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PI: Dr. Amer Zeidan

Title: GLAD-AML - Glasdegib (Pf-04449913) With Two Standard Decitabine Regimens for Older Patients With Poor-risk Acute Myeloid Leukemia

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Principal Investigator:	Amer Zeidan, MBBS, MhS	**Sponsor Protocol/HIC #:**	2000024738
Funding Source:	Yale University	**Protocol Number:**	PF-04449913
Sponsor ICF Template Version:	05/31/2019	**Sponsor Protocol Date:**	31-May-2019

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: SMILOW CANCER HOSPITAL

Study Title: A randomized, parallel-arm, phase 2 clinical trial of the combination of glasdegib (PF-04449913) with two standard decitabine regimens for patients with poor-risk acute myeloid leukemia who are unfit for or refuse intensive chemotherapy

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Funding Source: Yale University

Main Consent Form

INVITATION TO PARTICIPATE AND DESCRIPTION OF PROJECT

You are invited to take part in a research study. The research study is designed to look at the effectiveness and safety of a combination of a drug called glasdegib (Daurismo®, Pfizer Inc.) and decitabine at different dosing schedules. You have been invited to take part because you have a disease called Acute Myeloid Leukemia (AML) and you will not receive intensive chemotherapy.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study.

A member of the research team will discuss the study with you. This discussion should go over all aspects of this research: the purpose and nature of the research study, the procedures that will be performed, the risks of the study drug(s) and procedures, possible benefits, possible alternative treatments, your rights as a participant and other information about the research study. You should take whatever time you need to discuss the research study with your physician and family. The decision to participate or not is yours. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign and date where indicated on this form.

If you choose to participate, you will be told of any significant new findings that develop during the course of your participation in this study that may affect your willingness to continue to participate.

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Yale University is providing funding for the study and is responsible for the conduct of the study. Pfizer, Inc. is the maker of glasdegib and will be providing it for use in this study. Yale Cancer Center is called the Sponsor

PURPOSE

The purpose of this study is to investigate how well the study drug, glasdegib (Dautismo, Pfizer Inc.), in combination with decitabine works in treating patients with AML. The study will evaluate two dosing schedules of decitabine.

The study drug that will be used in this research study is known as glasdegib. Glasdegib is an oral medication which works by preventing the growth of cells that are thought to become AML cells. This may also help drugs like decitabine work better. Glasdegib is approved by the Food and Drug Administration for treatment of adult patients aged 75 years or older newly diagnosed with AML who will not receive intensive chemotherapy when used in combination with a low dose of another drug cytarabine. In this study the combination of Glasdegib and Decitabine is considered experimental.

Decitabine, also known as Dacogen^{TM}, is approved by the FDA in the United States for the treatment of subjects with myelodysplastic syndrome "MDS" (a disorder that disrupts the production of blood cells). Although decitabine is not approved in the United States specifically for the treatment of AML, it is sometimes used as an alternative to standard AML chemotherapy in some subjects who might not be able to tolerate standard chemotherapy.

You have been diagnosed with AML that is classified as poor-risk disease. Certain genetic abnormalities in your leukemia cells make you "poor-risk". This means you are less likely to respond to traditional and even intensive chemotherapy. Also, some patients who are not able to receive intensive chemotherapy. Because of these issues, novel ways of approaching patients diagnosed with poor-risk AML are needed and are showing promise. Decitabine is being used in this study for investigational use in combination with glasdegib to see if it improves outcomes of older patients with AML. Decitabine will be administered intravenously (into a vein) daily for the first 5 days of a cycle. The length of a cycle will be 21-28 days. Your doctor will decide the length of the cycle depending on how well your body tolerates chemotherapy and when you are ready to receive another cycle; this will depend on several factors such as your blood counts, electrolytes, and how you are feeling.

Decitabine is a drug that has been reported to induce responses for patients with poor-risk AML Decitabine has traditionally administered daily for five consecutive days on a monthly basis. Some studies have suggested that longer consecutive dosing (e.g. for ten days every month) is more effective without a significant increase in side effects. However, other studies shown no clear difference between these two dosing schedules.

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STUDY PROCEDURE

Your study doctor will decide how long you will receive study drug, depending on how well your disease responds to study regimen and how well you tolerate the therapy. The number of visits you will need to make to the clinic will depend on how long you continue the study regimen.

You will either receive glasdegib with decitabine on a five-day schedule or a ten-day schedule. You will be randomized to which group you are in. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group. Glasdegib will be given daily, every day starting from the day you start the study. Decitabine will be given daily for either five days or ten days (depending on to which group you are in). Each cycle lasts 28 days.

Prior to starting the study and periodically throughout the study period, you will undergo a bone marrow biopsy. During this procedure samples of your bone marrow are collected to look for any leukemia cells and to evaluate the status of your disease and determine the initial response to the treatment. Should you respond to the therapy, you could remain on the study for up to 24 months. If your disease has progressed, you will be taken off the study. Your Study Doctor will review the results with you and recommend the course of action at that time. There is always a risk that despite the initial response disease can relapse at any time during the study. If this happens, you will be taken off the study, and your Study Doctor will review the status of the disease and recommend the course of action at that time.

It is expected that approximately 51 subjects will participate in this study at approximately 4 study sites. Up to 26 subjects will participate in each of the groups. It is expected that approximately 20 subjects will be enrolled at Yale Cancer Center. Considering that the study includes a maximum of twenty-four 28-day cycles, this study is estimated to last up to 2 years after enrollment.

Tests and procedures that would be performed for your regular cancer care whether you are on this study or not, are called "standard of care." All of the tests and procedures listed below that will be performed at your study visits, should you choose to participate in this study, are standard of care unless noted with an asterisk (*****).

SCREENING PERIOD (SCREENING AND BASELINE)

If you agree to participate and sign and date this form, you will need to undergo a series of tests and procedures to determine if you are eligible to participate in this research study. You will come to the study site for screening tests and it is possible that more than one screening visit may be needed.

The following tests or procedures will be performed during the visit(s) within 28 days prior to the first dose of the study drug.

- Disease history of poor-risk AML;

- Medical history to review conditions and prior medical treatments, including questions on your ability to care for yourself, daily activity, and physical ability;
- Review and documentation of all medications you currently take;
- Physical examination, including height (at screening only), weight and vital signs.
- **C**onfirmation of all eligibility criteria;
- *Electrocardiogram (ECG), done 3 times in a row; this measures the electrical activity of your heart;
- Blood sample collection to evaluate your kidneys, liver, and electrolytes, and blood counts (hemoglobin, white blood cell count, and platelets); approximately 2 teaspoons of blood are drawn;
- Urine sample collection for urinalysis testing;
- Pregnancy test within 72 hours prior to the receiving first dose of study drug
- Review and documentation of all medications you currently take;
- Bone marrow biopsy and aspiration to measure the status of your leukemia.

At the end of screening, the study doctor will determine if you are eligible to continue into the study. If you are not able to continue in the study, the study doctor will explain why and will discuss other treatment options with you.

STUDY DRUG TREATMENT PERIOD

The following is a list of evaluations that you will undergo during the study drug treatment period of this study on day visits:

- **During the First Cycle**
  - Update of interval events and physical examination (on days 1 and 15);
  - Questions on your ability to care for yourself, daily activity, and physical ability;
  - Review and documentation of all medications you take at that time (on days 1 and 15);
  - Recording of any side effects from the study drug (on days 1 and 15);
  - *ECG, to measure the electrical activity of the heart; it is done on day 1; each time ECG is done 3 times in a row;
  - Pregnancy testing and contraception reminders (days 1 and 15);

- Blood samples to evaluate your kidneys, liver, and electrolytes and blood counts (hemoglobin, white blood cell count, and platelets); approximately 2 teaspoons of blood are drawn on days 1 and 15; these may be repeated as required;
- Drug administration:
    - Decitabine 20 mg/m^2 is administered by IV infusion (into a vein) over 1 hours on days 1-5 *or* days 1-10 depending on which dosing schedule to which you were randomly assigned
    - Glasdegib 100 mg daily is administered orally daily every day throughout the study period

- **During Cycles 2-6**
    - Update of interval events and physical examination (on day 1);
    - Questions on your ability to care for yourself, daily activity, and physical ability;
    - Review and documentation of all medications you take at that time (on day 1);
    - Recording of any side effects from the study drug (on day 1);
    - *ECG, to measure the electrical activity of the heart; it is done on day 1; each time ECG is done 3 times in a row;
    - Pregnancy testing and contraception reminders (day 1)
    - Blood samples to evaluate your kidneys, liver, and electrolytes and blood counts (hemoglobin, white blood cell count, and platelets); approximately 2 teaspoons of blood are drawn on day 1; these may be repeated as required;
    - Drug administration:
        - Decitabine 20 mg/m^2 is administered by IV infusion (into a vein) over 1 hours on days 1-5 *or* days 1-10 depending on which dosing schedule to which you were randomly assigned
        - Glasdegib 100 mg daily is administered orally daily every day throughout the study period
    - Review of drug diary

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- Bone marrow biopsy and aspirate to evaluate the status of leukemia and assess the amount of disease by measuring a metric called Measurable Residual Disease (MRD); the procedure is performed after the completion of cycles 2, 4 and 6

- **During Cycles 7-24**
  - Update of interval events and physical examination (on day 1);
  - Questions on your ability to care for yourself, daily activity, and physical ability;
  - Review and documentation of all medications you take at that time (on day 1);
  - Recording of any side effects from the study drug (on day 1);
  - *ECG, to measure the electrical activity of the heart; it is done on day 1; each time ECG is done 3 times in a row;
  - Pregnancy testing and contraception reminders (day 1)
  - Blood samples to evaluate your kidneys, liver, and electrolytes and blood counts (hemoglobin, white blood cell count, and platelets); approximately 2 teaspoons of blood are drawn on day 1; these may be repeated as required;
  - Drug administration:
  - Decitabine 20 mg/m^2 is administered by IV infusion (into a vein) over 1 hours on days 1-5 *or* days 1-10 depending on which dosing schedule to which you were randomly assigned
  - Glasdegib 100 mg daily is administered orally daily every day throughout the study period
  - Bone marrow biopsy and aspirate to evaluate the status of leukemia and assess the amount of disease by measuring a metric called Measurable Residual Disease (MRD); the procedure is performed after the completion of cycles 12, 16, and 24
  - Review of drug diary

Your study doctor may schedule visits (unplanned visits), in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect your wellbeing and assess the status of your disease. You will also be provided with an emergency contact card. The card will contain instructions to ensure access to medical advice in the event that study related medical questions or problems arise.

What Happened If I Stop Taking the Study drug?

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If you decide to stop taking the study drug combination, or if the study doctor decides that it is in your best interest to stop your study drug treatment period with the study drug combination, you will be asked to:

- Attend the clinic for an End of Treatment Visit;
- Take part in the Long-term Follow-up stage of the study

POST-STUDY DRUG TREATMENT (FOLLOW-UP/END OF STUDY)

Within 14 days after the last dose of the study drug, the following evaluations will be conducted:

- Physical examination
- Questions on your ability to care for yourself, daily activity, and physical ability;
- *ECG, to measure the electrical activity of the heart; it is done on day 1; each time ECG is done 3 times in a row;
- Pregnancy testing and contraception reminders (day 1)
- Blood sample collection to evaluate your kidneys, liver, and electrolytes as well as your blood counts (hemoglobin, white blood cell count, and platelets); approximately 2 teaspoons of blood are drawn;
- Recording of any side effects including those from the study drug;
- Review and documentation of all medications you currently take.
- Review of drug diary

If you have a suspected study drug-related side effect at the last follow-up visit, you will be followed until it resolves or until the event is considered irreversible. This may require additional clinical assessments and laboratory tests.

After the end of the study period in the clinical trial, your doctor will provide you with appropriate and available alternative therapy that will be the best for you. The study doctor or the study staff will contact you or your caregiver by phone every 3 months (90 days) for a total period of 2 years. They will collect information about your health status, further treatments (including start and stop date), and follow-up of any unresolved side effect of the study drug. You are free to refuse these contacts and just have to tell the study doctor or study staff. Your decision will not affect your future medical care.

How will I receive the study drug?

Glasdegib will be provided as tablets in childproof packaging. It is important that no one else take this study drug. Glasdegib should be stored at room temperature and handled with care. You

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should keep your study drug in the bottles provided by the study team and not transfer the tablets to any other container since accidental ingestion of this drug may cause serious toxicity, especially to children and pregnant women

Always bring your glasdegib bottle to the clinic with you.

You should take your study drug by mouth with approximately 8 ounces (240 mL) of water once a day, in the morning, with or without food, approximately at the same time each day. Tablets must be swallowed whole, not crushed, cut or chewed prior to swallowing.

Do not take more than the prescribed dose of glasdegib at any time.

If you forget to take your dose at the regularly scheduled time, and if less than 12 hours have passed since the scheduled dosing time, take that dose as soon as possible. If more than 12 hours have passed since the scheduled dosing time, do not take your dose that day (skip that dose). Continue your normal dosing schedule the next day.

If you do miss a dose, do not "make it up" the next day.

If you vomit at any time after taking a dose, do not "make it up," but resume subsequent doses the next day as prescribed.

If you inadvertently take 1 extra dose during a day, you should not take the next dose of glasdegib.

You will be issued a dosing diary in which you must ensure all doses (including any missed) are documented daily. This diary must be brought to each clinic visit.

On days of scheduled study visits, you will take your dose in the clinic when your nurse tells you to take it, so ECGs can be performed after the dose and blood can be drawn before and after this dose on some days. On these days, do not take glasdegib before your clinic visit.

Subject Responsibilities and Special Instructions
During this study, it is important that you:

- Follow your study doctor's instructions and come to the clinic for every scheduled visit;
- Tell your study doctor about all of the medications and treatments you are receiving within 28 days before starting the study, while you are being treated with study drug, and during the Follow Up. This includes "over the counter" medications, herbal and natural remedies, and vitamins in addition to prescription medications. Your study doctor will let you know if your medications can be taken with glasdegib and decitabine;

- On the days that you visit the clinic, do not take study drug until asked to by the study team;
- Record all of your doses of study drug and the time taken in the dosing diary and return the diary to the clinic;
- Store the study drug as instructed, and bring all your used and unused study drug and study drug containers with you to the study visits;
- Certain foods, such as grapefruit juice, and certain other medications will not be allowed during your participation in the study. Your doctor will review these prohibited medications with you;
- During study drug treatment with glasdegib, you are advised Not to donate blood or blood products for at least 180 days after the last dose.
- If you are a Male, you are advised not to donate semen during study drug treatment with glasdegib and for at least 180 days after the last dose.
- Inform the study doctor or staff if you decide you no longer wish to participate in the study. You will be required to complete a close out visit.
- Report any new problems, side effects, illnesses, scheduled surgeries or procedures, or changes in medication during the study;
- Report if you (or your partner, if you are a man) become pregnant;

POTENTIAL RISKS, SIDE EFFECTS, DISCOMFORTS AND INCONVENIENCES

While receiving study drug and undergoing procedures as a subject enrolled in this study, you may experience side effects. This section describes potential side effects of the study drugs and procedures based on previous studies. However, there might be additional risks that currently remain unknown. If significant new risks develop during the course of the study that could affect your willingness to participate, information will be reported to you as soon as possible.

Possible side effects that you may experience during this study will be fully explained to you by the study staff. Please ask as many questions as you feel necessary so that you can understand the possible adverse effects of specific drugs and procedures you will receive before you decide whether you want to be in this study. Please ask the study doctor or the study staff to explain any information or words that are not clear to you.

Unforeseen side adverse effects may occur, and you should inform your study doctor of any side effects that you experience, even if you do not think they are related to the study drug or are not mentioned in this consent form.

Some side effects may be serious and require treatment or additional testing.

Risks associated with glasdegib

Risks are possible side effects of glasdegib and those related to medical procedures performed in the study. Throughout the study your Study Doctor will guide you through assessment and, if necessary, treatment of study-drug related adverse effects.

The following are side effects of glasdegib according to how likely they are to occur:

MOST COMMON: (These side effects occurred in **20% or more** of patients taking glasdegib alone or glasdegib in combination with chemotherapy.)	
Dysgeusia (abnormal taste)	Hemorrhage (bleeding)
Decreased appetite	Febrile Neutropenia (fever due to low white blood cell counts)
Fatigue (feeling tired)	Thrombocytopenia (decreased platelet count)
Diarrhea	Edema (swelling)
Nausea	Mucositis (mouth blisters / sores)
Muscle Spasms	Musculoskeletal Pain
Anemia (low red blood cells)	Dyspnea (shortness of breath)
Creatinine Increase (abnormal kidney test)	Hyponatremia (low blood levels of sodium)
Hypomagnesemia (low blood levels of magnesium)	AST Increased (abnormal liver test)
Blood Bilirubin Increase (abnormal liver test)	ALT Increase (abnormal liver test)
Alkaline Phosphatase Increased (abnormal liver test)	Constipation
Rash	

COMMON: (These side effects occurred in **10-20%** of patients taking glasdegib alone or glasdegib in combination with chemotherapy.)	
Hair loss	Hyperkalemia (high potassium)
Vomiting	CPK Increased (muscle damage)
Decreased weight	Hypokalemia (low blood levels of potassium)
Arthralgia (joint pain)	Pyrexia (fever)
Chest Pain	Abdominal Pain
Cough	Dizziness

Headache	Pneumonia
Leukopenia (decreased white blood cells)	Atrial Arrhythmia (irregular heartbeat)
Renal Insufficiency (decreased kidney function)	

UNCOMMON: (These side effects occurred in **less than 10%** of patients taking glasdegib alone or glasdegib in combination with chemotherapy.)	
QT prolongation (a disorder of the heart's electrical activity, which can lead to death)	Dental Problems

Risks associated with decitabine

The following are side effects of decitabine according to how likely they are to occur:

MOST COMMON: (These side effects occurred in **20% or more** of patients taking decitabine alone or decitabine in combination with chemotherapy.)	
Neutropenia (low white blood cells)	Pneumonia
Thrombocytopenia (low number of platelets)	Hyperglycemia (high blood sugar)
Anemia (low number of red blood cells)	Hypoalbuminemia (low level of albumin)
Febrile neutropenia (fever due to low white blood cell counts)	Hypomagnesemia (low levels of magnesium in the blood)
Leukopenia (low white blood cells)	Hypokalemia (low levels of potassium)
Nausea	Arthralgia (joint pain)
Constipation	Headache
Diarrhea	Insomnia (difficulty sleeping)
Vomiting	Cough
Pyrexia (fever)	Ecchymosis (bruising)
Edema peripheral (swelling of the arms and legs)	Petechiae (tiny dots on the skin)
Rigors (chills)	Pallor (lightening of skin)
Fatigue	

COMMON: (These side effects occurred in **10-20%** of patients taking decitabine alone or decitabine in combination with chemotherapy.)	
Lymphadenopathy (lymph node swelling)	Ascites (fluid in the abdomen)
Abdominal pain	Edema (swelling)
Oral mucosal petechiae (small red or	Pain

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purple spots in the mouth)	
Stomatitis (mouth blisters / sores)	Lethargy (sleepiness)
Dyspepsia (heart burn)	Tenderness
Hyperbilirubinemia (abnormally high levels of bilirubin in the blood)	Cellulitis (skin infection)
Candidal infection (infection)	Cardiac murmur (abnormal heart sound)
Blood alkaline phosphatase increased (abnormal liver tests)	AST Increase (abnormal liver tests)
Blood urea increased (abnormal kidney test)	Hyponatremia (decreased levels of sodium)
Appetite decreased	Pain in limb
Hyperkalemia (high levels of potassium)	Dizziness
Back pain	Confusional state (confusion)
Hypoesthesia (numbness)	Pharyngitis (sore throat)
Anxiety	Breath sounds decreased
Crackles lung	Rash
Hypoxia (low oxygen level)	Skin sores
Erythema (skin redness)	Toothache
Pruritis (itchy skin)	Chills
Asthenia (weakness)	Upper Respiratory Tract Infection

UNCOMMON: (These side effects occurred in **less than 10%** of patients taking decitabine alone or decitabine in combination with chemotherapy.)	
Thrombocythemia (high blood platelet count)	Pulmonary edema (fluid in the lungs)
Vision blurred	Gingival bleeding
Hemorrhoids	Loose stools
Tongue ulceration	Dysphagia (difficult swallowing)
Oral soft tissue disorder	Lip ulceration
Abdominal distension	Abdominal pain upper
Gastro-esophageal reflux disease	Glossodynia (tongue pain)
Chest discomfort	Intermittent pyrexia (fever)
Fall	Malaise (lack of energy)
Crepitations (difficulty breathing)	Catheter site redness
Catheter site pain	Injection site swelling
Catheter related infection	Urinary tract infection
Staphylococcal infection (infection)	Oral candidiasis (oral infection)
Sinusitis (sinus infection)	Bacteremia (infection)
Transfusion reaction	Abrasion
Blood lactate dehydrogenase increased	Blood albumin decreased (abnormal blood test)

(abnormal blood test)	
Blood bicarbonate increased (abnormal blood test)	Blood chloride decreased (abnormal blood test)
Protein total decreased (abnormal blood test)	Blood bicarbonate decreased (abnormal blood test)
Blood bilirubin decreased (abnormal liver test)	Dehydration
Chest wall pain	Musculoskeletal discomfort
Myalgia (muscle pain)	Dysuria (difficult and/or painful urination)
Urinary frequency	Rales (difficulty breathing)
Postnasal drip	Alopecia (hairloss)
Urticaria (hives)	Swelling face
Hypotension (low blood pressure)	Hematoma (a bruise)
Pancytopenia (abnormal blood test)	Cardiac Failure Congestive
Tachycardia (irregular heart beat)	Ear Pain
Gastro-esophageal Reflux Disease	Dysphagia (difficulty swallowing)
Oral Pain	Oral Inflammation
Pneumonia	Tooth Abscess
Contusion (bruising)	Weight Decrease
Breath Sounds Abnormal	Muscle Spasms Muscle Weakness
Bone Pain	Musculoskeletal Pain

Risks associated with glasdegib in combination with Decitabine:
In studies where patients received low dose chemotherapy in combination with glasdegib the most common side effects were anemia (you don't have enough healthy red blood cells to carry adequate oxygen), febrile neutropenia (development of fever, often with other signs of infection), nausea (precursor to vomiting the contents of the stomach), decreased appetite, fatigue and thrombocytopenia (When you have a low blood platelet count).

OTHER RISKS:

Blood Collection and Intravenous (IV) catheter placement
Some tests done by having blood samples taken. The risks of taking blood may include pain, redness, swelling and/or bruising where the needle enters your body, light-headedness and fainting. Rarely, these may be a small blood clot or infection at the site of the needle puncture. Blood will be taken at each visit for standard medical and study-specific tests. A blood pressure cuff may also cause discomfort or bruising to the upper arm.

***Electrocardiogram (ECG)**
An ECG is an electrical tracing of your heart's activity. During the procedure, you will have electrodes (small sticky patches with wires attached to them) placed on your chest skin, arms and legs. There may be some pulling on your skin or irritation, similar to pulling off an adhesive

bandage, when the patches are removed. Some amount of adhesive material may remain on your skin, and usually is harmless. Mild redness may remain at the sites where a patch or patches were attached; usually the redness disappears within a few minutes. In rare instances, the redness may persist and/or itchiness at the site(s) where a patch or patches were attached may develop. In this case, a Study Doctor may recommend an antihistamine medication such as diphenhydramine (Benadryl).

Contraception and Pregnancy

If you are a man and considering to be a participant in the study, you must agree to use a condom during intercourse while taking the drug, and not to father a child during the study and for the period of 6 months following the last study treatment. In addition, it is advised that your female partner uses a highly effective form of birth control method (contraception, see below) if she may become pregnant. In case you father a child while in this study, you are asked to report the pregnancy to the Study Doctor. **A consent from your partner will be needed to allow your Study Doctor to medically follow this pregnancy until delivery to monitor the mother's and child's safety.**

Women who are pregnant or nursing a child cannot participate in this trial. Women should not nurse for at least 6 months after stopping the study drug. You must confirm, to the best of your knowledge, that you are not pregnant at the onset of the study, and that you do not intend to become pregnant during the trial.

For the purposes of this study you are considered to be able to become pregnant unless you previously had surgery to have your ovaries and/or uterus removed, or it has been more than 12 months since your last menstrual period. If you are a woman who is able to become pregnant, and considering to be a participant in the study, it is important that you use a highly effective form of birth control method (contraception, see below) during the trial and **6 months** after your study has ended. Highly effective methods of birth control have a less than 1% chance of unwanted pregnancy during one year, if used appropriately according to the instructions of the manufacturer. Please discuss with your Study Doctor the most appropriate birth control method for you that also respect your cultural and religious preferences. Examples of highly effective birth control methods are:

- Total abstinence (no sexual relations), when this is in line with your preferred and usual lifestyle. Periodic abstinence like calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception;
- Female sterilization, when you have been already surgically sterilized prior to the study by surgical removal of both ovaries (woman's reproductive system that stores and releases eggs for fertilization and produces female sex hormones), total hysterectomy (surgical removal of the uterus and cervix) or tubal ligation (getting your "tubes tied") at least six weeks before taking study drug;
- Your male partner has already been sterilized with the appropriate documentation. The sterilized male partner should be your sole partner;
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception (in case of oral contraception you

should have been using the same pill on a stable dose for a minimum of 3 months before taking study drug).

It is currently unknown whether glasdegib or decitabine may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception. If you become pregnant or suspect being pregnant during study drug period or within 3 months after completing study drug period, you must inform the Study Doctor immediately, and you have to stop ongoing study drug treatment immediately. You will not be allowed to continue this study if you are pregnant. Your Study Doctor will medically follow your pregnancy until delivery to monitor you and your child`s safety.

There are no well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant.

Other Side Effects

Infertility in Male Mice
Male mice given repeated doses of Glasdigib showed significant decreases in sperm count with resultant pregnancy rate reduction and an increase in pre-implantation loss in female mates. Men are advised to seek advice on effective fertility preservation before going on study drug (Glasdegib) treatment.

There may also be side effects, other than listed above that we cannot predict. Other drugs will be given to make side effects that occur less serious and less uncomfortable. Many side effects go away shortly after the drug or procedure is stopped, but in some cases side effects can be serious, long lasting, or permanent.

For more information about risks and side effects, ask the researcher or contact their office at 203-737-7078.

BENEFITS

If you agree to take part in this research study, we cannot guarantee that you will receive any benefits. We hope that the addition of Glasdegib to Decitabine will increase the rate of remission observed with the current standard of care. Moreover, we hope the information learned from this research study may benefit other patients with acute myeloid leukemia in the future.

ECONOMIC CONSIDERATIONS

You will not be paid for taking part in this study. Tests and procedures that would be performed for your regular cancer care whether you are on this study or not are called “standard of care.” All of the tests and procedures listed in this consent form that will be performed at your study visits are standard of care unless noted with an asterisk (*). There will be no charge to you or your insurance provider for the study drug(s), glasdegib and decitabine. The administration of the study drug(s), glasdegib and decitabine, will be charged to you or your insurance provider. There will

be no charge to you or your insurance provider for tests or procedures noted with an asterisk as these are performed for study purposes only. All other tests and procedures will be charged to you or your insurance provider in the usual way as these are standard of care. This may include other tests and procedures not listed in this consent if your doctor feels it is necessary for your care, such as additional laboratory tests.

You will still be responsible for any co-pays required by your insurance company for standard treatment

Taking part in this research study may lead to added costs for you or your insurance provider. You are encouraged to speak with your insurance provider prior to entering the research study to find out your individual coverage. If you have difficulty determining your individual insurance coverage, you may call Dr. Amer Zeidan's office for assistance at 203-737-7078.

There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you or your family.

You will not be paid for taking part in this study. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study.

ALTERNATIVE TO TAKING PART IN THIS STUDY

You do not have to participate in this study. There are alternative treatments that may be of benefit to you. These would include:

- Getting standard of care treatment for your cancer without being enrolled in a study;
- Taking part in another study;
- Receiving no further treatment.
- Comfort Care: This is a type of care that helps reduce pain, tiredness, appetite problems, and directed to alleviate symptoms caused by the cancer. Comfort Care does NOT treat cancer directly but aims to improve how you feel. Comfort Care tries to keep you as active and comfortable as possible.

Some patients may be able to receive treatment with VENCLEXTA® (venetoclax) in combination with low dose azacitidine or decitabine or low-dose cytarabine. This combination is approved by the FDA for treatment of newly diagnosed patients with AML who are 75 or older or who cannot receive intensive chemotherapy.

These alternatives will be discussed with you by your physician prior to your enrollment into this study. You may elect to have no further treatment and to receive supportive care only. You do not need to participate in this study to receive treatment for your condition.

Talk to your doctor about your choices before you decide if you will take part in this study.

Confidentiality and Authorization to collect, use and disclose Protected Health Information

For purposes of this study, Yale University, Yale-New Haven Hospital, and Dr. Amer Zeidan will use medical information collected or created as part of the study, such as medical records and test results, which identifies you by name or in another way. Your consent to participate in the study means you agree that Yale University, Yale-New Haven Hospital, and Dr. Amer Zeidan may obtain your medical information that they request for study purposes from your physicians and your other health care providers from the past or during your participation in the study.

The protected health information that will be collected in this study includes demographics, medical history, physical examinations, routine lab tests, review of adverse events and medications you take (past and present), vital signs, ECGs, bone marrow biopsies, pregnancy tests, blood or tissue samples for research purposes, information recorded in study questionnaires, survival follow-up information and records about any study drug(s) that you received.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases such as HIV or hepatitis. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the study staff will get information that identifies you and your protected health information. This may include information that might directly identify you, such as your name, date of birth, and medical record number**.** This information will be de-identified prior to providing it to the sponsor, meaning we will replace your identifying information with a code that does not directly identify you. The study doctor will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the Principal Investigator or selected members of the study team. Any information that can identify you will remain confidential.

The records for this trial will be stored in locked cabinets and/or offices and password protected computers. The study team will only give this coded information to others to carry out this research study or to sponsor representatives to comply with federal laws and regulations. It is anticipated that records containing the information that links you to your coded information will be maintained indefinitely, as there are no plans at this time to destroy these records at the end of the study.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g., health insurance company, disability provider.)

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee or Institutional Review Board that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential
- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The study doctor, Dr. Amer Zeidan, and the Yale study team

- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor or manufacturer of study drug, Pfizer, Inc. and/ or their representatives
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at Yale School of Medicine and Yale-New Haven Hospital is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be

subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Authorized representatives of the Food and Drug Administration (FDA**)** and the manufacturer of the study drug being tested, Pfizer, Inc., may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others.

The sponsor will see the research information we collect about you when they come to Yale to monitor the conduct of this research study. The "Sponsor" includes any persons that work for or are hired by the sponsor to conduct research activities related to this study. For this study the sponsor is Yale Cancer Center. Yale researchers will also send the sponsor your health information during the study or at the end of the study. When Yale researchers send information about you to the sponsor, they will not send information that directly identifies you such as your name.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, you will not be allowed to look at or copy your study related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

A description of this clinical trial will be available on, 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.

IN CASE OF INJURY

It is important that you follow carefully all the instructions given by the Study Doctor and his/her staff regarding this study.

If you encounter a physical injury or illness while on this study, you should seek prompt medical treatment and contact your study doctor right away to be treated or referred for treatment. You may seek treatment at any medical facility.

Yale Cancer Center, Yale University and Pfizer, Inc. do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Principal Investigator:	Amer Zeidan, MBBS, MhS	**Sponsor Protocol/HIC #:**	2000024738
Funding Source:	Yale University	**Protocol Number:**	PF-04449913
Sponsor ICF Template Version:	05/31/2019	**Sponsor Protocol Date:**	31-May-2019

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is voluntary. You are free to choose not to take part in this research study. Refusing to take part in this research study will not lead to penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the Study:

If you decide to participate in this research study, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. They will make sure that proper procedures are followed and a final visit is made for your safety.

You may request that the Sponsor destroy your blood sample(s) by contacting your study site. As long as it is possible to identify your samples (i.e., your samples have not been anonymized or the study site has not destroyed the first key), then the Sponsor will destroy the sample. However, data obtained from your samples prior to receiving your request for destruction will not be deleted. If you request destruction of your sample(s), you will not lose any benefits, medical treatment or legal rights to which you are otherwise entitled.

The researchers may withdraw you from participating in the research if necessary. The study doctor or the study sponsor may decide to take you out of the study without your agreement if:

- You do not follow the directions of the study team;
- The study doctor decides that the study is not in your best interest;
- The study is stopped by the study sponsor, the institutional review board (IRB) or independent ethics committee (IEC) (a group of people who review the research to protect your rights), or by a regulatory agency;
- You become pregnant, intend to become pregnant or are breast feeding a child during this study.

To help you leave the study safely, the study doctor may ask you to have more tests. The study doctor may also ask if you wish to take part in the follow up portion of the study. If you agree to continue with the follow up portion of the study, information about your health will continue to be collected as described above in the Follow Up Procedures section. The study doctor will discuss with you the different withdrawal options.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

APPROVED BY THE YALE UNIVERSITY IRB 7/17/2020

If you choose not to give your consent by not signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

Withdrawing Your Authorization to Use and Disclose Your Health Information:
You may withdraw or take away your permission to use and disclose your health information at any time. You do this by telling the study staff or by sending written notice to the study doctor, Amer Zeidan, MBBS, MhS, at the address listed on page one of this form. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

OPTIONAL SPECIMENS FOR FUTURE STORAGE/GENETIC TESTING
You are invited to allow some of your blood and bone marrow samples (called specimens) and related information to be stored (banked) for future research. Your blood and bone marrow samples collected will be shipped to, analyzed by, and temporarily stored at Yale University or at a laboratory selected by the Yale University. Most testing samples will be destroyed at the end of the testing process, but some samples may be kept and analyzed at a later time to learn more about your disease and its treatment.

The samples that are stored after the testing will be kept for an unlimited time at Yale University or a laboratory selected by Yale University. The tests that might be done at a later time will include looking for changes in the cancer cell genetic make-up and/or proteins inside the cancer cells that might be involved with your response to cancer therapy. Your genes are made up of DNA. DNA is short for deoxyribonucleic acid and contains information that determines, in part, the traits, such as eye color, height, or disease risk, that are passed on from parent to child. This study will not analyze your body's DNA. It will only look at changes in the DNA of your cancer cells to better understand your response to therapy. RNA is made from DNA. RNA is short for ribonucleic acid. RNA is a genetic material that has a major role in making proteins. Proteins are the building blocks of your body, cells, and organs. Future tests may include looking at the RNA or proteins inside your cancer cells. Afterwards, the samples are discarded by a certified hazardous waste management company.

When your specimens and information are stored, we are careful to try to protect your identity from discovery by others. Your samples and information will receive a unique code. Other researchers will only receive coded samples and information, and will not be able to link the code to you. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.

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Using your specimens for research will probably not help you. We do hope the research results will help people in the future.

There is a risk that your information could be misused. The chance of this happening is very small, and we have protections in place to lower this risk. There can also be a risk in uncovering genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Very rarely, health or genetic information could be misused by employers, health insurance companies, and others. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers (except those with fewer than 15 employees) to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Your specimens and information will be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you or your family.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

The choice to take part is up to you. You may choose not to let us store and use your samples, and your care will not be affected by this decision. If you decide that your samples can be kept, you may change your mind at any time. To withdraw your samples from the study, you can call a member of the research team or you may write to the Principal Investigator using the contact information on page one of this form at any time and tell them you do not want your samples used any longer. If your sample has not already been anonymized it will be destroyed.

Please indicate your choice below by checking yes or no:
_____Yes, I agree to allow my samples to be kept at Yale University or a laboratory chosen by

Yale University for analysis at a later time.

_____No, I do not agree to allow my samples to be kept at Yale University or a laboratory chosen

by Yale University for analysis at a later time.

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QUESTIONS

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

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Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project as described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to participate in this research.

I also confirm that I have received a Trial Alert Card providing contact details of the study doctor and agree to carry this card with me at all times.

Study Participant (print name)	Signature	Date
Person obtaining consent (print name)	Signature	Date
Person obtaining consent (print name) – only if applicable, otherwise blank	Signature	Date
Interpreter/ Witness (print name) – only if applicable, otherwise blank	Signature	Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Amer Zeidan, at (203) 737-7078. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688

APPROVED BY THE YALE UNIVERSITY IRB 7/17/2020