A Safety, Tolerability and Preliminary Efficacy Study of CC-90011 in Combination With Venetoclax and Azacitidine in R/R Acute Myeloid Leukemia and Treatment-naïve Participants Not Eligible for Intensive Therapy

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04748848	COMPLETED	FEBRUARY 10, 2021	MAY 2, 2022

STUDY DESCRIPTION

Brief Summary

CC-90011-AML-002 is a Phase 1/2, open-label, multicenter study to assess the safety, tolerability, and preliminary efficacy of CC-90011 given concurrently with Venetoclax and Azacitidine. This study will include 3 parts: a dose escalation part in R/R AML, a dose escalation part in ndAML (treatment-naïve participants with AML who are ≥ 75 years of age or are ≥ 18 to 74 years of age and otherwise not eligible for intensive induction chemotherapy), and a randomized dose expansion part in ndAML of Venetoclax and Azacitidine with or without CC-90011.

Condition or Disease: Leukemia, Myeloid

Intervention/treatment: Drug: CC-90011
Drug: Venetoclax
Drug: Azacitidine
Drug: Venetoclax
Drug: CC-90011

Phase: Phase 1

DETAILED DESCRIPTION

N/A

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 1 participants

Allocation : Randomized

Intervention Model : Sequential Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Safety, Tolerability and Preliminary Efficacy Study of CC-90011 in Combination With Venetoclax and Azacitidine in R/R Acute Myeloid Leukemia and Treatment-naïve Participants Not Eligible for Intensive Therapy

Actual Study Start Date: October 2021

Actual Primary Completion Date: March 2022

Actual Study Completion Date: March 2022

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: CC-90011 in combination with Venetoclax and Azacitidine in Dose Escalation CC-90011 in combination with venetoclax and azacitidine in dose escalation	Drug: CC-90011 CC-90011 will be given PO on Days 1, 8, and 15 of continuous 4-week (28-day) cycle. The dose escalation is designed to explore three dose levels of CC-90011, for example 20, 40, and 60 mg as determined by Bayesian design. Drug: Venetoclax Venetoclax is administered orally QD on Days 1 to 28 of each 28-day cycle with a brief dose ramp-up for Cycle 1 with the dosing of 100 mg on Day 1, 200 mg on Day 2, and 400 mg on Day 3. Venetoclax should be administered at 400 mg on subsequent days. Drug: Azacitidine Azacitidine is administered on Days 1 to 7 of each 28-day cycle as an IV infusion or SC injection at 75 mg/m2
Experimental: CC-90011 in combination with Venetoclax and Azacitidine in Dose Expansion CC-90011 in combination with venetoclax and azacitidine in dose expansion	Drug: Venetoclax Venetoclax is administered orally QD on Days 1 to 28 of each 28-day cycle with a brief dose ramp-up for Cycle 1 with the dosing of 100 mg on Day 1, 200 mg on Day 2, and 400 mg on Day 3. Venetoclax should be administered at 400 mg on subsequent days. Drug: Azacitidine Azacitidine is administered on Days 1 to 7 of each 28-day cycle as an IV infusion or SC injection at 75 mg/m2 Drug: CC-90011 CC-90011 will be given PO on Days 1, 8, and 15 of continuous 4-week (28-day) cycle at the recommended phase to dose of CC-90011 confirmed in dose escalation.

Experimental: Venetoclax and Azacitidine Venetoclax and Azacitidine control arm in dose expansion. The participants will be randomized to the treatment arm or control arm at a 2:1 ratio.	Drug: Azacitidine Azacitidine is administered on Days 1 to 7 of each 28-day cycle as an IV infusion or SC injection at 75 mg/m2 Drug: Venetoclax Venetoclax is administered orally QD on Days 1 to 28 of each 28-day cycle

OUTCOME MEASURES

Primary Outcome Measures:
1. Adverse Events (AEs) [Time Frame: From ICF signature until 28 days after last dose of CC- 90011 and all combination agents]
An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE
2. Recommended Phase 2 dose (RP2D) [Time Frame: Up to approximately Cycle 1 (each cycle is 28 days)]
The RP2D will include evaluation of DLTs and MTD using NCI CTCAE criteria

Secondary Outcome Measures:
1. Complete remission (CR) Rate [Time Frame: Up to approximately 10 months]
Defined as the rate of achieving CR (as assessed by the Investigator and by programmatic outputs by the Sponsor)
2. Complete remission with partial hematologic recovery (CRh) Rate [Time Frame: Up to approximately 2 years]
Defined as the rate of achieving CRh (as assessed by the Investigator and by programmatic outputs by the Sponsor)
3. Overall response rate (ORR) [Time Frame: Up to approximately 2 years]
Defined as the rate of achieving CR/CRMRD-/CRi/PR/MLFS
4. Duration of response (CR) [Time Frame: Up to approximately 2 years]
Time from the first CR to the date of documented disease relapse or death, whichever is earlier.
5. Duration of response (CR/CRh) [Time Frame: Up to approximately 2 years]
Time from the first CR or CRh to the date of documented disease relapse or death, whichever is earlier.
6. Duration of response (CR/ CRMRD-/ CRi/ PR/MLFS) [Time Frame: Up to approximately 2 years]
Time from the first CR, CRMRD-, CRi, PR or MLFS to the date of documented disease relapse, progression, or death, whichever is earlier.
7. Event-free survival (EFs)_Part III Only [Time Frame: Up to approximately 2 years]
Time from study randomization to the date of treatment failure, relapse from CR or death from any cause, whichever comes first.
8. Overall survival (OS)_Part III Only [Time Frame: Up to approximately 2 years]
Time from study randomization to the date of death due to any cause.
9. Minimal residual disease (MRD) Response Rate_Part II and III only [Time Frame: Up to approximately 2 years]
The rate of having at least a one log reduction in disease burden or an MRD negative (10-3) test result.
10. Minimal residual disease (MRD) Conversion Rate_Part II and III Only [Time Frame: Up to approximately 2 years]
The rate of participants achieving MRD negativity (10-3) at any time on therapy.
11. Complete response with incomplete hematologic recovery (CRi) rate [Time Frame: Up to approximately 2 years]
Defined as the rate of achieving CRi (as assessed by the Investigator and by programmatic outputs by the Sponsor)
12. Duration of response (CR/CRi) [Time Frame: Up to approximately 2 years]
Time from the first CR or CRi to the date of documented disease relapse or death, whichever is earlier.

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Participants must satisfy the following criteria to be enrolled in the study:
All participants (Parts I, II, and III):
1. Participant must understand and voluntarily sign an Informed Consent Form (ICF) prior to any study-related assessments/procedures being conducted.
3. Participant must have a projected life expectancy of at least 12 weeks. 4. Participant has Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Participants must have the required protocol baseline laboratory values 6. Participant has adequate organ function 7. Participant must be able and willing to undergo hospitalization, hydration, and treatment with a uric acid-reducing agent prior to the first dose of venetoclax and during Cycle 1.
Part I only:
8. Relapsed and/or refractory acute myeloid leukemia (AML) as defined by the World Health Organization (WHO) Classification and is ≥ 18 years of age at the time of signing the ICF who are not eligible to receive further intensive therapy and:
Has failed to have a complete remission (CR) or CR with incomplete hematologic recovery (Cri) after induction plus reinduction with intensive chemotherapy (anthracycline plus cytarabine containing regimens) or 2 cycles of low intensity therapy (either 2 cycles of the same regimen or 1 cycle of 2 different regimens) OR Has relapsed from CR from either intensive or low-intensity therapy. Participants with second relapse are also eligible
Part II and Part III only:
9. Histologically confirmed treatment naïve Acute myeloid leukemia (AML) as defined by the 2008 World Health Organization (WHO) Classification, including secondary AML and therapy related AML, and is ≥ 75 years of age at the time of signing the ICF, or is ≥ 18 to 74 years at the time of signing the ICF with comorbidities precluding the use of intensive induction chemotherapy 10. Participant has not received prior therapy for AML with the exception of hydroxyurea to treat hyperleukocytosis.
Exclusion Criteria:
The presence of any of the following will exclude a participant from enrollment:
All participants (Parts I, II, and III):
Participant is suspected or proven to have acute promyelocytic leukemia (APL) based on morphology, immunophenotype, molecular assay, or karyotype. Participant has favorable risk cytogenetics Participants with AML who may receive fms-like tyrosine kinase 3 (FLT3) inhibitor directed therapy. Participant has or is suspected of having active central nervous system (CNS) involvement. Participant has an active, uncontrolled infection except participants with infection under active treatment and controlled with antibiotics, antifungals, or antivirals are eligible. Participant with prior autologous hematopoietic stem cell transplant (HSCT) who, in the investigator's judgment, have not fully recovered from the effects of the last transplant (eg, transplant related side effects). Participant had prior allogeneic HSCT with either standard or reduced intensity conditioning ≤ 6 months prior to dosing. Participants on systemic immunosuppressive therapy post HSCT at the time of screening, or with clinically significant graft-versus-host disease (GVHD). The use of topical steroids for ongoing skin or ocular GVHD is permitted. Participant has immediate life-threatening, severe complications of leukemia such as disseminated/uncontrolled infection, uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation. The participant should be afebrile for at least 72 hours. Participants requiring treatment with strong or moderate CYP3A inhibitors/inducers. Participant has ongoing treatment with chronic, therapeutic dosing of anticoagulants. Participant has a history of concurrent secondary cancers requiring active, ongoing systemic treatment. Participant has known human immunodeficiency virus (HIV) infection.
Participant has known chronic active hepatitis B virus (HBV) or hepatitis C virus (HCV).
Participant who is seropositive due to HBV vaccination is eligible. Participant who has no active viral infection and is under adequate prophylaxis against HBV reactivation is eligible. Participant is known to have dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally. Participant has impaired cardiac function or clinically significant cardiac diseases Participant has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or Star fruit within 3 days prior to first venetoclax dose through last dose of venetoclax. Pregnant women are excluded from this study due to potential teratogenic and/or abortifacient effect of this therapy. Nursing mothers should stop breastfeeding in order to be eligible due to potential risk for Adverse Events (AEs) in a nursing infant. Participant has had previous treatment with a lysine-specific demethylase 1A (LSD1) inhibitor. Participant has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the participant from participating in the study. Participant has any condition including the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study. Participant has any condition that confounds the ability to interpret data from the study. Participant received live COVID-19 vaccines within 30 days prior to initiation of study treatment
Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the Investigator and the Medical Monitor.
Part I only:
Participant had prior treatment with venetoclax for AML, either as monotherapy or in combination with other agents.
Part II and Part III only:
Participant had prior treatment with hypomethylating agent (HMA) or chemotherapy for antecedent hematologic disorders. Prior treatment with hydroxyurea is permitted. Participant has received systemic anticancer therapy (including investigational therapy), radiotherapy, or immunotherapy < 14 days or 5 half-lives, whichever is shorter, prior to the first dose of CC-90011.

CONTACTS AND LOCATIONS

Contacts

Locations

Austria	Krankenhaus Hietzing	Wien
Austria	Salzburger Landkliniken St. Johanns-Spital	Salzburg
Austria	Medical University of Vienna	Vienna
United States, California	City of Hope	Duarte
United States, California	Local Institution - 110	Duarte
United States, Connecticut	Yale University School of Medicine	New Haven
United States, Florida	University of Miami Miller School of Medicine Jackson Memorial Hospital	Miami
United States, Georgia	Winship Cancer Institute of Emory University	Atlanta
United States, Illinois	Northwestern University Medical Center	Chicago

United States, New York	Mount Sinai Medical Center	New York
United States, North Carolina	Duke University Medical Center	Durham
United States, Ohio	Cleveland Clinic	Cleveland
United States, Ohio	Ohio State University Medical CenterJames Cancer Hospital	Columbus
United States, Texas	Baylor University Medical Center	Dallas
United States, Texas	The University of Texas - MD Anderson Cancer Center	Houston
United States, Washington	Swedish Medical Center	Seattle
Belgium	ZNA Stuivenberg Centrumziekenhuis	Antwerpen
Belgium	UZ Gent	Gent
Belgium	CHU de Liege	Liege
France	Hopital Aviecenne	BOBIGNY Cedex
France	CHRU Nantes	Nantes
France	Centre Hospitalier Lyon Sud - Hospices Civils de Lyon Groupement Hospitalier Sud	Pierre-Benite
France	Institut Claudius Regaud, IUCT-Oncopole	Toulouse
France	Gustave Roussy	Villejuif CEDEX
France	Local Institution - 401	Villejuif CEDEX
Italy	Azienda Ospedaliero Universitaria Di Bologna - Policlinico S Orsola Malpighi	Bologna
Italy	IRST Meldola	Meldola
Italy	Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico	Milano
Italy	Ospedale Santa Maria Della Misericordia Di Perugia	Perugia PG
Norway	Haukeland University Hospital	Bergen
Norway	Oslo Universitetssykehus	Oslo
Spain	Hospital Universitari Vall d'Hebron	Barcelona
Spain	Hospital de Bellvitge	Barcelona
Spain	Hospital General Universitario Gregorio Marañon	Madrid
Spain	Hospital Universitario Virgen del Rocio - PPDS	Sevilla

Sponsors and Collaborators

Celgene

Investigator

Study Director :	Bristol-Myers Squibb	Bristol-Myers Squibb

MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT04748848
Other Study ID Numbers :	CC-90011-AML-002, U1111-1251-6973, 2020-005341-16
First Posted :	February 10, 2021
Last Update Posted :	May 2, 2022
Last Verified :	April 2022
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Yes
Plan Description:	Information relating to our policy on data sharing and the process for requesting data can be found at the following link: https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Supporting Materials:	Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), Clinical Study Report (CSR), Analytic Code
Time Frame:	See Plan Description
Access Criteria:	See Plan Description

URL:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Keywords provided by Celgene:	*Acute Myeloid Leukemia* *CC-90011* *Venetoclax Azacitidine* *LSD-1 inhibitor* *Minimal residual disease*
Additional relevant MeSH terms :	*Leukemia* *Leukemia, Myeloid* *Leukemia, Myeloid, Acute* *Neoplasms* *Neoplasms by Histologic Type*