A Phase 1, Open-Label, Dose Escalation and Expanded Cohort, Continuous Intravenous Infusion, Multicenter Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of EPZ-5676 in Treatment Relapsed/Refractory Patients with Leukemias Involving Translocations of the MLL Gene at 11q23 or Advanced Hematologic Malignancies

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Primary objectives:*To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of EPZ-5676 when administered as a 21-day or 28 day CIV infusion to patients with refractory hematologic malignancies.*To assess the safety and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON41336

Source
ToetsingOnline

Brief title
EPZ-5676-12-001

Condition

- Leukaemias

Synonym
Blood cancer, Leukaemias

Research involving
Human

Sponsors and support

Primary sponsor: Epizyme, Inc.
Source(s) of monetary or material Support: Epizyme;Inc.

Intervention

Keyword: - Advanced Hematologic Malignancies, - Epizyme, - Leukemias withTranslocations of the MLL Gene at 11q23, Inc.

Outcome measures

Primary outcome

1. Incidence of treatment emergent adverse events (TEAEs) qualifying as

protocol-defined DLTs, and establishment of the protocol-defined MTD and/or

RP2D.

2. Incidence and severity of TEAEs according to the NCI CTCAE version 4.03.

Secondary outcome

1. Pharmacokinetic parameters for EPZ-5676 throughout the study.

2. Histone H3K79 methylation in PBMC, bone marrow mononuclear cells, and

potentially leukemia cells.

3. Response to EPZ-5676 in patients with leukemias with translocations

involving the MLL gene at 11q23 or partial tendem duplication of MLL, using

disease-appropriate standardized response criteria.

Study description

Background summary

Rearrangements of the mixed lineage leukemia (MLL) gene are associated with aggressive leukemias in children and adults with a poor prognosis. Rearrangements occur in approximately 5% of adult acute lymphoblastic leukemias and 5 to 10% of adult acute myeloid leukemias including secondary leukemias. A universal hallmark of MLL-rearranged leukemia is a chromosomal translocation affecting the MLL gene on chromosome 11q23.

The MLL gene codes for a histone methyltransferase (HMT) that is responsible for methylation of lysine 4 of histone H3, a modification associated with active transcription. Translocations of MLL result in the loss of the SET or catalytic domain of the protein. The most common translocation partners, AF4, AF9, and ENL, recruit another histone methyltransferase, DOT1L. The aberrant recruitment of DOT1L to MLL fusion target genes results in ectopic H3K79 methylation of lysine 79 of histone H3 (H3K79) and increased expression of genes involved in leukemogenesis of the MLL-rearranged leukemias, such as HOXA9 and MEIS1. DOT1L activity is required for the development and maintenance of MLL-rearranged leukemia in model systems.

EPZ-5676 is a small molecule inhibitor of the histone methyltransferase (HMTs), DOT1L, with sub-nanomolar affinity for this enzyme and >1000-fold selectivity against other HMTs.

Study objective

Primary objectives:
*To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of EPZ-5676 when administered as a 21-day or 28 day CIV infusion to patients with refractory hematologic malignancies.
*To assess the safety and tolerability of a 21-day or 28 day CIV infusion of EPZ-5676. (dose escalation phase)
*To assess the safety and tolerability of a CIV infusion, administered until disease progression, unacceptable toxicity, or achievement of best response, of EPZ-5676. (MLL-r/MLL-PTD restricted/ expansion phases)

Secondary objectives:
*To determine the pharmacokinetic profile of EPZ-5676 when administered as a 21-day or 28 day intravenous infusion every 28 days.
*To determine the 28-day pharmacokinetic profile of EPZ-5676 when given as a continuous IV infusion until disease progression, unacceptable toxicity, or achievement of best response.
*To assess the pharmacodynamic effects of EPZ-5676 on histone H3K79 methylation

in peripheral blood mononuclear (PBMC) and leukemia cells; and target gene expression in leukemia cells.
*To evaluate early evidence of anti-tumor activity as assessed by objective response (OR) in patients with leukemias with rearrangement of the MLL gene (reciprocal translocation or partial tandem duplication).

Study design

This will be an open-label, dose escalation, multicenter study. Patients will be screened for eligibility for the study within 14 days of receiving their first dose of EPZ-5676.

The starting dose of EPZ-5676 will be 12 mg/m2/day (actual BSA). The dose will be escalated in successive cohorts of patients who will be entered sequentially to each dose level. Dose escalation will be performed initially using cohorts of up to one patient per participating institution (2 patients maximum), with dose doubling from the lowest (starting) dose until *Grade 2 (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03) drug-related (defined as: any AE which cannot be clearly attributed by the Investigator to another cause, such as intercurrent illness or concomitant medication) toxicity in any patient occurs. At that point, three patients will be assigned to the cohort at which any *Grade 2 drug-related toxicity occurred and dose escalation will proceed according to the common 3+3 design with dose escalation in increments of 25 - 50%, the precise dose levels to be decided in consultation between the Investigator(s) and Epizyme, with due consideration given to the cumulative toxicity profile of the drug that has been revealed after each cohort. If none of the first 3 patients at a dose level experience first cycle dose limiting toxicity (DLT; see DLT definition below), new patients may be entered at the next higher dose level. If 1 of 3 patients experience a first cycle DLT, up to 3 more patients will be started at that same dose level. If 2 or more experience first cycle DLT, no further patients are started at that dose. The MTD is defined as the dose level below which >1 patient out of 3 or *2 patients out of 6 experience a DLT.

A DLT will be defined as a significant suspected adverse reaction or clinically significant abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications (only AEs that are definitely due to an extraneous cause will be excluded as a DLT) and of onset within the first 28 days on study that meets any of the following criteria:

Non-hematologic:
*CTCAE > Grade 3 aspartate transaminase (AST, also referred to as serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT, also referred to as serum glutamic pyruvic transaminase [SGPT]);
*CTCAE Grade 3 or 4 hyperbilirubinemia for any duration;
*CTCAE Grade 3 or higher electrolyte abnormalities that are either symptomatic

or not reversible within 7 days of withholding study drug;
*CTCAE Grade 3 or higher nausea/vomiting that persists for more than 3 days despite anti-emetic support;
*All other clinically significant CTCAE Grade 3 or 4 toxicities. (Alopecia will not be considered a DLT).

Hematologic:
*Prolonged myelosuppression, defined as:
*CTCAE Grade > 3 neutropenia or thrombocytopenia (by NCI CTCAE v4.03) for at least 42 days from the initiation of Cycle 1 of therapy, AND
*Marrow cellularity <5%, without evidence of leukemia.

New dose levels may begin accrual only if all patients at the current dose level have been observed for a minimum of 28 days, i.e. through the first 28-day cycle. However, if at Day 28 the patient has Grade 3 or 4 neutropenia or thrombocytopenia, (not attributable to persistent leukemia; see DLT definition above), the patient will not begin Cycle 2 and must be observed until Day 42 in order to determine whether a DLT has occurred. In this instance, dose escalation cannot proceed until at least Day 42 so that resolution may be assessed. If patients do not fulfill the definition of severe myelosuppression at Day 28, or if they recover between Days 28 and 42, no hematological DLT will be deemed to have occurred.

Absent a MTD, a composite of available pharmacokinetic (PK), pharmacodynamic (PD), safety, and response data will be used to identify a dose (or dose range) to be explored in the expansion phase of the study. Once the MTD or expansion phase initiating dose has been reached, the cohort will be expanded to approximately 20 patients. Safety will be assessed by AEs, SAEs, 12-lead electrocardiograms (ECGs), vital signs, physical examinations, and review of biochemistry, hematology, including bone marrow aspiration and urinalysis.

Blood samples for PK and blood samples for PD assessments will be obtained pre-dose and at various time points post-dose. In addition, samples of bone marrow aspirate and biopsy may be assessed.

Intervention

In the dose escalation phase, patients will receive a continuous IV infusion of EPZ-5676 for up to 21 days of a 28 day cycle. The IMP will be given through a central line catheter. The targeted length of minimum treatment will be two 28-day treatment cycles. However, additional 28-day cycles may be given.

In the dose escalation phase, patients achieving a complete remission (CR) or a complete remission with incomplete blood count recovery (CRi) may be allowed to receive up to an additional five cycles of treatment after documentation of complete response.

Study burden and risks

EPZ-5676 risks related :
All drugs carry a risk of side effects. EPZ-5676 has not been previously studied in humans. Based on the animal studies some possible side effects may be the following:
* Decreased liver function
* Pain and redness at the infusion site
* Decreased white blood cells
* Anemia
* Decreased sperm counts in males

Based on the first studies with EPZ-5676 in cancer patients, some possible side effects may be:
* Change in PR interval (a measurement of one portion of the heartbeat on an electrocardiogram: electrical measurement of heartbeat)
* Low blood levels of phosphorus (a body chemical)
* Elevation of your normal white blood cell count (leukocytosis)
* Decreased breathing rate (apnea)

Other possible side effects (experienced with other chemotherapy) may include:
* Nausea or vomiting
* Poor appetite
* Weight loss
There may be side effects which are not known at this time.

The following problems may occur from the IV infusion:
* irritation of the vein; your skin near the vein could become warm, swell, hurt, or get red
* damage to your vein
* damage to the skin or tissue around the injection site
* increase or decrease in electrolyte levels (the amount of certain salts and other chemicals in your blood), causing health problems
* a blood clot or an air bubble could form
Some of these problems could be very serious.

Besides, allergic reaction to EPZ-5676 is not excluded. Allergic reactions can lead to death when they are very serious. Some things that happen during an allergic reaction are:
· a rash
· having a hard time breathing
· wheezing
· a sudden drop in blood pressure
· swelling around the mouth, throat, or eyes
· a fast pulse
· sweating

Other risks related to this research study:
It is possible that receiving EPZ-5676 with regular medications or supplements may change how EPZ-5676, the regular medications, or the regular supplements work.

Risks of giving blood for this study:
* pain
* bruising
* dizziness or fainting
* infection

Risks of having a bone marrow biopsy done for this study:
* pain
* bleeding
* infection
* allergy to the local anesthesia used

Risks if a female subject is pregnant or nursing a child during the study:
If a woman becomes pregnant while taking EPZ-5676 during the study, there may be risks to the unborn baby. No information about the use of this medication in pregnant women is available to know what the risks are. As a result, women should not be in this study if they are pregnant, breast-feeding, or trying to become pregnant.

Contacts

Public
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Scientific
Epizyme, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Male or female * 18 years;2.Dose escalation phase: Patients with histologically confirmed acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute mixed lineage leukemia (MLL), myelodysplastic syndrome (MDS)(IPSS Int-2 or high-risk), myeloproliferative disorder, or chronic myeloid Leukemia (CML) meeting the following criteria:;*At least one prior therapy;*Refractory disease on most recent therapy, or disease recurrence following remission on most recent therapy;*Received and failed all known effective therapies for their disease;*Not a candidate for allogeneic stem cell transplantation;*In addition to the above criteria, the following disease-specific criteria must be met:;*AML: have received at least a standard anthracycline and cytarabinebased;induction regimen, unless not considered appropriate for aggressive induction therapy due to advanced age(>60 years old) or a significant comorbid medical condition. Patients>60 years old or with significant cormorbid medical conditions must have received an appropriate low-intensity induction regimen (e.g. low-dose cytarabine or hypomethylating agent-based). Patients with acute promyelocytic leukemia must have also received prior retinoid and arsenic trioxidebased therapy;*ALL: have received at least a standard anthracycline/vinca alkaloid/glucocorticoid-based induction regimen, unless not considered appropriate for aggressive induction therapy due to advanced age (>60 years old) or significant comorbid medical condition. Patients >60 years old or with significant comorbid medical conditions must have received appropriate low-intensity therapy (e.g. corticosteroid-based therapy). Patients with Philadephia chromosome-positive ALL must also have received prior imatinib or dasatinib.;*CML: have received prior imatinib, dasatinib, or nilotinib (and either dasatinib or nilotinib in the event of imatinib resistance or intolerance);3. MLL-r/MLL-PTD Restricted/ Expansion Phases: Patients with relapsed/refractory AML or ALL or acute MLL with rearrangement involving the MLL gene, including reciprocal chromosomal translocations involving 11q23 by FISH or cytogenetic analysis or MLL (PTD) partial tandem duplication by next generation sequencing or polymerase chain reaction and meeting the criteria below:
*At least one prior therapy;*Refractory disease on most recent therapy, or disease recurrence following remission on most recent therapy;*Received and failed all known effective therapies for their disease;*Not a candidate for allogeneic stem cell transplantation;*> 10% blasts by bone marrow aspirate or biopsy, OR biopsy documented leukemia cutis or myeloid sarcoma;*AML: must have received at least a standard anthracycline and cytarabine-based induction regimen, unless not considered appropriate for aggressive induction therapy due to

advanced age (age>60 years old) or a significant comorbid medical condition. Patients >60 years old or with significant cormorbid medical conditions must have received an appropriate low-intensity induction regimen (e.g. low-dose cytarabine or hypomethylating agent-based).;*ALL: must have received at least a standard anthracycline/ vinca alkaloid/ glucocorticoid-based induction regimen, unless not considered appropriate for aggressive induction therapy due to advanced age (>60 years old) or significant comorbid medical condition. Patients >60 years old or with significant comorbid medical conditions must have received appropriate low-intensity therapy (e.g. corticosteroid-based therapy).;4. The interval from prior treatment to time of study drug administration should be at least 2 weeks from prior anti-cancer therapy.;*Patients with AML may receive hydroxyurea to control peripheral blood leukemic cell counts at study entry or in the event of treatment associated leukocytosis.;*Patients with ALL may receive glucocorticoids to control peripheral blood leukemic cell counts at study entry or in the event of treatment associated leukocytosis.;5. White blood cell count <30,000/ul at the time of study entry (hydroxyurea or glucocorticoids may be used to control peripheral blood leukemic cell counts at the time of study entry).;6. All persistent clinically significant toxicities from prior chemotherapy must be < Grade 1.;7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.;8. Life expectancy of at least 3 months (in the Investigator's opinion).;9. Patients must have the following clinical laboratory values:;*Serum creatinine *2 mg/dL or creatinine clearance > 60 mL/min;;*Total bilirubin *2.0 times the ULN for the institution, unless considered due to Gilbert's syndrome;;*ALT and AST * twice the ULN, unless considered due to organ leukemic involvement;;*ANC *1,000/*L (unless due to documented leukemic involvement of the bone marrow at the time of study entry);*Platelets *100,000/*L (unless due to documented leukemic involvement of the bone marrow at the time of study entry);*PTor aPTT < 1.5 times the ULN;10. Able and willing to give written informed consent

Exclusion criteria

1. Uncontrolled intercurrent illness including, but not limited to uncontrolled infection, significant graft-versus-host-disease (GvHD) (Grade 2-4), symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.;2. Active heart disease including myocardial infarction within previous 6 months, symptomatic coronary artery disease, QTc (as calculated by the Fridericia correction formula) >470 msec, arrhythmias not controlled by medication, ejection fraction <40% or uncontrolled congestive heart failure defined as Class II to IV per New York Heart Association Classification or patients with PR interval >200 msec, history of underlying structural heart disease, pre-existing AV conduction system abnormalities, cardiomyopathies or arrhythmias not controlled by medication.;3. Receiving any other standard treatment for their hematologic malignancy, including anticancer therapies, systemic steroids, other investigational cytotoxic agents, radiation, biologic therapy or prophylactic use of hematopoietic colony stimulating factors (supportive measures will be permitted according to standards of care). Use of investigational agent(s) within 14 days or 5 half-lives, whichever is greater, and absence of >Grade 1 AE (except Heme) at time of study entry. ;4. Receiving strong CYP3A4 inhibitors/ inducers.;5. Known history of cerebrovascular accident in the past 6 months.;6. Known bleeding diathesis.;7. Active (symptomatic) involvement of the central

nervous system (CNS) by disease. Patients considered to be at high risk of development of CNS disease may receive standard intrathecal chemotherapy prior to enrollment and continue once dosed with study drug.;8. On immunosuppressive therapy, excluding patients with ALL receiving glucocorticoids for management of circulating blast count or patients on a stable dose (<20mg/day prednisone or equivalent) of systemic or topical glucocorticoid therapy with *Grade 1 GvHD.;9. Known infection with human immunodeficiency virus (HIV) or Acquired Immune Deficiency Syndrome (AIDS). (Testing not required.);10. Active Hepatitis B or C infection.;11. Being actively treated for a second malignancy. However, patients on stable doses of maintenance hormonal therapy (dose unchanged for at least 2 months) for breast or prostate cancer may be enrolled into the study.;12. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an appropriate method of contraception from at least 7 days prior to first dose of study medication administration until completion of follow-up procedures.;13. Male patients not willing to use a condom, plus another form of contraception (e.g., spermicide, intrauterine device (IUD), birth control pills taken by female partner, diaphragm with spermicide) if engaging in sexual intercourse with females who could become pregnant. Male patients not willing to adhere to these contraceptive criteria from administration of study medication to completion of follow-up procedures and for a total of 90 days post their last dose of experimental therapy.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-06-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available

Generic name:	not available

Ethics review

Approved WMO Date:	12-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-002355-15-NL
ClinicalTrials.gov	NCT01684150
CCMO	NL45780.078.13