Romidepsin Maintenance After Allogeneic Stem Cell Transplantation

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT02512497	RECRUITING	JULY 31, 2015	JANUARY 7, 2020

STUDY DESCRIPTION

Brief Summary

The goal of this clinical research study is to learn if giving romidepsin before and after a stem cell transplant in combination with fludarabine and busulfan can help to control leukemia or lymphoma. Researchers also want to learn the highest tolerable dose of romidepsin that can be given with this combination. The safety of this combination and the safety of giving romidepsin after a stem cell transplant will also be studied. This is an investigational study. Romidepsin is FDA approved and commercially available for the treatment of CTCL in patients who have received at least 1 systemic (affecting the whole body) therapy before. Busulfan and fludarabine are FDA approved and commercially available for use with a stem cell transplant. The use of the combination of romidepsin, busulfan, and fludarabine to treat the type of leukemia or lymphoma you have is considered investigational. Up to 30 participants will be enrolled in this study. All will take part at MD Anderson.

Condition or Disease:
Cutaneous T-cell Lymphoma
T-Prolymphocytic Leukemia
T-Large Granulocytic Leukemia
T-Lymphoblastic Leukemia/Lymphoma
Peripheral T-Cell Lymphoma

Intervention/treatment:
Drug: Romidepsin
Drug: Busulfan
Drug: Fludarabine
Procedure: Stem Cell Transplant
Drug: Thymoglobulin

Phase: Phase 1

DETAILED DESCRIPTION

Study Parts and Study Drug Dose Levels:
If you are found to be eligible to take part in this study, you will start Part 1 of the study. During Part 1, you will receive the study drugs before having a stem cell transplant. If the disease is well controlled after the transplant and you are still eligible, you will start Part 2. During Part 2, you will continue to receive romidepsin. The study treatments given in each part are described in more detail below.
The dose of romidepsin you receive will depend on when you join this study. The first group of participants will receive the lowest dose level. Each new group will receive a higher dose than the group before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of romidepsin is found.
All participants will receive the same dose level of fludarabine. Busulfan dose levels are explained below.
Study Drug Administration and Transplant (Part 1):
The days before you receive the stem cell transplant are called minus days. The day you receive the stem cell transplant is called Day 0. The days after you receive the stem cell transplant are called plus days.
On Days -13 and -12, you will receive busulfan by vein over 3 hours. Blood (about 1 teaspoon each time) will then be drawn for pharmacokinetic (PK) testing up to 11 times over the 11 hours after the first busulfan dose. PK testing measures the amount of study drug in the body at different time points. The study staff will tell you more about the PK testing schedule. The test results will help the doctor decide what dose of busulfan you will receive during the study.
A heparin lock line will be placed in your vein before the PK testing to lower the number of needle sticks needed for these draws. If for any reason it is not possible for the PK tests to be performed, you will receive the standard dose of busulfan.
On Day -7, you will be admitted to the hospital.
On Day -6 through -3, you will receive romidepsin by vein over 4 hours, fludarabine by vein over 1 hour, and then busulfan by vein over 3 hours. PK testing up to 11 times over 11 hours will also be performed on Day -6 if the doctor thinks it is needed.
If you are going to be receiving a transplant from a matched unrelated donor, you will also receive antithymocyte globulin (ATG) by vein over 4 hours on the 3 days before the transplant. This drug is designed to further weaken your immune system to reduce the risk of rejecting of the transplant.
Beginning on Day -2, you will receive tacrolimus by vein over 24 hours every day until you are able to take it by mouth. Tacrolimus is designed to weaken the immune system and lower the risk of graft-versus-host-disease (GVHD - a reaction of the donor's immune cells against your body). Once you are able to take tacrolimus by mouth, you will take it every day for about 3 months, or until the doctor thinks it is safe to stop taking.
On Day 0, you will receive the donor's stem cells by vein. The infusion will last anywhere from about 30 minutes to several hours.
On Days +1, +3, +6, and +11, you will receive methotrexate by vein over about 15 minutes. Methotrexate is also designed to weaken the immune system and lower the risk of GVHD.
If the doctor thinks it is needed, you will be given other standard drugs to help lower the risk of side effects. You may ask the study staff for more information about how the drugs are given and their risks.
Romidepsin Maintenance Therapy (Part 2):
Starting between Day +28 and Day +100, if you are eligible for Part 2 based on the disease status, you will continue to receive romidepsin by vein over 1 hour once or twice a month. You may receive the doses at MD Anderson or at an oncologist's office close to where you live. The study doctor will discuss this with you.
Study Visits:
As a baseline test at the beginning of the study (within 7 days before starting romidepsin), blood (about 4 tablespoons) will be drawn for comparison purposes to learn if and how romidepsin may affect the disease and your immune system. If a bone marrow aspirate will be performed at this time, additional bone marrow aspirate will be collected for testing to see how romidepsin may have affected the disease and your immune system.
You will remain in the hospital for as long as the doctor thinks is needed.
Whenever your doctor thinks it is needed, blood (about 2 tablespoons) and/or urine will be collected for routine tests.
About ½-1, 3, 6, and 12 months after the transplant:
- You will have a physical exam.
- Blood (about 8 tablespoons) will be drawn to see how well the transplant has taken and to learn if and how romidepsin may have affected the disease and your immune system.
- If the doctor thinks it is needed, you will have a bone marrow aspiration to check the status of the disease. To collect a bone marrow aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow is withdrawn through a large needle. Additional bone marrow aspirate will be collected for testing to see how romidepsin may have affected the disease and your immune system.
The above tests/procedures may be performed sooner, if your doctor thinks they are needed. You may also have additional tests if your doctor thinks they are needed.
Before your first dose of romidepsin in Parts 1 and 2:
- You will have an electrocardiogram (EKG) to check your heart function.
- Blood (about 4 tablespoons) will be drawn to learn if and how romidepsin may have affected the disease and your immune system. Part of this blood sample will be used for a pregnancy test if you can become pregnant.
If you are in Part 2, every 2 weeks (before each dose of romidepsin), blood (about 4 tablespoons) will be drawn for routine tests. Part of this blood sample will be used for a pregnancy test if you can become pregnant. This may be repeated more often, if your doctor thinks it is needed.
If you are in Part 2, once a month:
- You will have an EKG.
- You will have a physical exam.
Part 2 participants may have the blood tests done before each romidepsin dose and monthly EKGs and physical exams performed either at MD Anderson or your local oncologist's office. If they are performed locally, the results should be sent to the study staff. You will need to return to MD Anderson to have tests and procedures performed at 3, 6, and 12 months after the transplant.
Length of Study:
You may receive up to 4 doses of romidepsin in Part 1. You may also receive chemotherapy on certain days between Day -13 and Day -3, and the stem cell transplant on Day 0. In Part 2, you may receive up to 24 cycles of romidepsin maintenance therapy as part of the study. Your participation on the study will be over after the follow-up visits. After 1 year, you will have routine follow-up with your transplant doctor.
You may be taken off study early if the doctor thinks it is in your best interest, if the disease gets worse or comes back, if intolerable side effects occur, if you have graft failure (the transplanted cells do not grow), or if you are unable to follow study directions.
If for any reason you want to leave the study early, you must talk to the study doctor. It may be life-threatening to leave the study after you have started to receive the study drugs but before you receive the stem cell transplant because your blood cell counts will be dangerously low.

STUDY DESIGN

Study Type:	Interventional
Estimated Enrollment :	10 participants
Intervention Model :	Single Group Assignment
Masking:	None (Open Label) ()
Primary Purpose:	Treatment
Official Title:	Romidepsin Therapy in Conditioning and Maintenance in Patients With T-Cell Malignancies Receiving Allogeneic Stem Cell Transplant

Actual Study Start Date:	December 2017
Estimated Primary Completion Date:	December 2020
Estimated Study Completion Date:	December 2020

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Romidepsin + Busulfan + Fludarabine + Stem Cell Transplant Part 1: Busulfan administered at the dose calculated to achieve a total (including first two doses delivered on Day -13 and -12) systemic exposure of 20,000 ± 12% µMol-min based on the pharmacokinetic studies. Fludarabine 40 mg/m2 by vein on Days -6 to -3. Romidepsin dosed per actual body weight/actual body surface area. Romidepsin administered on Day -6, -5, -4, and -3 at escalating doses of 1 mg/m2, 2 mg/m2, and 3 mg/m2 by vein to determine the optimal dose. Participants receiving a graft from a matched unrelated donor receive rabbit Thymoglobulin; 0.5 mg/kg on Day -3, 1.5 mg/kg on Day -2 and 2.0 mg/kg on Day -1. Stem cell infusion on Day 0. Romidepsin Maintenance Therapy - Part 2: Starting between Day +28 and Day +100, if participant is eligible based on disease status, they will continue to receive Romidepsin 8 mg/m2 by vein over 1 hour on Day 1 of each 2-week cycle.	Drug: Romidepsin Part 1: Romidepsin dosed per actual body weight/actual body surface area. Romidepsin administered on Day -6, -5, -4, and -3 at escalating doses of 1 mg/m2, 2 mg/m2, and 3 mg/m2 by vein to determine the maximal tolerated dose. Romidepsin Maintenance Therapy - Part 2: Starting between Day +28 and Day +100, if participant is eligible based on disease status, they will continue to receive Romidepsin 8 mg/m2 by vein over 1 hour on Day 1 of each 2-week cycle. Drug: Busulfan Part 1: First 2 doses of Busulfan of 80 mg/m2 administered on day -13 and -12. Busulfan administered at the dose calculated to achieve a total (including first two doses delivered on Day -13 and -12) systemic exposure of 20,000 ± 12% µMol-min based on the pharmacokinetic (PK) studies. An additional standard of care (SOC) option is now added for those with an HCT-CI >4 or deemed unfit by the investigator to receive full dose (AUC 5000 umol-min) Time-Sequential (TS) Busulfan. SOC busulfan is administered per OSU SCT SOP with a targeted AUC of 4000 umol-min/day for a total exposure of 16,000 umol-min +/- 12% u-Mol-min based upon PK studies. Busulfan 'test-dose' PK studies will be performed prior to administration of full dose of busulfan per SOC. Romidepsin and fludarabine will be administered in an identical fashion using the SOC busulfan as with the TS busulfan. TS busulfan method of busulfan administration will be the preferred method of conditioning therapy for patients enrolled. Drug: Fludarabine Part 1: Fludarabine 40 mg/m2 by vein on Days -6 to -3. Procedure: Stem Cell Transplant Stem cell infusion on Day 0. Drug: Thymoglobulin Participants receiving a graft from a matched unrelated donor receive rabbit Thymoglobulin; 0.5 mg/kg on Day -3, 1.5 mg/kg on Day -2 and 2.0 mg/kg on Day -1.

OUTCOME MEASURES

Primary Outcome Measures: 1. Toxicity of Romidepsin with Busulfan and Fludarabine Conditioning Therapy for Allogeneic Stem Cell Transplantation [Time Frame: 30 days]
Toxicity defined as death from any cause, grade 3 or 4 graft-versus-host disease, grade 3-4 mucositis lasting for more than 3 days at peak severity, or or grade 3 or 4 non-hematologic non-infectious toxicity within 30 days of receiving the first Romidepsin administration on day -6 (day 24 post allosct).
2. Efficacy of Romidepsin with Busulfan and Fludarabine Conditioning Therapy for Allogeneic Stem Cell Transplantation [Time Frame: 30 days post allosct]
Efficacy defined as the participant being engrafted and alive at day 30 post allosct.

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 to 70 Years (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
- Age 18 to 70 years of age.
- Diagnosis of either Cutaneous T-Cell Lymphoma; T-Prolymphocytic Leukemia; T-Large Granulocytic Leukemia; T-Lymphoblastic Leukemia/lymphoma; or Peripheral T-Cell Lymphoma, Natural Killer/T-cell lymphoma for whom allogeneic stem cell transplantation is indicated.
- An 10/10 or 8/8 HLA matched (high resolution typing at A, B, C, DRB1, DQ1) sibling or unrelated donor.
- EF>/= 50% on MUGA scan or Echocardiogram.
- FEV1, FVC and corrected DLCO >/= 40%.
- Adequate renal function, as defined by estimated serum creatinine clearance >/=50 ml/min (using the Cockcroft-Gault formula: creatinine clearance = [(140-age)*kg/(72*serum creatinine)] * 0.85 if female) and/or serum creatinine 40% of their IBW, then adjusted body weight will be utilized.
- Serum bilirubin </= 1.5 x upper limit of normal. - SGOT and SGPT /=10,000 copies/mL, or >/= 2,000 IU/mL).
- Evidence of either cirrhosis or stage 3-4 liver fibrosis in patients with chronic hepatitis C or positive hepatitis C serology.
- HIV infection.
- Hematopoetic Transplant Co-Morbidity Index (HCT-CI) >4 unless deemed clinically insignificant by primary investigator for patients receiving Time-Sequential Busulfan (total exposure 20000 umol-min).
- Active uncontrolled bacterial, viral or fungal infections.
- Exposure to other investigational drugs within 4 weeks before enrollment.
- Grade >/= 3 non-hematologic toxicity from previous therapy that has not resolved to 500 ms.
- Myocardial infarction within 1 year of study entry. Subjects with a history of myocardial infarction between 6 and 12 months prior to study entry who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event may participate;
- Other significant EKG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min);
- Symptomatic coronary artery disease (CAD), e.g., angina Canadian Class II-IV. In any patient in whom there is doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;
- An EKG recorded at screening showing evidence of cardiac ischemia (ST depression depression of >/= 2 mm, measured from isoelectric line to the ST segment). If in any doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;
- Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions and/or ejection fraction <40% by MUGA scan or /= 160/95; patients who have a history of hypertension controlled by medication must be on a stable dose and meet all other inclusion criteria; or,
- Any cardiac arrhythmia requiring an anti-arrhythmic medication (excluding stable doses of beta-blockers).
- Patients taking drugs leading to significant QT prolongation where the interaction is too great to proceed with romidepsin.
- Concomitant use of CYP3A4 inhibitors where the interaction is thought too great to proceed with romidepsin.

CONTACTS AND LOCATIONS

Contacts

Contact:

Locations

United States, Ohio	The Ohio State University Cancer Center	Columbus

Sponsors and Collaborators

Ohio State University Comprehensive Cancer Center

Celgene Corporation

Investigator

Principal Investigator :	Jonathan Brammer, MD	The Ohio State University Comprehensive Cancer Center

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MORE INFORMATION

Responsible Party :	Ohio State University Comprehensive Cancer Center
ClinicalTrials.gov Identifier :	NCT02512497
Other Study ID Numbers :	OSU-16242, NCI-2015-01555
First Posted :	July 31, 2015
Last Update Posted :	January 7, 2020
Last Verified :	January 2020
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	No
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No

Keywords provided by Ohio State University Comprehensive Cancer Center:	*Fludara* *FK228* *Busulfan* *Cutaneous T-cell Lymphoma* *T-Prolymphocytic Leukemia* *T-PLL* *T-Large Granulocytic Leukemia* *T-LGL* *T-Lymphoblastic Leukemia/Lymphoma* *T-ALL* *Peripheral T-Cell Lymphoma PTCL* *Allogeneic stem cell transplantation* *Romidepsin* *Istodax* *Depsipeptide* *CTCL* *Busulfex* *Myleran* *Fludarabine phosphate* *Fludarabine*
Additional relevant MeSH terms :	*Lymphoma* *Leukemia* *Precursor Cell Lymphoblastic Leukemia-Lymphoma* *Leukemia, Lymphoid* *Lymphoma, T-Cell* *Lymphoma, T-Cell, Peripheral* *Lymphoma, T-Cell, Cutaneous* *Leukemia, Prolymphocytic* *Leukemia, Myeloid* *Leukemia, Prolymphocytic, T-Cell*