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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: CC#110819: A Pilot Trial of Clofarabine Added to Standard Busulfan and Fludarabine for Conditioning Prior to Allogeneic Hematopoietic Cell Transplantation

The use of 'you' throughout this document refers to the patient or research subject.

This is a clinical trial, a type of research study. Your study doctor(s), Christopher Dvorak, MD, and his associates from the UCSF Division of Pediatric Blood and Marrow Transplant and Department of Clinical Pharmacy will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have a myeloid malignancy (a certain type of blood cancer) or a non-cancerous disease such as a bone marrow failure syndrome, transfusion-dependent red blood cell (RBC) defect, congenital immunodeficiency, metabolic disease, or severe immune dysregulation that is high-risk for recurrence following a hematopoietic stem cell transplant from another person. This study plans to add clofarabine to a standard busulfan and fludarabine conditioning regimen (treatment) prior to allogeneic hematopoietic cell transplantation (HCT) for high-risk patients.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, the addition of clofarabine, a new chemotherapy agent, to a standard busulfan and fludarabine conditioning treatment has on you and your disease. The study will also look at what causes some people to have high drug levels of these medications in their body compared to other people that may have low drug levels even if they all receive the same dose of medication.

Clofarabine is a new FDA approved chemotherapy drug that may provide extra killing of your cancer cells or lymphocytes, but may also be more toxic than standard treatments. You will be given both fludarabine and clofarabine as part of your chemotherapy. Busulfan is an FDA approved chemotherapy drug frequently used to prepare children for bone marrow transplantation. Busulfan is used to make space in the marrow to allow donor cells to grow, or engraft. Fludarabine is an FDA approved drug that effectively prevents rejection of the donor cells. The combination of clofarabine, busulfan and fludarabine is considered experimental which means it has not been approved by the US Food and Drug Administration.

Funding for this study is being provided by the University of California, San Francisco Division of Pediatric Blood and Marrow Transplant.

How many people will take part in this study?

About 31 people will take part in this study at UCSF.

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

Before you begin the main part of the study...
You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. These exams, tests or procedures are part of regular care prior to a transplant and may be done even if you do not join the study. You will also have some procedures that are only being done because you are in the study. These are called study procedures and are noted as "study test" in the list of procedures below. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. Your screening visit may take up to 2 hours.

- Assessment of disease status, including bone marrow aspirate – Bone marrow aspirate collection will only be done for patients with cancer. A sample of your bone marrow aspirate may be collected to assess your bone marrow and to measure how much cancer is in your bone marrow. This test is done by inserting a needle into your hip bone to remove a sample of bone marrow aspirate (about 2 teaspoons). You will receive a medicine to numb the surface of your skin on your hip. This will take about 15-30 minutes. The bone marrow aspirate is considered a part of your standard medical care.
- Echocardiogram - This examination uses sound waves to make pictures of your heart, which helps determine how well your heart squeezes blood. You will be asked to lie on your left side while a technician places a probe with gel on your chest to create images of your heart to determine the function and size. The procedure is done in the cardiology department and will take approximately 45-60 minutes. The echocardiogram is considered a part of your standard medical care.
- Pulmonary function tests - You will have a breathing test performed where you breathe in and out of a machine to measure your breathing capacity. This will include a measurement of your blood oxygen which involves obtaining a sample of blood from the pulse area in your wrist. This is done in the Pulmonary department and takes about 20 minutes to complete. The pulmonary function test is considered a part of your standard medical care.
- You will have blood drawn
    - For routine blood tests
    - To measure your kidney function
    - For a pregnancy testing (as appropriate)

During the main part of the study...

If the exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, then you will need the following tests and procedures.

Placement of a central venous line - To make your chemotherapy treatment easier, a small thin tube (called a central venous catheter) will be placed under the skin below your collarbone (near

your shoulder) that will connect to a large vein. This will allow for easy infusion of the chemotherapy drugs into your vein. This procedure is routinely performed by a surgeon in the outpatient setting. You will sign a separate consent form for this procedure.

During your treatment, you will be in the hospital for at least 6-8 weeks. Following admission to the Blood and Marrow Transplant Unit at UCSF, you will have the following procedures.

Day -13 / Day -1 (1 to 13 days before hematopoietic stem cell transplant)

- Administration of alemtuzumab for 3 days on Days -13 to -10 – only for patients with non-malignant / stem cell defects. Your doctor will let you know if you need to have this treatment.
- Administration of busulfan for 5 days on Days -10 to -6.
- Administration of fludarabine for 4 days on Days -5 to -2.
- Administration of hydrocortisone for 4 days on Days -5 to -2 prior to clofarabine infusion to decrease the chance of an allergic reaction, such as itching or rash.
- Administration of clofarabine for 4 days on Days -5 to -2.
- Administration of rabbit anti-thymocyte globulin (rATG) for 4 days on Days -4 to -1. – for patients with malignancies getting unrelated donors or for patients receiving peripheral blood stem cells from a matched related donor. Your doctor will let you know if you need to have this treatment.
- Blood draws (the blood will be drawn from your existing catheter)
    - At time of admission - For a study to see how your DNA (your genes) may affect the level of study medications in your body. This study is discussed in the *About Using Blood Samples for Research* section of this consent form. *Optional.*
    - Daily - for routine blood tests, including monitoring of your blood salt levels
    - Daily from Day -5 to Day +6 (six days post stem cell transplant) to monitor your liver – study test
    - For 4 days on Days -5 to -2 - to see how much of the medications are in your blood - study test.
        - On Day -5, blood will be collected at 2, 4, 8, and 24 hours after you receive fludarabine.
        - On Day -4 to -2, blood will be collected at 2 and 24 hours after administration of fludarabine for a total of 4 blood samples

Day 0 - hematopoietic stem cell transplant

- Infusion of donor hematopoietic stem cells

Day 1 (after hematopoietic stem cell transplant) until discharge from the hospital

- A minimum of twice weekly monitoring of blood tests. Blood will be drawn from your existing catheter
    - For routine blood tests
    - To monitor your blood salt levels
    - To monitor your liver (this test will be done daily until Day 6 - six days post stem cell transplant) – study test

- Blood studies of donor cell engraftment beginning on approximately Day +30 and then monthly until stable.

When you are finished receiving clofarabine...

After discharge from the hospital, you will be asked to return to the clinic on the following schedule:

- every 1-4 weeks for the first six months
- then, every 3 months until 2 years post-transplant
- then, every 6 months until 3 years post-transplant
- yearly thereafter until 5 years post-transplant

At these visits, blood (2-4 teaspoons) will be taken to monitor your immune system in addition to assessing the function of the kidneys and liver. These tests are considered a part of your standard medical care. If you no longer have a central venous line, the blood sample will be drawn by inserting a needle into a vein in your arm.

Study location: All study procedures will be done at the UCSF Benioff Children's Hospital inpatient bone marrow transplant unit.

How long will I be in the study?

You will stay in the hospital for approximately 6-8 weeks to monitor you for side-effects of your transplant and the treatment with clofarabine. However, we would like to continue to monitor your health for at least 5 years after your transplant. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study. We will ask you to return to the clinic every 1-4 weeks for the first six months, then every 3 months until 2 years post-transplant, every 6 months until 3 years post-transplant, and yearly thereafter until 5 years post-transplant.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. You may also tell your nurse and he/she will notify the study doctor that you no longer want to participate in the study. Your doctor will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the clofarabine can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the clofarabine. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Clofarabine is approved at a specific dose for use in treating children with a specific form of leukemia. Many risks and side-effects have been reported with that dose of clofarabine. You will receive a dose of clofarabine that is only 15% of the approved dose. However, you will receive clofarabine in combination with two other chemotherapy drugs, busulfan and fludarabine, and this combination may alter the types or severity of side-effects you experience. In adults undergoing transplant, busulfan has been combined with clofarabine doses.

Risks and side effects related to the study drug Clofarabine:

Known risks and side effects related to standard-doses of clofarabine are listed below. Side-effects that have been reported in four trials of clofarabine use in combination with other chemotherapy drugs prior to a transplant are listed first and are **bolded**.

Likely

- **Nausea and/or vomiting**
- **Diarrhea**
- **Elevation in the blood of certain enzymes found in the liver and bilirubin (a substance that comes from the liver breaking down waste products) which may mean the liver is not working as well as normal**
- **Fever**
- **Skin rash**
- A fast heartbeat which may cause pain in the chest
- A feeling of extreme tiredness not relieved by sleep
- A decrease in blood pressure
- Pain in the abdomen (belly)
- Fever with a low white blood cell count which could mean that you have an infection and might require hospitalization and treatment with antibiotics
- Chills
- Anxiety
- Loss of appetite
- Headache
- Skin rash with inflammation

- Itching
- Red spots on the skin from low platelets
- Bloody nose
- Fewer white blood cells, red blood cells and platelets in the blood (may be prolonged). A low number of white blood cells can make it easier to get infections. A low number of red blood cells can make you feel tired and weak. A low number of platelets causes you to bruise and bleed more easily
- Abnormal levels of potassium or magnesium in the body which may require that you take extra potassium by mouth or vein
- An increase in an enzyme (called lipase) that helps break down fats in the body

Less Likely

- **Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)**
- **Increased levels of a chemical (creatinine) in the blood which could mean kidney damage**
- **The skin and the whites of the eyes appears yellow as a result of too much bilirubin (a substance that comes from the liver breaking down waste products) in the blood**
- **Severe rash with redness and pain on the palms of the hand and soles of the feet (Hand-Foot Syndrome)**
- **Numbness and tingling in the fingers and toes**
- **Rash with redness or red bumpy rash**
- The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys
- Fluid build-up in the tissues
- Sleepiness and weakness
- Changes to your emotions such that you feel depressed, anxious, agitated, irritable or confused
- Shaking chills
- High blood pressure
- Cough or shortness of breath
- Reddening of the face with feelings of warmth when the drug is infusing
- A fast rate of respiration that may cause pain in the chest
- Allergic reaction
- A change in alertness, concentration, and memory
- Constipation
- A life-threatening form of severe blood infection that usually results from the presence of bacteria and their toxins in the bloodstream and is characterized especially by persistent hypotension (low blood pressure) with reduced blood flow to organs and tissues and often organ dysfunction
- Tremor (shakiness usually of the hands)
- Difficulty sleeping or falling asleep
- Fainting

- Low levels of oxygen in the blood which may make you feel short of breath
- Pain including back, bone, arm, or leg pain
- Weight loss
- Aches and pains in the muscles and joints
- Bleeding from the bladder, gut, mouth, or gums
- Vomiting or coughing blood
- Fluid build-up in the lungs that can make you feel short of breath
- A life threatening condition in which the level of oxygen in the blood becomes too low or the level of carbon dioxide in the blood becomes too high
- Damage to the sac around the heart which can lead to a build-up of fluid around the heart which may be painful and affect the ability of the heart to work normally but in most cases is only mild and temporary
- Bruising of the skin from low platelets
- Occasional sudden sharp pain in the rectal area
- Infections including those caused by bacteria, virus, and fungus and can be found in the lung, the blood, the skin and other places in the body
- Dizziness
- Abnormal high level of potassium in the blood which may cause irregular heart beat and require drug treatment to lower the level
- An increase in an enzyme (called amylase) that helps break down starch and sugars in the body
- A problem in nerve function that may cause pain, numbness, tingling, and muscle weakness in various parts of the body and may affect the ability to perform tasks that require fine movements

Rare But Serious

- **Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearance to the skin and fluid collection in the abdomen which makes it look larger**
- Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such as sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening
- Capillary leak syndrome: a condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure. Capillary leak syndrome may lead to multiple organ failure such as kidney, heart or liver failure and shock
- Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive chemicals) which may affect the function of the pancreas and which may cause pain in the abdomen (belly) which can be severe and may increase the blood sugar
- Severe inflammation and damage to the large intestine wall which can be life threatening
- Abnormal clotting of the blood that can lead to formation of blood clots and/or bleeding with abnormal findings on neurologic exam

- Severe rashes which can result in loss of skin and damage to mucous membranes and which may be life-threatening (occurred in combination of other drugs known to cause this effect)
- Severe kidney damage (which may be permanent)
- Failure of the bone marrow to produce blood cells and platelets which can be life threatening
- A change to the heart such that it does not pump the blood as well which may make you tired, weak, feel short of breath, and retain fluid

OTHER RISKS

Study Drug Combination risks: The complete side effects of the combination of clofarabine, busulfan, and fludarabine are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection. However, all of the study labs will be done while you are an inpatient and thus are planned to be drawn from your central venous line. Once you are far out from transplant, labs required for routine transplant follow-up care may be drawn directly from your veins.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the addition of clofarabine to standard busulfan and fludarabine prior to transplant will be more useful compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about the addition of clofarabine to standard busulfan and fludarabine prior to transplant. This information could help future transplant patients.

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

Your other choices may include:

- Getting treatment or care for your cancer or non-malignant condition without being in a study. The standard transplant conditioning regimen for a patient like you consists of only busulfan, fludarabine, and alemtuzumab or rabbit ATG, without the addition of clofarabine. This is available off-study.
- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer or non-malignant condition. It does not treat the cancer or non-malignant condition directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.
- The University of California

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of taking part in this study. Some health plans will not pay these costs for taking part in studies. Your study doctors or their clinical staff will obtain authorization from your insurance company prior to beginning your treatment. Taking part in this study may or may not cost you or your insurance company more than the cost of getting a regular transplant. In general, because most

chemotherapy drugs are not approved by the FDA specifically for use prior to a transplant, transplant doctors have flexibility in what drugs they choose to administer, and it is unusual for a health plan/insurance company to refuse to pay these costs.

Your transplant will be charged to your insurance company, including the cost of the clofarabine and the tests used to monitor for side-effects from the clofarabine. Additionally, you and/or your insurance provider will have to pay for the drugs busulfan and fludarabine, as these are considered part of your standard of care.

The extra labs done to measure the levels of the study drugs in your blood will be paid for by the study and will not be charged to you.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call **1-800-4-CANCER (1-800-422-6237)** and ask them to send you a free copy.

Will I be paid for taking part in this study?

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

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Christopher Dvorak, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her [redacted].

Treatment and Compensation for Injury:

If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Christopher Dvorak, MD, [redacted].

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

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.

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Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies. You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About Using Blood Samples for Research

At the time of admission, we would like your permission to collect a single blood sample for the transplant to study how your DNA (your genes) might affect drug levels in the body. Your DNA will only be used for research related to this study. You or your doctor will not be told any information about your DNA. After the study is complete, your DNA will be destroyed.

Results from this analysis may be published but your data will not be reported individually. Reports about research done with your blood sample will not be given to you or your doctor. These reports will not be put in your health record.

Things to Think About

The choice to let the researchers conduct research tests on your blood sample is optional and is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you do not want your blood used for this optional research.

If you decide now that your blood can be collected for research, you can change your mind at any time. Just contact the study doctor Christopher Dvorak, MD at the address below, and let us know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

Christopher Dvorak, MD
University of California San Francisco
[redacted]
San Francisco, CA 94143-1278

Benefits

Identifying and understanding specific factors that can influence drug levels in the body is important in order to help doctors better dose these drugs and prevent unwanted side-effects. The research that will be done with your blood may not help you. It might help people who have cancer and other diseases in the future. The benefits of research using blood include learning more about how your DNA may affect whether the study drug affects the disease.

Risks

The greatest risk to you is the risk of loss of privacy. Your blood samples will not be identified using your personal information. Your personal information will not be shared with the researchers. However, the researchers may have access to information about your health. There is a very small chance that your personal information may be released. We will do our best to make sure that your personal information is kept private.

Making Your Choice

Please read each sentence below and think about your choice. After reading the sentence, put your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call the UCSF Committee on Human Research at (415) 476-1814.
No matter what you decide to do, it will not affect your care.

My blood can be collected to study my DNA.

YES	*NO*

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Person Obtaining Consent

_____ _____
Date Signature of Witness (Required if participant is a non-English speaker)

IF (patient is between 13-17 years old):
The person being considered for this study is unable to consent for himself/herself because he/she is a minor. By signing below, you are giving your permission for your child to be included in this study.

Print name of subject _____

_____ _____
Date Parent or Legal Guardian

_____ _____
Date Parent or Legal Guardian

_____ _____
Date Person Obtaining Consent

_____ _____
Date Signature of Witness (Required if participant is a non-English speaker)