation (RIST)

In the past, allogeneic SCT was performed with very high doses of chemotherapy and/or radiation. This thorough treatment was used to get rid of as much of the recipient's cancer as possible, and it also helped to prevent graft rejection by weakening the recipient's immune system. However, such intensive chemotherapy or radiation can cause serious side effects, including death. Because of these risks, only relatively young and healthy patients were considered for this form of treatment. A newer method uses smaller, less toxic doses of chemotherapy and/or radiation before allogeneic SCT. This method is often called "reduced-intensity", or "nonmyeloablative". It was first studied in patients who could not receive high-intensity ("myeloablative") allogeneic SCT because of their age or other medical conditions. In reduced-intensity stem cell transplants (also called RIST), the recipient's stem cells and immunity are not completely eliminated, but they are weakened enough to prevent the donor's cells from being rejected. In most studies of RIST, serious complications are less common than for myeloablative allogeneic SCT. However, GVHD can still be a significant side effect with RIST. Also, graft rejection and relapses of cancer have happened more often in some studies of RIST than with myeloablative transplants. These problems may have occurred because the lower doses of treatment in RIST can leave the recipient's immune system strong enough to resist being replaced completely by the donor's cells, and more cancer cells may survive after reduced-intensity chemotherapy or radiation than after myeloablative treatment. As part of this research study you will receive a reduced-intensity allogeneic stem cell transplant (RIST).

We have been studying RIST to try to improve the results of allogeneic SCT for patients with hematologic (blood-related) cancers and pre-cancerous conditions. In previous studies, we gave patients 1 to 3 cycles of "induction chemotherapy" before transplantation. This induction chemotherapy was designed to stabilize their cancer and slowly weaken their immune system to

help prevent graft rejection. Patients then received reduced-intensity transplant chemotherapy, followed by transplantation from an HLA-matched sibling. With this approach, we were able to perform RIST without any patients having graft rejection. Nearly all recipients treated in this manner had total replacement of their own stem cells and immune system by the donor's cells (called "full donor chimerism") within 4 weeks after transplantation.

This research study will use induction chemotherapy that will weaken your immune system that is similar to what we have used in our earlier studies. The type of induction chemotherapy you will receive is based on what type of disease you have. We believe that this chemotherapy will decrease the chance of graft rejection after RIST from a HLA-matched unrelated donor. If the study doctors feel your immune system is already weakened and your disease is well controlled you will not receive "induction chemotherapy". This study will also use reduced-intensity transplant chemotherapy to try to decrease the side effects of the transplant. The reduced-intensity transplant chemotherapy we will use in this study is the same as in our previous studies, and will be described in more detail in the following sections. All patients in this study will receive the same type of transplant chemotherapy.

Prevention of Graft-Versus-Host Disease

A clearly superior treatment to prevent GVHD has not been established in patients who have received SCT from HLA-matched unrelated donors. The best results that have been reported in the available medical literature are with the combination of a drugs called alemtuzumab plus cyclosporine [also called: AC], and the combination of drugs called tacrolimus, methotrexate, and sirolimus [also called: TMS]. These two drug combinations work in very different ways, and potentially have very different effects upon how the immune system rebuilds itself after transplant. This has not been well studied after either of these drug combinations. It is our intent to study the effects that these two drug combinations have on the immune system as it rebuilds itself after receiving immune-depleting chemotherapy and reduced-intensity allogeneic SCT from HLA-matched unrelated donors. This study is considered experimental. It is hoped that experimental studies like this one will lead to a better understanding of the biologies associated with this form of transplantation and allow doctors and scientists to develop new strategies and treatments to improve results after transplant.

What will happen if you take part in this research study?

The following will be done as part of this research study (details are included in later sections):

- First, we must establish proof of a full genetic match (8/8 HLA genes) or partial genetic match (7/8 HLA genes) between you and your potential unrelated donor.
- We will arrange to have your donor's stem cells collected at a center in cooperation with the National Marrow Donor Program.

- You will receive one, two, or three cycles of "induction chemotherapy" (based on the type of disease you have; described below) to treat your disease and to weaken your immune system. If the study doctors feel your immune system is already weakened and your disease is well controlled you will not receive "induction chemotherapy".
- After you have finished receiving induction chemotherapy, you will receive 4 days of reduced-intensity transplant chemotherapy, also called the "conditioning regimen," to prepare you for the transplant.
- Two days after this transplant chemotherapy, you will receive the transplant with your unrelated donor's stem cells and immune cells.
- Before and after the transplant you will receive one of two possible combinations of drugs (AC or TMS) to prevent GVHD. The regimen you receive is randomly decided ("flip of a coin") at the time you agree to participate on the study.
- You will be hospitalized approximately 3-4 weeks after your transplant.
- When the study doctors think your condition is stable, you will be discharged from the hospital and be seen frequently at the NIH as an outpatient.
- You will continue on medications at home to lower the risk of GVHD and infections.
- You may receive additional cells from the donor, also called a "donor lymphocyte infusion" or DLI, after the transplant, these additional cells are given to help to rebuild or enhance your immune system.
- You will visit our clinic regularly for the first six months after the transplant, and then less often for at least five years.

Pre-Transplant Evaluation

Once it is determined that you have a potential donor, you will be seen at the NIH Clinical Center, at which time you will have a complete medical history and physical examination in the NCI Medical Oncology Clinic. Members of the transplant team will review your medical history and explain the transplant procedure. A blood sample will also be used to check the health of your kidneys and liver. We will also test for exposure to a variety of infections, including hepatitis B and C, syphilis, and a virus called cytomegalovirus (CMV). As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of your HIV infection. You will also be tested for the following viruses: hepatitis A, HTLV-1 and -2, adenovirus, Epstein-Barr virus, herpes simplex virus, and the parasite Toxoplasma. A total of approximately 4-12 teaspoons of blood will be collected. If the study doctor feels it is necessary, you will have a PPD skin test (to test for tuberculosis). You will be asked to collect your urine for 24 hours to measure your kidney function. If you are a woman, you will have a urine test for pregnancy. If you are a woman who is breast-feeding or pregnant, you may not take part in this study because we don't know how the transplant will affect your baby or unborn

child. If you think that you or your partner is pregnant, you should tell your study doctor or nurse immediately.

In addition, you will have a special breathing test, a test for heart health, and several X-ray studies, including a CT scan of your chest, abdomen, pelvis, and possibly your neck. You will have a CT scan or MRI of your head. If you have lymphoma, we will obtain a test called a positron emission tomography (PET) scan. You may also have a bone marrow aspiration and biopsy. This test is performed by numbing the iliac (hip) bone with a local numbing medicine called lidocaine. A small cut will be made in the skin, a needle is inserted into the hip bone, and about two tablespoons of liquid samples are removed from the bone marrow through the needle. A small fragment of the bone marrow may also be removed with the needle. If you are at risk of having your cancer involve the brain or central nervous system, you may also have a spinal tap (also known as a lumbar puncture). This test is performed by numbing an area over the lower portion (lumbar) of your spine with a numbing medicine called lidocaine. A thin needle is then inserted into your spinal canal and a small amount (about 5 tablespoons) of spinal fluid is removed. You will also be seen by a dentist, and meet with a social worker. You will be encouraged to name someone as your "durable power of attorney". This should be someone whom you trust to make medical decisions for you if you become physically or mentally unable to make your own treatment decisions. You should know that being in this study may keep you from being in other research studies that limit the number or types of treatments that you are allowed to have received previously.

The Central Venous Catheter

If you do not already have one before you enroll in this study, you will receive an intravenous (I.V.) line placed in the upper part of your chest and tunneled under the skin into a neck vein. This line is called a central venous catheter that can be used throughout your transplant procedure and follow-up treatment. This kind of catheter is sometimes called a "Hickman catheter". If the catheter becomes infected or clogged, it can be replaced. It will be flushed once daily to prevent clogging. The nursing staff will teach you how to do this yourself.

The catheter will be used to give you chemotherapy, your transplant, DLI (if needed), blood transfusions (if needed), and other medications such as antibiotics. It can also be used for drawing blood samples for tests. Since blood will be drawn often during your treatment, the catheter will make it easier and less painful.

Induction Chemotherapy

In this study you will receive one, two, or three cycles of "induction chemotherapy" to treat your disease and to weaken your immune system. For patients with chronic lymphocytic leukemia, prolymphocytic leukemia, multiple myeloma, and most forms of lymphoma, this chemotherapy will include the following drugs: fludarabine, cyclophosphamide, etoposide, doxorubicin,

vincristine, and prednisone (also called: "EPOCH-F"). Patients with lymphoblastic lymphoma, acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and other "pre-leukemic" diseases will receive induction chemotherapy with fludarabine, cytarabine, and filgrastim (also called: "FLAG"). Patients with certain forms of lymphoma and leukemia may also receive a drug called rituximab. Each of these medications have been approved by the Food and Drug Administration (FDA). The study doctors will test a biopsy specimen from your cancer to help them decide if you should receive rituximab with your induction chemotherapy. To start, you will receive common doses of these drugs for five days followed by a 16-day (EPOCH-F) or 23-day (FLAG) rest period (this time period is 1 cycle). The EPOCH-F regimen is generally given in outpatient setting. The FLAG regimen is given in the hospital, so you will be admitted as an inpatient, and you will remain in the hospital until your blood counts recover, usually 3 to 4 weeks. The effect of the chemotherapy on your immune system and on your disease will determine how many cycles of induction chemotherapy you receive. If blood tests show that your immune system is weakened enough after one cycle, you will go directly to the transplant. If your immune system is not very weakened and your disease is not growing after one cycle of induction chemotherapy, you will receive one or two more cycles (5 days of the same chemotherapy you received for cycle 1, followed by 16 (EPOCH-F) or 23 (FLAG) days of rest per cycle). If your disease grows in spite of the induction chemotherapy then the induction chemotherapy will be stopped, and you will be removed from the study. If your white blood cell count remains low for a long time after induction chemotherapy, meaning your immune system has weakened, you will go directly to the transplant. At most, you will receive 3 cycles of chemotherapy.

Transplantation of the Blood Stem Cells From Your Donor

Before you begin your induction chemotherapy, your unrelated donor will have had a medical examination by a doctor in the National Marrow Donor Program (NMDP) network that includes extensive testing to make sure they do not have any of the following: HIV, Hepatitis B, Hepatitis C, and possible infectious diseases that may be transmitted by stem cell donation. The donor's exam will also ensure that they remain available and are physically well enough to undergo the donation procedure. The NMDP will notify NIH if there are any abnormalities that increase the risk of transmitting infectious diseases to you during the transplant. These findings will be discussed with you. The donor's medical clearance will be verified by the NIH study doctor before you receive any chemotherapy.

The stem cells from your donor will be given to you within 48 hours from the time of their donation. This means that your conditioning chemotherapy will begin prior to the donor's cells being collected. The donor will receive daily injections of a medication that stimulates the stem cells to be released from the bone marrow and into the bloodstream. One or two days before your transplant, the donor will have these cells removed through a process called apheresis. The donor will have blood removed through an intravenous catheter and circulated through a machine which separates the peripheral blood stem cells. These cells are removed, and the rest

of the blood is returned through the catheter. This collection occurs at the NMDP apheresis center closest to the donor. The cells are hand-carried by a trained courier to NIH. Once they arrive at NIH, the cells will be infused through your catheter within 24 hours. In rare cases, the stem cells may be frozen before they are given to you.

Unrelated donor transplants are confidential and the identity of the donor will be anonymous. This means that you will not know who your donor is or where they are. You will know the age and gender of the donor and any history or medical exam findings that could possibly change the risk of your transplant. Likewise, the donor will not know who you are or where you are. He/she will know your age, gender, and the type of disease that you have. The donor will be given basic updates about your condition 30 days, 6 months, and 1 year after your transplant. The only information they will receive is whether or not the stem cells "engrafted" (taken hold), and if you have been discharged from the hospital. The donor will also be notified in the event of your death.

Depending on the policy of the particular donor center, you may be able to communicate without revealing your identities in an anonymous manner with your donor beginning at the time of your transplant. In some cases, if both you and the donor agree, you may be able to learn who your donor is after one year. There are some cases when a donor and patient may never communicate or meet. Your transplant coordinator will tell you the details of if and how you may contact the donor once the donor has completed his or her medical exam.

Transplant Procedures

You will be admitted into the hospital approximately seven days before transplantation to the NCI's Experimental Transplantation Unit at the NIH Clinical Center. You will receive 4 days of transplant chemotherapy called the "conditioning regimen," which will permit you to accept your donor's stem cells. This regimen uses fludarabine and cyclophosphamide at higher doses than were given as part of induction chemotherapy. Two days after completing this chemotherapy, you will receive the stem cell transplant. Your donor's stem cells will be infused through your central venous catheter. This is referred to as "day 0".

While you are in the hospital for your transplant, you will be monitored very closely for possible complications, which are described below. You will receive drugs to help prevent and/or treat infection, growth factors (G-CSF), blood transfusions, and intravenous nutrition (if needed). Blood will be drawn frequently during your treatment. Your blood will be tested to monitor your health during and after the chemotherapy and transplant procedure. In general, 4 to 10 teaspoons of blood will be drawn an average of 2 to 3 times per week. Some blood will be drawn for research purposes. In general, 3 to 4 tablespoons of blood will be drawn for research on average of once per week for the first 100 days after transplant.

The average time you will stay in the hospital is three to four weeks after transplant, but it could be longer if there any complications.

You will receive one of two combinations of drugs to prevent GVHD before and after your transplant. The combination of drugs that you will receive is randomly assigned at the time of enrollment onto the study.

One of the possible combinations of drugs to help prevent GVHD that you may receive contains drugs called: tacrolimus, methotrexate, and sirolimus. Beginning three days before you receive the stem cell transplant, you will receive the drugs tacrolimus and sirolimus to help prevent GVHD. Sirolimus is given by mouth once a day for approximately six months after transplant. Tacrolimus is given either through an I.V. or by mouth once a day for approximately six months after transplant. Methotrexate is given for four doses intravenously (through the vein) before you are discharged from the hospital, shortly after the transplant.

The other possible combination of drugs to prevent GVHD that you may receive contains alemtuzumab and cyclosporine. Alemtuzumab is started eight days before your stem cell transplant and is given for five daily doses through an I.V. Cyclosporine is given through an I.V. the day before the transplant. Cyclosporine is given either through an I.V. or by mouth every day for approximately six months after transplant.

Once the stem cells have taken hold and you are strong enough, you will be discharged from the hospital and followed closely as an outpatient. You will be required to remain in the Washington, D.C. area for approximately three months after transplantation so the NIH doctors can monitor you in case of any complications. You may require re-admission to the hospital for complications. You will be followed by the doctors in the NCI clinic for the first six months after transplant, and then you will be followed less frequently for at least five years.

After the transplant, if tests show that your blood and immune cells have not fully converted to your donor's type ("mixed chimerism"), then the drugs you are taking to prevent GVHD (depending on which arm that you are assigned to), will be lowered to help change your blood and immunity to full donor chimerism. Sometimes a donor lymphocyte infusion (DLI) may be given to you intravenously (I.V.) to reach a state of full donor chimerism, as described above. If your cancer is still present or grows after the transplant, cyclosporine or tacrolimus may be reduced in an attempt to permit a stronger graft-versus-tumor effect. After this, if there are no signs of significant GVHD, then you may receive one or more DLI at increasing doses. These DLI are intended to "boost" your new immune system and can enhance the graft-versus-tumor effect in some, but not all, patients. DLI can sometimes lead to the development of GVHD, so we will monitor you very closely for signs of GVHD after these infusions. If you experience significant GVHD after a DLI, we will give you treatment for GVHD, but you will not receive any further DLI. You may also be eligible to receive chemotherapy or other standard therapy

(like radiation therapy or immune therapies) after the transplant if your cancer requires further treatment. This therapy can be given alone or combined with DLI.

If we are required to stop this study because too many patients have serious side effects, we will continue to provide care for you according to the study protocol.

The skin and mouth are the two organs most commonly affected by chronic GVHD. In order to better understand chronic GVHD, the following tests will be performed.

- Punch Skin Biopsy: This is performed so that a piece of skin may be examined under the microscope to get a closer look at what is going on in your skin and for diagnostic purposes. After cleaning the skin with alcohol and/or another antiseptic, a local numbing medicine (Lidocaine with or without epinephrine)--similar to what a dentist injects to numb your gums--is injected into the planned biopsy site. A sharp instrument which looks like a miniature cookie-cutter is used to remove a round plug of skin about the size of a pencil eraser. The biopsy site may be left open or may be closed by putting in one or two stitches, and a small dressing is applied. Sometimes more than one such skin sample may be needed. You will be expected to keep the dressing over the biopsy site dry for 1 to 2 days. Thereafter, the dressing may be changed daily until the suture(s) are ready to come out, usually in 7 days. Depending on circumstances, the suture(s) may be removed by one of us, by your own doctor and/or your doctor's assistant.
- Oral mucosa biopsy: The procedure is done in a similar manner as a skin biopsy, except that a dressing cannot be applied, because it is not possible to keep the area dry enough to keep the dressing on.
- Collection of saliva (natural mouth fluid). We will collect saliva from you after swabbing your tongue with a solution that tastes like lemon juice. We will collect the saliva that pools in your mouth, the saliva that collects under your tongue, and the saliva that comes into the mouth next to your upper back teeth. The techniques we use are non-invasive, and investigators at NIH have been collecting saliva with these methods for more than 20 years. This is a simple procedure that does not have any risks or discomforts. We will use saliva samples to study in our laboratory factors that may be associated with the development of GVHD including the types of bacteria that live in the mouth. We believe these studies will help us understand more about oral GVHD and lead to better treatments for this painful condition.

These tests will be performed on in all patients at the time of start of decrease of medicines that suppress your immune system, prior to the time a clinical diagnosis of chronic GVHD is made. If you do not develop GVHD, these tests will be performed for the second time at 6 months post transplant. It is important for you to know that both the skin and mouth biopsies are being performed for research purposes to help us with our understanding of chronic GVHD. They would not routinely be performed unless they were needed to confirm the presence of chronic GVHD.

Frequent Follow-up at the NCI in the First Year after Transplant

If you are in good health after the three month period after your transplant, you will then be allowed to return home to the care of your primary physician. You will be required to return to the NIH monthly until approximately six months after transplantation so you can be monitored for late transplant complications including GVHD and infection. Thereafter you will be seen at NIH at 9, 12, 18 and 24 months after your transplant and then every year following your transplant, unless an earlier visit is required, per the study doctors. After 5 years after the transplant, you will no longer be asked to return to NIH. We will still contact you by phone annually. At each visit when you return to NIH, you will have a physical exam and blood draws (approximately 4-10 teaspoons of blood will be taken). During some visits you may have a bone marrow aspirate and biopsies, and other appropriate tests (for example: CT, MRI, PET scan) to monitor disease status. Study-related medications will be provided by the NIH during your hospital stay and after you leave the NIH.

Risks or Discomforts of Participation

Risk of Death from Allogeneic SCT: Patients undergoing allogeneic SCT are at risk of dying from the transplant procedure and its possible complications. In some studies of allogeneic SCT, as many as half of the patients have died as a direct result of the transplant or its complications. In transplant studies similar to this one, up to 50 percent of patients have died from the transplant procedure. The risk of death or other complications can vary greatly, depending on the age of the patient, the way the transplant is performed, and other factors.

Other risks from allogeneic SCT include:

Veno-Occlusive Disease (VOD) - A severe liver complication known as VOD occurs in less than 5 percent of allogeneic transplants. VOD is a chemotherapy side effect that causes blood vessels in the liver to be blocked. Severe VOD can lead to liver failure and death.

Graft Rejection: There is a chance that you may reject your donor's stem cells. If that were to happen, you would most likely recover your own blood cells. However, there is the rare possibility that your own cells may not recover. This may result in prolonged low blood counts, which may result in infection or bleeding and may lead to death. In this event, we would attempt to support you with transfusions, growth factors and antibiotics until your own blood counts recover. A blood test will be performed at 14, 28, 42, 70 and 98 days after your transplant to find out if your body has accepted the donor cells. If no donor cells can be found, then we will conclude that you rejected them. In that case, your blood counts will probably return to the same levels as before the transplant in about 2 to 3 weeks. You will receive the growth factor filgrastim to help the cells engraft. In the event that your cells do not engraft, we may ask your donor to donate more cells.

Graft-Versus-Host Disease (GVHD): You will be at risk for the development of GVHD for the rest of your life after transplantation. GVHD occurring within the first 100 days after transplantation is referred to as acute GVHD. Acute GVHD most commonly attacks the liver, intestines, and skin. Symptoms of skin GVHD may be as mild as a rash with itching, or as severe as blistering and loss of the skin. Symptoms of intestinal GVHD may be as mild as heartburn and mild diarrhea, or as severe as cramping abdominal pain and bloody diarrhea. Liver GVHD may be as mild as slight disturbances in liver function, or severe as jaundice (yellowing of the skin) with liver failure. Mild GVHD (skin rash only) can be treated with steroid creams that you apply on your skin. Severe GVHD can be very dangerous and needs to be treated aggressively. Treatment of severe GVHD initially includes weakening of the immune system, usually with intravenous (I.V.) steroids. Weakening of the immune system increases the risk of infection.

A delayed form of GVHD, known as chronic GVHD, may occur after day 100 post-transplant. Some degree of chronic GVHD affects about half of patients after transplantation. It most commonly attacks the skin, the liver and the intestines, but it may also affect other organs such as the lungs, eyes, muscles, joints, and the bone marrow. Symptoms of chronic GVHD may include dryness of the mouth and eyes, a loss of appetite, weakness, hair loss, weight loss, liver damage (including yellowing of the skin), and lung damage leading to shortness of breath and cough. Patients with severe chronic GVHD are also at increased risk of infection and death. Chronic GVHD is also treated with drugs that weaken the immune system such as steroids. Taking steroids may increase your risk of infection.

Late Transplant Complications: There are other potential complications that can occur long after transplantation. These complications could affect any organ in the body including the heart, lungs, kidneys, liver, muscles, and brain. Rarely, patients who receive an allogeneic SCT are at risk for developing a second cancer such as leukemia or lung cancer.

Other complications are also possible following your transplant. The most common complication is infections. Because you will be receiving drugs (e.g. cyclosporine) that weaken the immune system, you are at greater risk to develop infections from uncommon organisms. These infections can be life-threatening, and could cause death.

There is about a 40 percent chance of death from complications of conventional allogeneic bone marrow transplants. Although we will use new/unconventional ways to try to reduce these odds, it is possible that our approach may not work or that it may even increase the chances of death. There is also the risk of complications that cannot be predicted.

Bone Marrow Aspiration and Biopsy: This procedure usually causes only mild pain for a short time at the biopsy site. Very rarely, bleeding or an infection may occur at the biopsy site.

Blood Draws: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness and rarely, fainting. When a large amount of blood is drawn, your red blood cell count may drop causing anemia. Anemia can cause a lack of energy and other symptoms. Transfusions of red blood cells are sometimes needed to treat anemia.

Central Venous Catheter: Side effects of placing a central venous line in your chest wall include bleeding, bruising, blood clot, or pain in the area of insertion. This line will be placed by physicians with experience in this procedure. These physicians will discuss the above risks at the time of the line insertion. Rarely, placement of a central venous catheter can result in a collapsed lung. If a collapsed lung occurs, it may require hospitalization and temporary insertion of a plastic tube in your chest to re-expand the lung.

Skin Punch Biopsies: Whenever possible, we will perform biopsies on covered areas of the body. There may be minor bleeding right after the procedure and this can easily be controlled by applying pressure on the spot for a few minutes.
Rarely, a bruise might form and this eventually goes away on its own. Sometimes a small infection may occur at the biopsy site. This can usually be treated with topical antibiotics. On the very rare occasion that a larger or deeper infection occurs, oral antibiotics may be needed for 7-10 days. An infection can be recognized by redness, soreness, and pus at the site. It generally starts 2 days or more after the procedure and does not clear up in another couple of days. These biopsy/excision sites generally heal very well, leaving red, white, dark or skin-colored flat scars. Sometimes, the scar that forms may be a bit thicker than usual. Rarely, a keloid (large, painful or itchy scar) may form. Keloids are more likely to form on the chin, earlobes, chest and upper backs of Blacks and Asians between adolescence and the 30's.

Oral mucosa biopsy: There may be minor bleeding, bruising, numbness and slight swelling. There is also the possibility of infection. Mouth sores have occurred in some patients, but this is uncommon.

Induction Chemotherapy: As described previously, the type of induction chemotherapy you will receive depends on the type of disease you have. Some patients will receive fludarabine, cyclophosphamide, etoposide, doxorubicin, vincristine, and prednisone (called: EPOCH-F), while others will receive fludarabine, cytarabine, and filgrastim (called: FLAG). In addition, some patients will receive rituximab, as discussed before. It is important for you to know that this type of induction chemotherapy is likely to reduce your white blood cells for many days. This will place you at increased risk of infection. Such infections can be very serious and may result in death. For this reason, if you develop a fever higher than 101° F, you must see your doctor immediately. If necessary, you will be treated with antibiotics. Also, this chemotherapy will likely cause your platelet count to fall. This may place you at increased risk of bleeding. If your platelet count becomes dangerously low, you will receive platelet transfusions. The chemotherapy may also cause you to develop a low red blood cell count, called anemia. Anemia can cause a lack of energy and other symptoms. Transfusions of red blood cells are sometimes

needed to treat anemia. Because the induction chemotherapy on this protocol is a new combination of drugs, there is a chance that unexpected toxic effects will occur. The following are known specific risks of each drug used within the specific regimen that you will receive:

EPOCH-F (with or without rituximab):

Etoposide:

Likely:	Less Likely:	Rare:
• low blood counts, • hair loss	• nausea and vomiting, • diarrhea, • mouth sores	• low blood pressure, • shortness of breath, • secondary leukemia (a different type of cancer)

Prednisone:

Likely:	Less Likely:	Rare:
• weight gain, • sodium and water retention, • mood changes, • elevated blood sugar, • increased risk of infection	• stomach or bowel ulcers, • high blood pressure, • diabetes, • thinning of bones with greater risk of fracture (long term use); • puffing of the face (long term use); • acne, • thinning of skin, • muscle wasting	• none

Vincristine (a.k.a **O**ncovin®):

Likely:	Less Likely:	Rare:
• nerve damage resulting in a feeling of "pins and needles" in hands and feet; • constipation, • hair loss	• nerve damage leading to pain or weakness in hands or feet; • loss of reflexes (foot drop), • low blood counts, • hoarseness and pain in the jaw	• paralytic ileus (bowel function completely stops), • water retention

Doxorubicin (which contains a chemical **H**ydroxyl group):

Likely:	Less Likely:	Rare:
• low blood counts, • hair loss	• nausea and vomiting, • diarrhea, • mouth sores	• heart damage, • secondary leukemia (a different type of cancer), • tissue damage if the drug leaks from the vein into surrounding tissue, • bleeding bowel or stomach

Cyclophosphamide:

Likely:	Less Likely:	Rare:
• low blood counts, • hair loss	• nausea and vomiting, • painful and bloody urination, • sterility, • water retention	• heart damage, • secondary leukemia (a different type of cancer), • skin rash

Mesna is a drug given with cyclophosphamide to prevent bladder injury, and side effects may include: nausea, vomiting, and diarrhea.

Fludarabine:

Likely:	Less Likely:	Rare:
• low blood counts, • lowered level of immune cells, • increased risk of infection	• nausea and vomiting • diarrhea, • fever, • mouth sores, • loss of appetite, • swelling (edema), • skin rash, • muscle aches, • headache, • agitation. • hearing loss, • fatigue, • weakness, • numbness / tingling ("pins and needles")	• GI bleeding, • lung damage, • kidney damage, • severe neurologic (brain and/or spinal cord) toxicity has occurred after very high doses including: blindness, deterioration of mental status, and death.

Rituximab:

Likely:	Less Likely:	Rare:
• mild infusion reactions (fever, chills)	• severe infusion / hypersensitivity reactions (e.g. lowering of blood pressure, shortness of breath or difficulty breathing)	• tumor lysis syndrome (metabolic complications), • severe skin reaction/rash, • kidney failure, • death, • chest pain, • cardiac arrhythmias (heart beating irregularly)

FLAG:

FLudarabine:

Likely:	Less Likely:	Rare:
• low blood counts, • lowered level of immune cells, • increased risk of infection	• nausea and vomiting • diarrhea, • fever, • mouth sores, • loss of appetite, • swelling (edema), • skin rash, • muscle aches, • headache, • agitation. • hearing loss, • fatigue, • weakness, • numbness / tingling ("pins and needles")	• GI bleeding, • lung damage, • kidney damage, • severe neurologic (brain and/or spinal cord) toxicity has occurred after very high doses including: blindness, deterioration of mental status, and death.

Cytarabine (**A**ra-C):

Likely:	Less Likely:	Rare:
• low blood counts, • lowered level of immune cells, • nausea and vomiting, • mouth sores, • hair loss	• diarrhea, • loss of appetite, • flu-like symptoms • fevers, • liver damage • eye irritation	• loss of coordination or balance • sleepiness • speech difficulties • coma

Filgrastim (**G**-CSF):

Likely:	Less Likely:	Rare:
• bone pain, • reversible lab abnormalities	• headache, • pain at the needle site, • fevers, • tiredness	• G-CSF can cause rupture of the spleen, which can cause death

Transplantation Chemotherapy: The main side effect of fludarabine and cyclophosphamide at these doses is severe bone marrow and immune system weakening, which decreases the production of red blood cells, white blood cells, and platelets. The doses that will be used could cause longer than normal bone marrow weakening, if the transplanted stem cells were rejected. Until the transplanted stem cells start to produce adequate numbers of blood cells, you will be at significant risk for infections, bleeding and severe fatigue. These conditions will be treated with antibiotics and transfusions. Other potential side effects of fludarabine and cyclophosphamide are described above.

Graft-versus-Host Disease Prevention: As described above, you will receive one of two combinations of drugs to prevent GVHD; the combination of drugs that you will receive is randomly assigned at the time of enrollment onto the study. One of the possible combinations of drugs to help prevent GVHD that you may receive contains tacrolimus, methotrexate, and sirolimus. The other possible combination of drugs to prevent GVHD that you may receive contains alemtuzumab and cyclosporine.

Tacrolimus, Methotrexate, and Sirolimus:

Tacrolimus:

Likely:	Less Likely:	Rare:
• decrease in kidney function • headache • tremors* • high blood pressure • increased infection	• gum inflammation, • seizures*, • high blood potassium levels, • nausea • diarrhea or constipation • loss of appetite • abdominal pain • insomnia • high blood sugar • increase in blood lipid levels, • lowering of body magnesium levels requiring supplementation • liver damage • numbness or tingling in hands or feet	• coma • delirium
*Because of the risk of seizures and decreased reflexes while taking this medicine, you should not drive a car while taking tacrolimus.		

Methotrexate:

Likely:	Less Likely:	Rare:
• delay in the return of blood cells after transplant	• mouth sores • minor liver damage	• nausea • vomiting • diarrhea

Sirolimus:

Likely:	Less Likely:	Rare:
• your infection risk is likely increased. Because sirolimus as an immune suppression drug, it is likely the risk for some infections may be increased.	• diarrhea • nausea • damage to the liver • low blood counts • very high levels of fats (triglycerides) • increased cholesterol (increased lipid blood levels) • mouth ulcers • headache • increased risk of infection • red blood cell lysis with associated reduced kidney function	• severe swelling of the pancreas • secondary cancers (a different type of cancer)

Alemtuzumab and Cyclosporine:
Alemtuzumab:

Likely:	Less Likely:	Rare:
• fever • chills • rigors • nausea • vomiting • low blood counts • lowered level of immune cells, • increased risk of infection	• low blood pressure • rash • hives or wheals • itching • shortness of breath • cough • headache • diarrhea	• fainting • heart arrhythmias • heart attack • heart or lung failure

Cyclosporine:

Likely:	Less Likely:	Rare:
• decrease in kidney function • high blood pressure • increased facial hair • lowering of body magnesium levels requiring supplementation • increased risk of infection	• tremor • gum hyperplasia • seizures* • liver damage • flushing or lowering blood pressure with intravenous administration • depression	• coma
*Because of the risk of seizures while taking this medicine, you should not drive a car while taking cyclosporine.		

Stem Cell Infusion: The donor cells may be frozen with a chemical called DMSO to protect them from the effects of freezing. Patients receiving thawed cells often develop side effects from the DMSO. DMSO side effects may include fever and allergic reactions, such as skin rash, itching, difficulty breathing, and low blood pressure. These reactions are usually mild and temporary, and they can be easily treated with IV fluids and medications.

Other Medications: You will routinely receive several other drugs to prevent or treat various infections and other transplant-related complications. These medications and their common side effects are listed as follows:

Ursodeoxycholic acid: Ursodeoxycholic acid, also known as ursodiol, can cause nausea, vomiting, "heartburn", a metallic taste, abdominal pain, an inflamed gallbladder, constipation, mouth pain, flatulence, diarrhea, itching, rash, dry skin, hives, headache, fatigue, anxiety,

depression, and sleep disorders. Less common side effects include sweating, thinning of hair, back pain, muscle and joint pains, runny noses, and cough.

Diphenhydramine may cause tiredness, dizziness, upset stomach, disturbed coordination, dry mouth, flushing, or difficulty urinating.

Valacyclovir can cause nausea, vomiting, headache, dizziness, abdominal pain, bone pain, allergic reactions, mild liver inflammation, kidney injury, and abnormal nervous system function.

Fluconazole can cause nausea, vomiting, headache, skin rash, abdominal pain, and diarrhea. Rare but sometimes serious liver toxicity has also been reported. Fluconazole can increase the blood levels of other drugs, which can increase their effectiveness and/or their side effects.

Trimethoprim/sulfamethoxazole (Bactrim) may cause nausea, vomiting, loss of appetite, allergic skin rashes, and suppression of bone marrow function. Rare but severe reactions may affect the skin and bone marrow; these have sometimes been fatal.

Additional Therapies: Treatments covered under this protocol which are standard therapies given for disease control may include a single medication or a combination of medications, surgery or radiation. The treatment to be used will be determined by your NIH doctors based on your diagnosis, the type and extent of your illness, your prior treatments, and your ability to tolerate additional treatment. These treatments will not be experimental. Your doctors will describe their treatment plan to you in detail including the name of the treatment(s), the schedule, the possible harmful effects, the potential benefit, and possible alternatives to you before having you sign this consent form. If surgery or radiation therapy are required to treat your illness, you may be asked to sign a separate consent form by the surgeon or radiation therapist.

Reproductive Risks: This treatment is likely to result in sterility (the inability to produce children). However, we cannot predict for certain that you will become sterile during this treatment. It is unknown what effects the chemotherapy and other drugs included in this treatment may have on an unborn child, but they would most likely be harmful. For this reason, if you have not been placed on a contraceptive (birth control) as part of this study, you will need to use an effective form of contraception while on this study, and for one year after transplant (examples include: intrauterine device (IUD), hormonal (birth control pills, injections, or implants), tubal ligation/hysterectomy (self or partner), partner's vasectomy, barrier methods (condom, diaphragm, or cervical cap), or abstinence.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the

information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Potential Benefits of Participation

The chemotherapy you receive may cause improvement in your cancer, although it is not likely to result in a cure by itself. The allogeneic SCT may improve the chance that your disease will enter into a long remission and possibly be cured. However, you should understand that this cannot be guaranteed. All of the evaluations, tests, and hospitalizations that you receive at the NIH will be free of charge to you. In addition, your participation in this study may contribute to understanding and developing new ways of using allogeneic SCT for the treatment of cancer.

Alternative Treatment

To be eligible for this study, you must have already received the standard treatment for your disease, but there are other options other than participating on this trial:

- You may consider other treatments such as other forms of chemotherapy, radiation, surgery, or immune therapies. In some cases, you may be eligible for an autologous bone marrow or stem cell transplant, in which your own stem cells are returned to your body following high dose chemotherapy treatment.
- Taking part in another research study
- Instead of participating in a research study such as this, you may also be eligible to receive a standard allogeneic stem cell transplant with high dose chemotherapy and/or radiation therapy to completely wipe out your bone marrow before donor cells are transplanted.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

- Another option is not to receive any further treatment at all.

You should discuss with your referring doctor and your doctors at the NCI whether or not any of these other treatments might be a reasonable choice for your disease.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- If he/she believes that it is in your best interest
- If your disease comes back after treatment
- If you have side effects from the treatment that your doctor thinks are too severe
- If new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

Participation in this research study is voluntary. You may stop your participation in the study at any time. There are no penalties for withdrawing from the study. However, if you withdraw after the transplant chemotherapy ("conditioning regimen") without receiving the infusion of donor stem cells, you would be at high risk for serious complications, including death. If you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Dr. Pavletic or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.

- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- We may share data from this study with a blood and bone marrow registry called: The Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR (Hwww.cibmtr.org) is committed to respecting your privacy and the data we share with is sent without revealing any personal information. The information that is sent to the CIBMTR is combined with information from other transplant centers to better understand how transplants work and to improve patient care.

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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.
You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Steven Pavletic, M.D.; Building 10-CRC, Room 4-3130, Telephone: 240-760-6174. If you have questions about the use of your specimens or data for future research studies, you may contact the NIH Clinical Director at 240-760-6070. You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE OCTOBER 29, 2018 THROUGH NOVEMBER 12, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____