INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0073 PRINCIPAL INVESTIGATOR: Nirali N. Shah, M.D.

STUDY TITLE: A Phase I Study of NK CellIn fusion Following Allogeneic Peripheral Blood Stem Cell Transplantation from Related or Matched Unrelated Donors in Pediatric Patients with Hematologic Malignancies

Continuing Review Approved by the IRB on 08/21/17
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Recipient

INTRODUCTION

We invite 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.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

In the body, there are "stem cells" which mature into the cells of the blood: red cells (that carry oxygen), white cells (that fight infection), and platelets (that stop bleeding). The stem cells are found both in the bone marrow and in the blood stream. Stem cells can be collected and

transplanted to treat a variety of types of cancer. This technique is called hematopoietic stem cell transplantation (HSCT). When stem cells are taken from another person, most commonly a sibling or a family member or identical twin, this is referred to as allogeneic HSCT. When the stem cells are taken from an identical twin, this is referred to as syngeneic HSCT. When stem cells are taken from an unrelated person, who has matched blood typing, this is referred to as a matched unrelated donor (MUD). Allogeneic HSCT has proven to be an especially effective treatment for patients with some types of cancers of the blood (leukemia) and certain solid tumors such as sarcoma or neuroblastoma. The transplanted stem cells travel to the patient's bone marrow and begin producing normal blood cells. In addition, transplanted immune cells from the donor can attack the patient's cancer cells. This immune attack, which is called the "graft-versus-leukemia" (GVL) is a main reason why some patients with leukemia are cured of their cancer after HSCT. This treatment approach has not been studied as well in other forms of cancer but, recently, a similar "graft-versus-tumor" (GVT) effect has been seen in patients with breast cancer and kidney cancer.

Although a reaction of the donor's immune cells against your body might be beneficial if it targets the tumor cells, it is also possible that attack against normal cells might cause graft versus host disease (GVHD). This will be discussed in greater detail later. To prevent this immune attack from being too strong, medications can be given to suppress this reaction early after the transplant. Another way to prevent GVHD is to reduce the number of cells (T cells) from the donated stem cells that are primarily associated with the development of GVHD. In this study we will use this technique, T cell depletion to help prevent the development of GVHD.

In this study, we will be using allogeneic HSCT to treat patients who have your type of cancer. Relatives who have a similar blood type may serve as stem cell donors. Also unrelated donors who have matching blood types may serve as donors. If your donor is a matched donor, GVHD occurs in at least half of all patients undergoing HSCT.

Because the cancer returns in a significant number of patients after allogeneic HSCT, in this study, participants will also receive another type of immune cells from the donor's white blood cells (donor lymphocytes) called 'Natural Killer' Cells or NK-DLI (Donor Lymphocyte Infusion). In the laboratory NK cells have been shown to kill tumor cells, but we do not know if this will occur when given to patients after HSCT. Outside of the NIH, NK-DLI have been given to patients with leukemias and have been shown to have an effect against the leukemia. The NK-DLI portion of this study is experimental and has not been approved by the US Food and Drug Administration (FDA) for the treatment of cancer, but the FDA has given us permission to use these types of cells in this research study.

The purpose of this study is to test the safety of giving NK cells after an allogeneic HSCT and to identify what side effects occur after this treatment. We will also be trying to answer the following questions:

1. Determine if your body accepts the HSCT after receiving NK cells, also known as 'donor engraftment';

2. Investigate how many patients develop GVHD after this experimental regimen; and
3. Compare how long patients remain without cancer after HSCT versus after HSCT plus NK-DLI.
4. Study the immune system's response to this experimental regimen.

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

You are being asked to participate in this study because you have a type of cancer we are studying and you have a related or unrelated donor with a matching blood type who can donate blood for your treatment regimen. All patients must have cancer despite previous standard treatments, and must meet the safety criteria set forth as eligibility in this study, such as blood tests, heart and lung tests, and kidney tests.

How many people will take part in this study?

Up to 43 patients (with 43 donors) may take part in this study. Patients may have leukemia or lymphoma.

Description of Research Study

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

Before you begin the study

Before you start this study, you will be evaluated with a history and physical examination, blood tests, and disease staging, to include scans (MRI, CT or PET), x-rays, or spinal fluid samples or bone marrow aspiration and biopsy, depending upon your type of cancer, and an evaluation of your lungs and heart.

During the study

If you are eligible, the following procedures will be done (details follow in later sections):

- Stem cell collection: The donor's stem cells will be collected by a procedure known as "apheresis" (a procedure explained below). The cells may be frozen for transplant and some will be separated and specially treated to make NK-DLI cells so that they can be given to you at a later date.
- Induction chemotherapy: You may receive one to three cycles of chemotherapy to treat the underlying cancer and weaken your immune system in order to accept the donor cells. Some patients may not need this induction chemotherapy and this will be determined by your physician.
- HSCT: You will then receive several days of pre-transplant chemotherapy and possibly radiation therapy, called the preparative regimen. Some patients will receive a "reduced intensity" or "non-myeloablative" preparative regimen. Most leukemia patients will receive a

"high-intensity" or "myeloablative" preparative regimen, unless they are unable to tolerate this, then a reduced intensity regimen will be used. Two days after the last dose of this chemotherapy, you will receive the donor stem cells by a transfusion. This part of the study is considered 'standard care' and is approved by the FDA for treatment of cancer.

- NK-DLI: On Day 21 after the HSCT you will receive an infusion of NK-DLI. This will be repeated approximately 28 days later (about Day 49). This is the part of the study that is considered 'experimental'.
- Post-HSCT follow-up: When your condition is stable, you will be discharged from the hospital. You will be followed closely as an outpatient for the first six months after the transplant, and then less frequently for at least five years. In general, you will be required to stay at the NIH for approximately three months for the treatment. After that, you may return home but will be evaluated at the NIH for follow-up visits.

Induction Chemotherapy

The chemotherapy you receive for this portion of the study will depend upon what type of cancer you have. If your cancer is a lymphoma, you may receive the following chemotherapy drugs:

Fludarabine, cyclophosphamide (cytoxan), etoposide (VP-16), doxorubicin (adriamycin), vincristine, and prednisone. You will receive these drugs in standard doses over five days followed by at least a 17-day rest period. All of these will be given by IV as a continuous infusion with the exception of prednisone, which will be given by mouth. You will receive up to 3 cycles of this chemotherapy.

If you have leukemia, you may receive the following chemotherapy drugs:

Fludarabine and cytarabine by infusion in standard doses over five days followed by at least a 17-day rest period for up to 3 cycles.

Because we will be giving you many drugs by I.V. and drawing blood for tests, you will need to have a central venous catheter (CVC) or a catheter in a large vein.

During the experimental regimen

HSCT

At the time that you are ready to start your pre-transplant therapy, you will be admitted to the NIH Clinical Center as an inpatient. You will receive several days of high-dose chemotherapy and/or radiation therapy as indicated for your type of disease. Chemotherapy will be given by I.V. Two days later (Day 0) you will receive the donor stem cells by I.V.

The primary purpose of this study is to test the safety of giving the NK-DLI after transplant. We will test the safety in stages:

1. The first patients (who must be over 18 years of age) will receive ONE dose of NK-DLI after the blood count (neutrophils or ANC) reaches a normal level, or within 42 days after the transplant on Day 0, to let us observe for side effects or inability of the transplant to 'engraft' (where the body accepts the transplant cells).

2. NK-DLI will be given in increasing doses: This is a 'dose escalation' study, meaning that we are trying to find the dose of cells that is effective yet safe. There will be three dose levels of NK-DLI cells. The first 3-6 patients enrolled get the smallest dose and the dose is increased in groups of 3-6 patients, once a dose level has been determined to be safe. Discuss with your doctor which dose of NK-DLI cells you will be given.

After treating about 8 people we observed that patients who received transplant cells from unrelated donors developed graft-versus-host disease (GVHD) more often with this regimen that patients who received cells from related donors. Therefore, the dose of NK-DLI cells will be increased in these two groups separately.

In the dose escalation part of the study, you will receive your first dose of NK-DLI cells by I.V. over 20-30 minutes on approximately Day 21 after the HSCT. If you do not have any unacceptable reaction, the NK-DLI infusion will be repeated approximately Day 49. The expected hospital stay will be about 3 weeks and it could be longer if complications arise.

Schema for Dose Escalation Groups:

Induction Chemo – (Non-myeloablative regimens)	**Pre HSCT Chemo**	**HSCT**	**NK-DLI**	**Evaluations**
Lymphoma Fludarabine (Day 1,2,3) Etoposide (Day 1,2,3,4) Doxorubicin (Day 1,2,3,4) Vincristine (Day 1,2,3,4) Cyclophosphamide (Day 5) Prednisone (Day 1,2,3,4,5) *Leukemia* Fludarabine (Day 1,2,3,4,5) Cytarabine (Day 1,2,3,4,5)	*Non-myeloablative regimen:* Fludarabine (Transplant Day -5, -4, -3, -2) Cyclophosphamide and Mesna (Transplant Day -5, -4, -3, -2) *Myeloablative Regimen:* Fludarabine and Busulfan (Transplant Day -5,-4,-3, -2) *ALL (only)* Total body irradiation or TBI* (Transplant Day -6,-5,-4) Cyclophosphamide and Mesna (Transplant Day -3, -2) *Cranial irradiation as indicated	Day 0: Pre-medications: 30-60 min before cells: Fluids in IV HSCT infusion Start filgrastim (shot under the skin) every day until blood counts increase	Approximately Day 21 and Day 49: NK-DLI given in the vein over 20-30 minutes	Pre Induction Chemo: Physical exam, blood tests, urine tests, disease staging Pre HSCT Chemo: Physical exam, blood tests, urine tests, disease staging, research blood draw HSCT in hospital and Follow Up: Every day: Physical exam, blood tests, urine tests Research blood tests (3 X before starting Pre HSCT chemo, Day -7, 0, 14, 28, 42, 60, 100, 180) Disease Staging: (Day 28, 100 and every 3 months for the 1st year, every 4 months for 2nd year, every 6-12 months for up to 5 years.

Post-HSCT

You may leave the hospital when you have near normal white blood cell count, no fever or infection, are able to take in enough foods and fluids by mouth, and no signs of serious graft-versus-host disease (GVHD, which is explained below). After leaving the hospital, you will be watched closely as an outpatient and continue to receive many medications. It is likely that the total number of medications required will be greater than five and that these medications will be needed for up to 100 days. Additional hospitalization may be needed if complications develop. During the first 100 days after transplant, you will be seen at least 1-2 times per week in the outpatient clinic. At each visit, you will have a medical history, physical exam, and blood tests. We will also give you I.V. immunoglobulin (antibody preparation) and possible additional I.V. antibiotics if needed to help fight infections. You may also need transfusions of red blood cells and platelets. After the first 100 days, the risk of serious complications decreases and your outpatient visits may be less frequent. At this time, it may be possible to return home. You will be followed for at least five years after the transplant.

Protocol Evaluation

During the course of study, you will have repeated medical evaluations to check on your cancer and to look for possible side effects of the treatment. You will also receive other treatments including transfusions and antibiotics. We will do routine blood studies every week while you are receiving the treatment to watch for any side effects. We will also do tests to evaluate your condition after the HSCT through Day 100 twice per week. After Day 100 we will ask you to return to NIH for clinical evaluation at least every three months for the first year and then every four months for the second year, every 6 months for the third year, and then yearly for years 4 and 5. Depending on the location of your disease and your clinical condition, we may do tests, such as urine testing, x-rays or scans, spinal fluid samples, bone marrow biopsy or aspiration, or others that will be discussed with you should the need arise.

One important component of this research is to study the cells we collect from patients with cancer and their donors to allow researchers to learn more about immune responses and the inner workings of cancer cells. For this reason, blood will be drawn for research purposes to study your immune system, cell numbers in the blood, and the amounts of certain blood cell products. We will take blood for research tests approximately 10 times during the first 100 Days, and then 4 times per year for the first year. These cells will be used to determine whether immune responses can be generated against the tumors that are treated with this protocol and explore new molecular responses.

The maximum amount of blood taken from you for research is based on your age and will not be more than the strict blood volume limit set for research by the NIH. In adults that limit is 37 tablespoons in an 8 week period. If you are under age 18, we will not draw more than 1 teaspoon of blood for every kilogram (2.2 pounds) of your body weight in a single day and not more than 2 teaspoons of blood for every kilogram (2.2 pounds) of your body weight in an 8 week period.

For example, if you weigh 85 pounds (weight of some 12 year olds), your weight in kilograms is about 38 kg; therefore we would not draw more 38 teaspoons (12.5 tablespoons) in one day and not more than 76 teaspoons (or 25 tablespoons) of blood in an 8 week period.

If in the future you are an adult and have a tumor that is easily accessible (e.g. a tumor that can be biopsied through the skin and does not require surgery to obtain), you may be asked to undergo biopsy for research evaluation. It is expected that you will receive sedation and/or anesthesia for this procedure. Standard techniques will be used for biopsies and may include CT and / or ultrasound guidance. Although direct benefit to you from research conducted on this tumor biopsy is unlikely, participation in this research may lead to a greater understanding of your cancer and potentially benefit others in the future. This is completely optional, will only be requested of adult participants, and does not affect your ability to participate in this protocol. If you agree to a biopsy, the risks of the procedure will be fully explained to you and consent will be obtained from you at that time.

1. If I have tumor that is easily accessible, I will allow a biopsy of tumor for use in research to learn about, prevent, or treat cancer.

Yes No Initials_____

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3-6 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

When you are finished taking the drugs (treatment)

After you complete the regimen on this study, we would like you to return to NIH at intervals to assess you condition. If you proceed to other therapies or cannot return to NIH, we will contact you or your physician to ask about your condition.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- In some cases, you might be eligible for an autologous BMT where your own stem cells are returned to you following high-dose chemotherapy.
- You could consider treatment with standard chemotherapy, radiation and/or surgery. You should discuss these alternatives including their possible risks, benefits, advantages, and disadvantages with your referring doctor and the NIH doctors.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

HSCT is a serious form of treatment with many possible risks. It is probable that you will experience some of the side effects listed, but it is unlikely you will experience all of them. In general, patients receiving a myeloablative transplant will be at a higher risk for experiencing many of the complications listed below. You will be watched closely and attempts will be made to prevent or reverse any complications.

Because this is the first time that we are aware of that NK-DLI has been given with HSCT, there may be risks or side effects that we cannot predict. Based on other studies in patients who received NK-DLI cells alone, patients may experience chills, fever, nausea or vomiting after receiving NK cells, or have an allergic reaction, with hives, rash, shortness of breath. Of the first 6 people treated with this experimental regimen, some patients experienced fever, lowered blood pressure, rash and diarrhea after receiving the NK-DLI cells.

Patients 18 years of age or older will need to name someone as a "durable power of attorney". This should be someone that you trust to make medical decisions for you if you become physically or mentally unable to make your own healthcare decisions.

Being in this study may keep you from being in other research studies in the future. You can also expect that this treatment may require you to remain home from work/school for about one year.

Risks associated with routine procedures

The following risks may occur as a result of the routine procedures performed on this study:

Risks associated with routine procedures		
Blood Drawing or Bone Marrow Aspiration or Biopsy		
Common	Less Common	Rare
▪ Mild discomfort from putting in the needle	▪ Bruising	▪ Bleeding ▪ Infection ▪ Blood clot (apheresis)
Central Venous Catheter		
Common	Less Common	Rare
▪ Mild discomfort	▪ Bruising ▪ Bleeding ▪ Infection	▪ Lung collapse

If you experience lung collapse from a central venous catheter, the lung would be quickly re-inflated using a tube inserted in your chest. If the catheter becomes clogged or infected, it may need to be replaced.

Risks associated with chemotherapy

The chemotherapy drugs are used in attempt to decrease the amount of your cancer and to suppress your immune system to allow the donor stem cells to grow. Chemotherapy also affects normal blood cells decreasing red cells (with risk of anemia), white cells (with risk of infection), and platelets (with risk of bleeding). Red blood cell and platelet transfusions will be given as needed. There are risks from transfusions including transfusion reactions and infections (such as AIDS and hepatitis). Antibiotics will be given to decrease the risk of infection. Even after discharge from the hospital you will be at risk for infection because it will take about 12 months after the transplant before you immune system returns to normal. Infections after BMT can be very serious and can result in death. You should seek immediate medical attention for fever over 100.5 ° F or any signs or symptoms of infection.

The following are known risks of each chemotherapy drug:

Risks associated with chemotherapy

Fludarabine side effects

Common	Less Common	Rare
▪ Changes in blood counts	▪ Fever ▪ Loss of appetite, nausea, vomiting ▪ Diarrhea, stomach pain ▪ Mouth sores ▪ Headache ▪ Fatigue or weakness ▪ Muscle or joint aches ▪ Swelling ▪ Skin rash ▪ Agitation ▪ Hearing loss ▪ Numbness and tingling (pins and needles)	▪ Bleeding bowel or stomach ▪ Organ damage: lung, kidney, liver ▪ Severe brain or spinal cord toxicity has occurred at very high doses, incl. blindness, deterioration of mental status, and death ▪ Transfusion associated GVHD (will be prevented by using irradiated blood products) ▪ Thrombotic thrombocytopenic purpura- a disorder that includes kidney damage

Etoposide (VP-16) side effects

Common	Less Common	Rare
▪ Low blood counts ▪ Hair loss	▪ Loss of appetite, nausea, vomiting ▪ Diarrhea ▪ Mouth sores ▪ Bad after-taste ▪ Skin rash	▪ Low blood pressure ▪ Difficulty breathing ▪ Secondary leukemia (a different type of cancer) ▪ Muscle cramps ▪ Bleeding bowel or stomach ▪ Liver damage ▪ Allergic reaction ▪ Reversible nervous system problems, i.e. confusion, temporary blindness ▪ Secondary cancer

Prednisone side effects

Common	Less Common	Rare
▪ High blood sugar ▪ Fatigue ▪ Stomach upset ▪ Headache	▪ High blood pressure ▪ Water retention or swelling ▪ Weight gain ▪ Increased risk of infection ▪ Increased appetite ▪ Skin changes (i.e. slow wound healing, easy bruising, acne, stretch marks) ▪ Mood changes, trouble sleeping ▪ Excessive hair growth	▪ Growth problems ▪ Thinning of bones with risk of fractures ▪ Eye problems, i.e. cataracts, glaucoma ▪ Convulsions ▪ Stomach or intestinal ulcers or bleeding

Vincristine side effects

Common	Less Common	Rare
▪ Nerve damage resulting in 'pins and needles' in hands and feet ▪ Constipation ▪ Hair loss	▪ Nerve damage resulting in pain or weakness in hands or feet ▪ Loss of reflexes	▪ Bowel stops working (paralytic ileus) ▪ Water retention ▪ Skin burns (if leaks out of I.V.)

Doxorubicin side effects

Common	Less Common	Rare
▪ Low blood counts ▪ Hair loss	▪ Nausea and vomiting ▪ Diarrhea ▪ Mouth sores	▪ Heart damage (risk greater with higher total doses) ▪ Secondary cancer (such as leukemia) ▪ Skin burns (if leaks out of I.V.) ▪ Bleeding bowel or stomach

Cyclophosphamide side effects

Common	Less Common	Rare
▪ Low blood counts ▪ Hair loss	▪ Loss of appetite, nausea, vomiting, ▪ Mouth sores ▪ Bladder irritation with bloody urine ▪ Water retention ▪ Loss of fertility	▪ Heart damage ▪ Secondary leukemia (a different type of cancer) ▪ Skin rash ▪ Headache ▪ Blurred vision or dizziness ▪ Swelling (edema) ▪ Allergic reaction

Busulfan side effects

Common	Less Common	Rare
▪ Low blood counts ▪ Nausea or vomiting ▪ Mouth sores ▪ Loss of appetite, with weight loss ▪ Diarrhea ▪ Difficulty sleeping ▪ Anxiety ▪ Changes in blood levels of electrolytes, such as magnesium or calcium or potassium ▪ Changes in blood sugar level ▪ Fever ▪ Stomach pains ▪ Headache ▪ Numbness and tingling ▪ Pain ▪ Rapid heart rate	▪ Allergic reaction ▪ Chest pain ▪ Swelling of the hands and feet ▪ Increase in your blood pressure ▪ Clots in the veins ▪ Constipation ▪ Dry mouth ▪ Changes in blood levels of electrolytes, such as calcium ▪ Changes in blood tests that may indicate liver damage, such as bilirubin, AST ▪ Changes in blood tests that may indicate kidney damage, such as creatinine ▪ Dizziness ▪ Cough ▪ Nose bleed ▪ Difficulty breathing ▪ Rash or itching	▪ Liver damage ▪ Severe infection ▪ Lung damage

Cytarabine side effects

Common	Less Common	Rare
▪ Low in blood counts ▪ Loss of appetite, nausea, vomiting ▪ Abnormal liver tests ▪ Fever ▪ Rash ▪ Oral or anal ulcers	▪ Risk of infection ▪ Sore throat, or inflammation of the esophagus (swallowing tube) ▪ Headache ▪ Dizziness ▪ Hair loss ▪ Itchy rash ▪ Difficulty urinating ▪ Skin ulcer at the IV site	▪ Severe infection ▪ Pneumonia ▪ Allergic swelling (edema) ▪ Nerve damage ▪ Liver damage ▪ Severe allergic reaction (difficulty breathing/swelling)

Risks associate with Total Body Irradiation (TBI) and CNS boost (*in patients with ALL ONLY)*

You will go to the Department of Radiation Oncology to receive TBI, twice a day for three days. TBI is painless but may cause some nausea. Before the radiation, you can receive medicine to control the nausea. It is extremely important that you lie still during the TBI. You will be alone in the room during the TBI but we will be watching you closely on a closed-circuit TV and an intercom so we can watch you and talk to you during the therapy. Specific risks include the following:

Total Body Irradiation Side Effects (People with ALL receiving a myeloablative regimen only)		
Common	Less Common	Rare
▪ Loss of appetite, nausea, vomiting, weight loss which is often severe ▪ Diarrhea, stomach pain ▪ Mouth sores, difficulty swallowing, dry mouth, metallic taste, sticky saliva ▪ Fatigue ▪ Skin changes including pinkness, dryness and itching ▪ Hair loss ▪ Inflammation of the lung, dry cough or difficulty breathing which may or may not require a breathing tube ▪ Fever ▪ Prolong changes in blood counts	▪ Loss of skin color ▪ Hearing loss (which may be temporary) ▪ Vision changes ▪ Damage to the liver which may result in changes in your liver tests or severe liver failure	▪ Change in kidney function that may or may not cause symptoms or require treatment ▪ Scarring of the lung causing shortness of breath ▪ Cataract formation ▪ Risk of developing a secondary cancer ▪ Early onset of sterility (you may wish to consider banking sperm/eggs prior to starting on this study)
CNS Boost (People with ALL receiving a myeloablative regimen only)		
Common	Less Common	Rare
▪ Skin changes including pinkness, dryness and itching ▪ Hair loss ▪ Fatigue	▪ Headaches ▪ Weakness ▪ Numbness ▪ Nausea/vomiting	▪ Decreased blood cell count ▪ Severe memory loss ▪ Cataracts ▪ Permanent loss of brain cells ▪ Seizures ▪ Hearing loss ▪ Brain tumor

Risks associated with other medications

Do not take any medications without discussing them with your doctor first.

The possible side effects of the other main drugs used during this study are as listed in the table below; here are some of the main medications you will be asked to take:

Mesna: This drug will be given by IV to try to prevent the bleeding in the bladder that may be caused during the high-dose cyclophosphamide.

Filgrastim or G-CSF (or Pegfilgrastim): G-CSF is a natural substance normally produced by the body that helps make white blood cells. It will be used after chemotherapy and after HSCT to help speed the recovery of your white blood cells. Filgrastim will be given by subcutaneous injection (a shot under the skin much like insulin) daily starting the day after chemotherapy stops and continuing until your white blood cell count is high enough. We will teach you or a family member how to give these shots at home, or if needed, a nurse can administer the filgrastim. The shots will be given in the arm or thigh. Filgrastim is very safe and generally well tolerated. If you have any problems with your kidneys, your doctor may choose to give you Pegfilgrastim, instead of Filgrastim. Pegfilgrastim will be given one time, within 2 days after your chemotherapy stops, by subcutaneous injection.

Tacrolimus or cyclosporine A will be started on day -1 before the stem cell infusion through your IV to help prevent GVHD. The tacrolimus or cyclosporine-A will be given every 12 hours through your IV, until you can tolerate food, then it can be given to you as a capsule or solution.

Corticosteroids (prednisone and similar drugs) may be used to treat GVHD if it develops. The risk of side effects developing is greater if high doses or long-term treatment are required. In addition to risks outlined below under "Prednisone," long-term use can decrease the body's response to stress.

IVIG is a preparation of antibodies (needed to fight certain infections) that will be given after the transplant until you begin to produce adequate amounts. It is given into the vein (through the catheter) every 2 weeks until about 6 months after the transplant. Sometimes medications such as acetaminophen (Tylenol) and/or diphenhydramine (benadryl) are given to prevent these symptoms.

Fluconazole is used to prevent certain yeast and fungal infections. It is usually given by mouth. Side effects are unlikely. Rarely damage to the liver can occur.

Trimethoprim/Sulfamethoxazole is given by mouth to prevent a certain lung infection that is caused by a parasite called pneumocystis. As an alternative, a medication called Pentamidine may be used to prevent pneumocystis. It will be inhaled once a month. It can cause a metallic taste in your mouth, low blood sugar, or coughing or spasm of your airway (in patients who smoke or have asthma).

Palifermin, also called keratinocyte growth factor, that may help to prevent mucositis (mouth sores) that are often seen after high-dose chemotherapy or radiation therapy. It is given through

the vein for 3 doses prior to starting the pre-transplant therapy and for an additional 3 doses after receiving the stem cells.

Acetaminophen (Tylenol): This will be given as a premedication prior to stem cells (or with other treatments such as blood transfusions and IVIG). Side effects are extremely unlikely. Very high doses of acetaminophen can cause liver damage.

Ranitidine (Zantac): This will be given as a premedication prior to stem cells. Possible side effects include tiredness, dizziness, headache, and diarrhea.

Diphenhydramine (Benadryl): This will be given as a premedication prior to stem cells (or with other treatments such as blood transfusions and IVIG). Possible side effects include sleepiness, dizziness, restlessness, and irritability.

Support Medications – side effects

Common	Less common	Rare
Mesna (To prevent bleeding in the bladder from cyclophosphamide)		
	▪ Bad taste in mouth ▪ Pain in vein where drug is given	▪ Stomach pain ▪ Nausea or vomiting ▪ Headache ▪ Limb or joint pain ▪ Sleepiness ▪ Rash ▪ Diarrhea Low blood pressure
Filgrastim, also called G-CSF (To increase production of white blood cells) or Pegfilgrastim		
Common	**Less common**	**Rare**
▪ Bone pain or muscle aches ▪ Pain or bruising from injections	▪ Severe headache ▪ Tiredness	▪ Severe breathing problems ▪ Rupture of your spleen ▪ Changes in certain laboratory tests
Tacrolimus (To prevent GVHD)		
Common	**Less common**	**Rare**
▪ Increased blood pressure ▪ Headache ▪ Uncontrollable shaking of the body ▪ Diarrhea ▪ Nausea ▪ Heartburn ▪ Stomach pain ▪ pain ▪ Difficulty falling asleep or staying asleep	▪ Changes in blood sugar levels ▪ Constipation ▪ Vomiting ▪ Loss of appetite ▪ Changes in liver or kidney function ▪ Burning, numbness, pain or tingling in the	▪ Decreased urination ▪ Pain or burning on urination ▪ Swelling of the arms, hands, feet, ankles or lower legs ▪ Weight gain ▪ Unusual bruising or bleeding ▪ Rash or itching ▪ Difficulty breathing ▪ Seizures

▪ Dizziness ▪ Weakness ▪ Back or joint pain ▪ Changes in blood electrolyte levels including potassium, magnesium ▪ Changes in red blood cell count	hands or feet ▪ Fever ▪ Changes in white blood cell count	▪ Coma ▪ Allergic reaction

Cyclosporine (To prevent GVHD)

Common	Less common	Rare
▪ Decrease in kidney function ▪ High blood pressure ▪ Increase in facial hair ▪ Lowered blood levels of magnesium requiring supplements ▪ Increased risk of infection	▪ Tremor ▪ Gum hyperplasia ▪ Seizures ▪ Liver damage ▪ Flushing or lowering blood pressure when given through the IV ▪ Depression	▪ Coma

Corticosteroids (prednisone and similar drugs) (To treat GVHD)

Common	Less common	Rare
▪ Headache ▪ Nausea, vomiting, diarrhea, abdominal pain ▪ Itching		▪ A skin disorder called Stevens Johnson Syndrome, which can be fatal ▪ Liver damage which may be permanent

IVIG (To fight certain infections)

Common	Less common	Rare
▪ Headache ▪ Hives	▪ Low blood pressure ▪ Rash	▪ Severe allergic reactions

Trimethoprim/Sulfamethoxazole, also called Bactrim (To prevent a certain lung infection, pneumocystis)

Common	Less common	Rare
	▪ Fever ▪ Nausea, vomiting, ▪ Skin rash with itching ▪ Reduced number of white blood cells ▪ Allergic reaction	

Palifermin (used to reduce the occurrence or severity of mouth sores)		
Common	**Less common**	**Rare**
▪ Rash, redness, swelling or itching ▪ Changes in taste ▪ Unusual sensations in the mouth, tongue color change or tongue thickening ▪ Increase in blood pressure ▪ Protein in the urine	▪ Fever ▪ Breathing problems ▪ Swelling ▪ Pain ▪ Joint pain ▪ Increase in blood pancreas enzymes	

OTHER RISKS OF PARTICIPATION:

Risk of not being able to proceed to transplant

After receiving induction chemotherapy, you will be evaluated to be sure that it is safe and appropriate to proceed to the HSCT. It is possible that your condition at that time would have changed so that the experimental HSCT would no longer be recommended. Possible reasons for this might include organ damage, severe infection, or worsening of your cancer. If something like this has occurred, this will be explained to you and you will be referred for appropriate medical attention.

It is also possible that you may not be able to proceed to transplant if the donor or donor cells become unavailable (i.e. donor withdrawal or illness, accidental cell loss).

Possible Side Effects after Your Transplant(s):

In the first few days to weeks after the transplant, you may get a fever. Fever is a sign of infection. Your white blood cell counts may be low after the transplant and your body not yet strong enough to fight off infection. So, in the event of fever, you will receive antibiotics. You may also receive red blood cells or platelets. Mouth ulcers and intestinal irritations are common during this time. If these occur, you will be given painkillers to make this period of time less unpleasant. Intestinal irritations usually disappear when your blood counts return to normal. However, it may take weeks to months for your normal appetite and taste to return. Weight loss and nutritional deficiencies can be seen during this time. You may also have decreases in minerals and electrolytes that need supplementation. Many people experience fatigue and malaise during this time.

Graft-versus-Host Disease (GVHD)

In GVHD, the transplanted donor cells (graft) attack the recipient (host). GVHD may never appear, it may be mild and brief, or it may lead to severe complications. The donor selected for your transplant is the best match available at this time, but it may not be a perfect match if a perfectly matched donor is not available. Even with a matched donor, GVHD occurs in at least half of all patients undergoing HSCT. If the donor is not perfectly matched, the risk of GVHD increases. All recipients will receive immunosuppression with either tacrolimus or cyclosporine A to help reduce the risk of GVHD. Acute (early onset) GVHD usually causes skin rash, diarrhea, and/or liver damage. When chronic (long lasting), GVHD can also affect other organs including dryness of the mouth and eyes, weight loss, liver damage (including yellow jaundice), lung damage leading to cough and shortness of breath, joint pain and stiffness like arthritis, weak immune system, or thickening of the skin. If GVHD develops, medications may be used to treat this condition. Long-term treatment (months to years) may be required. Even with such therapy, however, GVHD can last and may lead to death. Skin biopsies, and possible liver or intestine biopsies, may be required to diagnose GVHD.

Risks of donor cell infusions

The risks involved in the infusion of the donor's cells include transfusion reactions such as fever, chills, muscle aches, allergic reactions, and hemolysis (red cell breakdown due to incompatible blood types). This last reaction can also happen later (2-6 weeks) after transplant and be particularly severe and cause kidney failure. If you and the donor have different blood types, we will watch closely for signs of this type of reaction. The donor cells are frozen in a drug called DMSO, and mild reactions to this drug are common. DMSO will give a garlic-like smell on the breath. It may also cause nausea, vomiting, and a temporary change in the blood pressure. Medications may be required to increase urine flow and decrease blood pressure to normal. The urine may turn a pink-red color for 12-24 hours. Heart rhythm abnormalities can occur and may require drug treatment. In addition, infusion of donor lymphocytes cells after transplant may increase the risk of developing GVHD. It is thought that infusion of NK donor lymphocytes may reduce this risk, but this is not known for sure.

Graft Rejection

Periodic blood tests will be performed after your transplant to find out if your body has accepted the donor cells. If no donor cells can be found, then the stem cells did not engraft or you rejected them. In that case, your blood counts may return to pre-transplant levels in about 2 to 3 weeks. It is possible that this could result in you not being able to make normal blood cells, which could be fatal.

Veno-Occlusive Disease (VOD)

A complication known as VOD occurs in about 5 percent of allogeneic transplants. It happens when blood vessels in the liver are blocked. Severe VOD can lead to liver failure and death. It

is hoped that the lower doses of chemotherapy used in this experimental HSCT will decrease the risk of VOD compared to the more common type of a transplant (myeloablative allogeneic HSCT).

Transplant-associated microangiopathy (TAM)

A rare, serious complication known as TAM is possible after receiving a transplant; it is the process of spontaneous destruction of platelets and red blood cells and the exact cause is not well understood. The most common symptoms include bleeding, damage to the blood vessels, easy bruising and changes in kidney function. Very rarely there may be neurologic symptoms such as confusion or delirium. Treatment is difficult, may consist of steroids, heparin and anti-platelet treatment, but may require multiple plasma exchange. Plasma exchange is a procedure in which your blood is separated into its different parts: red cells, white cells, platelets and plasma. The plasma is then removed from the blood and a plasma substitute returned in its place. In rare instances, progressive TAM may cause death.

Other Risks

Some additional risks may occur and we may NOT know if they are caused by the chemotherapy, by the other medications or by NK cells, unless they occur before you are given the NK infusions. These risks include a change in your body water (increased or decreased) causing swelling, abnormal levels of body electrolytes (high or low), including but not limited to sodium, potassium, chloride, magnesium, calcium, or glucose. We will be watching you closely and correct any of these abnormal levels if they occur.

Viral reactivation including, but not limited to, Cytomegalovirus (CMV) Infection, Varicella Virus (VZV), Ebstein Barr Virus (EBV), adenovirus, Human Herpes Virus -6 (HHV6): You will receive medications during the transplant to help prevent reactivation of some of these viruses. If you still get one of these viruses, we will treat you with additional anti-viral medications if available, or other supportive measures.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The primary aim of this study is to see if this experimental regimen is safe. As part of this study we will also test whether it will cause your cancer to shrink or disappear. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. Potential benefits of your participation could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the cells' effect on your cancer, we do not know if you will benefit from taking part in this

study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

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

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.

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.

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 during 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.

You can stop taking part in the study at any time. However, 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 to make sure that you are safe.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process *http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf*. 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.

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be 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 decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and data. Then any specimens that remain will be destroyed, and we will not use your and data for further research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials_____

2. My specimens and data may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Initials_____

3. Someone may contact me in the future to ask permission to use my specimen(s) and/or data in new research not included in this consent.

Yes No Initials_____

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, Nirali Shah, M.D., Building 10-CRC, Room 1-1621, Telephone: 301-451-0390. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

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 FROM AUGUST 21, 2017 THROUGH AUGUST 20, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____