A PHASE 1B/2 OPEN-LABEL, RANDOMIZED STUDY OF 2 COMBINATIONS OF ISOCITRATE DEHYDROGENASE (IDH) MUTANT TARGETED THERAPIES PLUS AZACITIDINE: ORAL AG-120 PLUS SUBCUTANEOUS AZACITIDINE AND ORAL AG-221 PLUS SC AZACITIDINE IN SUBJECTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA HARBORING AN IDH1 OR AN IDH2 MUTATION, RESPECTIVELY, WHO ARE NOT CANDIDATES TO RECEIVE INTENSIVE INDUCTION CHEMOTHERAPY

Published: 02-05-2016
Last updated: 21-09-2024

This study has been transitioned to CTIS with ID 2024-511722-31-00 check the CTIS register for the current data. Phase 1b Dose-finding Stage Primary Objectives· To assess the safety and tolerability of the combination treatments of oral AG-120 when...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON54569

Source
ToetsingOnline

Brief title
Celgene AG-221-AML-005

Condition

- Leukaemias

Synonym
cancer of the blood

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene Corporation

Intervention

Keyword: ACUTE MYELOID LEUKEMIA, IDH1/IDH2 MUTATION

Outcome measures

Primary outcome

Efficacy

Secondary outcome

Safety

Plasma PK/PD of AG-120 and AG-221

Exploratory Biomarkers

Investigational product accountability

Study description

Background summary

The combination of inhibitors of IDH mutant proteins with a DNA methyltransferase inhibitor such as azacitidine may lead to an additive or synergistic antitumor effect. Furthermore, the combination of AG-221 and azacitidine has been shown to enhance the differentiation and apoptosis of a leukemic cell line (TF-1) that harbors an IDH2R140Q mutation.

Study objective

This study has been transitioned to CTIS with ID 2024-511722-31-00 check the CTIS register for the current data.

Phase 1b Dose-finding Stage

Primary Objectives
· To assess the safety and tolerability of the combination treatments of oral AG-120 when administered with subcutaneous (SC) azacitidine and oral AG-221 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive IC.
· To establish the recommended combination dose (RCD) of oral AG-120 and oral AG-221 when administered with SC azacitidine.

Secondary Objective
• To assess the preliminary efficacy of the combination treatments of oral AG-120 when administered with SC azacitidine and oral AG-221 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive IC.

Phase 1b AG-120 Expansion Stage

Primary Objectives
· To assess the safety and tolerability of the combination treatments of oral AG-120 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 mutation who are not candidates to receive intensive IC.

Secondary Objective
• To assess the preliminary efficacy of the combination treatments of oral AG-120 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 mutation, who are not candidates to receive intensive IC.
• To characterize the pharmacokinetics (PK) of oral AG-120 when administered with SC azacitidine.

Phase 2 AG-221 Randomized Stage

Primary Objective
· To assess the efficacy of oral AG-221 when administered with SC azacitidine versus SC azacitidine alone in subjects with newly diagnosed AML with an IDH2 mutation, who are not candidates to receive intensive IC.

Secondary Objectives
· To evaluate the safety of oral AG-221 when administered with SC azacitidine.
· To characterize the PK of oral AG-221 when administered with SC azacitidine.
· To evaluate the effect of oral AG-221 when administered with SC azacitidine versus SC azacitidine alone on health-related quality-of-life (HRQoL) outcomes.

Study design

This Phase 1b/2 study is an open-label, randomized, multicenter trial to evaluate the safety and efficacy of oral AG-120 + SC azacitidine and oral AG-221 + SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively. The study population consists of subjects who are not candidates to receive intensive IC. The study comprises a Phase 1b dose-finding and AG-120 expansion stage and a Phase 2 randomized stage.

Intervention

Phase 1b (Dose-finding and AG-120 Expansion) Stage:
Phase 1b dose finding will use a 3 + 3 design. For AG-120 one dose level will be explored enrolling a minimum of 3 subjects. Cohort 1 will be initiated with oral AG-120 500 mg once a day and azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle. A Cohort -1 will be explored with AG-120 250 mg once a day and azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle if 2 or more subjects in Cohort 1 have a dose-limiting toxicity (DLT) in cycle 1. Upon declaration of the RCD by the DRT an expansion cohort of up to 15 patients will be enrolled at the RCD for further safety evaluation and PK sampling.
For AG-221 two dose levels will be explored. Cohort 1 will be initiated with oral AG-221 100 mg once a day and azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle. If no DLTs are observed, the RCD will be confirmed by the DRT and the 100 mg dose will be used as the starting dose for Phase 2 of the study. Dose escalation to Cohort 2 will be initiated with oral AG-221 200 mg once a day and azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle to explore the tolerability of AG-221 + SC azacitidine at this dose level. A Cohort -1 with oral AG-221 50 mg daily and azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle will be explored if 2 or more subjects have a DLT in Cohort 1.
The DRT will evaluate all toxicities of each subject after 1 cycle and

determine whether further dose modifications are needed for individual subjects.

Phase 2 AG-221 Randomized Stage:
AG-221 + Azacitidine Arm (Arm 1):
· Subjects with an IDH2 mutation will receive AG-221 at the RCD orally QD on Days 1-28 of each 28-day cycle + azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle.
Azacitidine Arm (Arm 2):
• Subjects with IDH2 mutation will receive azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle.

Study burden and risks

Burden
- Questionnaires: 1x per cycle and during EOT visit
- ECHO/MUGA scan: at least 1x
- ECG: 1x per cycle en during screening and EOT visit
- Blood sampling: every visit
- Bone marow aspiration/biopsy: 1x per cycle and during screening, EOT visit and follow up
- Subcutaneous administration Azacitidine: Once daily, during 7 days per cycle
- 2 hours before and 1 hour after AG-120 or AG-221 administration, the patient needs to be fasting. Water is allowed.

See also protocol section 5 (Table of Events).

AG-120
very common in blood cancer patients and solid tumor patients:
AG-120 may cause changes inthe electrical activity of your heart (QT prolongation)
Blood Cancers, common
-IDH Differentiation Syndrome: swelling in the arms or legs, an abnormally high number of white blood cells circulating in the blood, unexplained fever, shortness of breath, build-up of fluid around the lungs, low blood pressure, or unexplained weight gain
-Leukocytosis is higher than normal amount of white blood cells in your blood
-Tumor Lysis Syndrome (TLS): weakness, low blood pressure, muscle cramps, kidney damage, irregular heartbeat and/or other organ damage.

Risks that may or may not be caused by AG-120 treatment:

Both blood and solid cancer clinical studies: Very Common
Diarrhea; Nausea; Fatigue; Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion; Arm/leg swelling; Fever; Decreased appetite; Constipation; Vomiting; Headache; Low blood levels of magnesium (symptoms may include weakness, muscle cramps and/or irregular heartbeat); Abdominal pain.

Blood cancer clinical studies: Very Common
Fever with dangerously low white blood cell counts Shortness of breath Cough Low blood level of potassium (possible weakness); Joint pain; Dizziness; Nose bleed; A low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening. Back pain; rash; Low blood pressure (symptoms dizziness / fainting); Difficulty sleeping; Chest pain; Build-up of fluid around the lungs (difficulty breathing or shortness of breath); Itching; Mouth blisters/sores

In blood cancer clinical studies: Common (very serious)
Low white blood cell counts (increase the risk of infection. It may become life-threatening. Symptomps: fever, pain, redness and/or difficulty breathing); An abnormally high number of white blood cells; A serious condition known as sepsis that occurs in response to an infection and causes widespread inflammation, resulting in poor blood supply to vital organs Symptoms: fast heart rate, fever, confusion, and rapid breathing.

Advanced blood cancer clinical studies: Very Common
An abnormally high number of white blood cells circulating in the blood; increased risk of infection, such as pneumonia (an infection of the lungs). A low number of white blood cells may increase the risk of infection. It may become life-threatening. Symptoms of infection may include fever, pain, redness and/or difficulty breathing. Loss of strength; High blood levels of uric acid (possible painful joints and/or kidney failure); Arm/leg pain

AG-221
constipation; weight decrease; dizziness; feeling unwell, tired and weak (asthenia and fatigue); back pain, abdominal pain, joint aches (arthralgia); anxiety and difficulty sleeping (insomnia); headache; rash; decreased blood pressure (hypotension); swelling in extremities (oedema peripheral); shortness of breath (dyspnea); cough; lung infection (pneumonia); infection in the blood (sepsis); decrease in number of red blood cells in blood which may make you feel weak or tired (anemia); decrease in number of platelets which are cells that help your blood clot (thrombocytopenia); nose bleeds (epistaxis), fever with low number of white blood cells in blood that help fight infection (febrile neutropenia); fever (pyexia), decrease kidney function (acute renal failure and increased blood creatinine).

Azacitidine
• anemia (a decrease in the number of red blood cells which may make you feel weak or tired)
• low number of white blood cells with or without fever
• a decrease in the number of platelets, the cells that help your blood to clot
• infections, including pneumonia or of the lung, mouth, skin, or urinary tract (which may be bacterial, fungal or viral)
• nausea

• vomiting
• diarrhea
• stomach pain
• constipation
• feeling tired, unwell, or weak
• fever
• sore throat with swelling or pain of the nasal membranes or nose
• decreased appetite
• weight loss
• low blood levels of potassium
• pain (including muscle, joints, back, and chest pain)
• dizziness
• headache
• difficulty sleeping
• shortness of breath with or without exercise
• rash
• itchiness
• bruising, including, tiny red or purple spots under the skin or other tissue
• nosebleed
• injection site reaction, including itching, pain, rash, redness, bleeding, bruising, swelling or damage where the injection/infusion was given

Contacts

Public
Celgene Corporation

Morris Avenue 86
NJ Summit, NJ 07901
US
Scientific
Celgene Corporation

Morris Avenue 86
NJ Summit, NJ 07901
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must satisfy the following criteria to be enrolled in the study:
1. Subject is >= 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has newly diagnosed, primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms [MPN], or therapy-related) AML according to the WHO classification (Appendix B) with >= 20% leukemic blasts in the bone marrow:
a. Have an IDH1 or IDH2 gene mutation (R132, R140, or R172)
o IDH mutational status will be assessed locally; for sites without local testing capabilities, a referral lab will be identified.
b. By the investigator*s assessment who are not candidates to receive intensive IC.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (Appendix D).
6. Subject has adequate organ function defined as:
• Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) <= 3 x ULN, unless considered due to leukemic organ involvement.
• Serum total bilirubin < 1.5 x ULN. Higher levels are acceptable if these can be attributed to ineffective erythropoiesis, 3 times the upper limit of normal for Gilbert*s syndrome (eg, a gene mutation in UGT1A1), or leukemic organ involvement.
• Serum creatinine < 2 x ULN or creatinine clearance * 30 mL/min based on the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR):
GFR (ml/min/1.73 m2) = 175 x (Scr)-1.154 x (Age)-0.0203 x (0.742 if female) x (1.1212 if African American)
7. Agree to serial bone marrow aspirate/biopsies.

8. Females of childbearing potential (FCBP)* may participate, providing they meet the
following conditions:
• Agree to practice true abstinence or to use at least two highly effective contraceptive methods (eg, combined [containing estrogen and progestogen] or progestogen only associated with inhibition of ovulation, oral, injectable, intravaginal, patch, or
implantable hormonal contraceptive; bilateral tubal occlusion; intra-uterine device;
intrauterine hormone-releasing system; or male partner sterilization [note that a vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the FCBP trial participant and that a vasectomized partner has received medical assessment of the surgical success]) at screening and
throughout the study, and for 4 months following the last study treatment; and
• Have a negative serum β-subunit of human chorionic gonadotropin (β-hCG) pregnancy test (sensitivity of at least 25 mIU/mL) at screening; and
• Have a negative serum or urine (investigator's discretion under local regulations) β-hCG pregnancy test (sensitivity of at least 25 mIU/mL)
within 72 hours prior to the start of study treatment in the Treatment Period (note that
the screening serum pregnancy test can be used as the test prior to the start of study
treatment in the Treatment Period if it is performed within the 72-hour timeframe).
9. Male subjects (with a female partner of childbearing potential who must agree to
conditions in criterion 8) must agree to practice true abstinence from sexual intercourse or agree to the
use of highly effective contraceptive methods (as described above) with non-pregnant female partneres of child bearing potential at screening and throughout the course of
the study and should avoid conception with their partners during the course of the study and for
4 months following the last study treatment (6 months following the last dose of azacitidine in Canada). Furthermore, the male subject must agree to use a condom while treated with azacitidine and for at least 4 months following the last azacitidine dose.

Exclusion criteria

The presence of any of the following will exclude a subject from enrollment:
1. Subject is suspected or proven to have acute promyelocytic leukemia based on morphology, immunophenotype, molecular assay, or karyotype.
2. Subject has AML secondary to chronic myelogenous leukemia (CML).

3. Subject has received a targeted agent against an IDH1 or IDH2 mutation.
4. Subject has received prior systemic anticancer therapy, HSCT, or radiotherapy for AML.
Note that hydroxyurea is allowed prior to enrollment for the control of peripheral leukemic blasts in subjects with leukocytosis (however, hydroxyurea should not be given within 72 hours prior to and after administration of azacitidine). For subjects with secondary AML (eg, MDS or MPN) treatment for prior
cancer is not exclusionary; full treatment information will be collected within the CRF. The use of all trans retinoic acid (ATRA) for suspected APL is not exclusionary provided it is discontinued prior to initiation of treatment in the protocol
5. Subject has received more than 1 cycle of prior treatment with azacitidine or subject has received any prior treatment with decitabine for MDS.
6. Subject has or is suspected of having central nervous system (CNS) leukemia. Evaluation of cerebrospinal fluid is only required if CNS involvement by leukemia is
suspected during screening.
7. Subject has immediate life-threatening, severe complications of leukemia such as
uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation.
8. Subject has significant active cardiac disease within 6 months prior to the start of study
treatment, including New York Heart Association (NYHA) class III or IV congestive
heart failure; acute coronary syndrome (ACS); and/or stroke; or left ventricular ejection fraction (LVEF) < 40% by echocardiogram (ECHO) or multi-gated
acquisition (MUGA) scan obtained within 28 days prior to the start of study treatment.
9. Subject has prior history of malignancy, other than MDS, MPN, or AML, unless the
subject has been free of the disease for >= 1 year prior to the start of study treatment.
However, subjects with the following history/concurrent conditions are allowed:
• Basal or squamous cell carcinoma of the skin
• Carcinoma in situ of the cervix
• Carcinoma in situ of the breast
• Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node,
metastasis clinical staging system)
10. Subject is known seropositive for or has active viral infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or
hepatitis C virus (HCV)
11. Subject is known to have dysphagia, short-gut syndrome, gastroparesis, or

other
conditions that limit the ingestion or gastrointestinal absorption of drugs administered
orally
12. Subject has uncontrolled hypertension (systolic blood pressure [BP] > 180 mmHg or
diastolic BP > 100 mmHg)
13. Subject is taking the following sensitive CYP substrate medications that have a narrow
therapeutic range are excluded from the study unless the subject can be transferred to
other medications at least 5 half-lives prior to the start of study treatment: phenytoin
(CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline, and
tizanidine (CYP1A2).
14. Subject is taking the breast cancer resistance protein (BCRP) transporter-sensitive
substrate rosuvastatin; subject should be excluded from the study unless he/she can be
transferred to other medications at least 5 half-lives prior to the start of study treatment.
15. Subject has active uncontrolled systemic fungal, bacterial, or viral infection (defined as
ongoing signs/symptoms related to the infection without improvement despite
appropriate antibiotics, antiviral therapy, and/or other treatment).
16. Subject has known or suspected hypersensitivity to any of the components of study
therapy.
17. Subject is taking medications that are known to prolong the QT interval unless he/she can be transferred to other medications within >= 5 half-lives prior to the start of
study treatment. (If equivalent medication is not available, QTc will be closely monitored)
18. Subject has QTc interval (ie, Fridericia*s correction [QTcF]) >= 450 ms or other factors
that increase the risk of QT prolongation or arrhythmic events (eg, heart failure,
hypokalemia, family history of long QT interval syndrome) at screening.
19. Female subject who is pregnant or lactating.
20. Subject has any significant medical condition, laboratory abnormality, or psychiatric
illness that would prevent the subject from participating in the study.
21. Subject has any condition, including the presence of laboratory abnormalities, that places
the subject at unacceptable risk if he/she were to participate in the study.
22. Subject has any condition that confounds the ability to interpret data from

the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-02-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	AG-120
Generic name:	ivosidenib
Product type:	Medicine
Brand name:	AG-221
Generic name:	enasidenib
Product type:	Medicine
Brand name:	Vidaza
Generic name:	Azacitidine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-511722-31-00
EudraCT	EUCTR2015-003951-23-NL
ClinicalTrials.gov	NCT02677922
CCMO	NL56633.029.16