Trial record **1 of 1** for: AG-221-AML-005

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A Safety and Efficacy Study of Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus Subcutaneous Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia (AML)

ClinicalTrials.gov Identifier: NCT02677922

Recruitment Status : Recruiting
First Posted : February 9, 2016
Last Update Posted : December 25, 2017

See **Contacts and Locations**

Sponsor:
Celgene

Information provided by (Responsible Party):
Celgene

Study Details | **Tabular View** | **No Results Posted** | Disclaimer

How to Read a Study Record

Study Description

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Brief Summary:

This Phase 1b/2 study is an open-label, randomized, multicenter trial to evaluate the safety and efficacy of oral AG-120 + Subcutaneous (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 Inductive chemotherapy (IC). The study comprises a Phase 1b dose-finding and AG-120 expansion stage and a Phase 2 randomized stage.

Condition or disease	Intervention/treatment	Phase
Leukemia, Myeloid, Acute	Drug: AG-120 Drug: Azacitidine Drug: AG-221	Phase 1 Phase 2

Detailed Description:

The study was redesigned to expand the number of patients analyzed during the Phase 1b stage of the study to determine a safe and effective dose of AG-120 administered with azacitidine for future studies.

The Phase 1b (AG-120 expansion) stage will evaluate the safety, tolerability, and clinical activity of oral AG-120 when administered with Subcutaneous azacitidine.

The Phase 2 stage of the study will no longer include AG-120 administered with azacitidine (IDH1 subjects) and IDH1 patients will not longer be included in the azacitidine alone arm.

Study Design

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Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	127 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	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
Actual Study Start Date :	June 3, 2016
Estimated Primary Completion Date :	December 15, 2018
Estimated Study Completion Date :	January 28, 2019

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics:
- Core binding factor acute myeloid leukemia
- Cytogenetically normal acute myeloid leukemia
- Familial acute myeloid leukemia with mutated CEBPA

MedlinePlus related topics: Acute Myeloid Leukemia
- Leukemia

Drug Information available for: Azacitidine

Genetic and Rare Diseases Information Center resources: Myeloid Leukemia
- Acute Myeloid Leukemia
- Acute Non Lymphoblastic Leukemia

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Oral AG-120 + Subcutaneous (SC) azacitidine Subjects with an IDH1 mutation will receive AG-120 at the RP2D 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.	Drug: AG-120 Drug: Azacitidine
Experimental: Oral AG-221 + Subcutaneous (SC) azacitidine Subjects with an IDH2 mutation will receive AG-221 at the RP2D 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.	Drug: Azacitidine Drug: AG-221

Experimental: Subcutaneous (SC) azacitidine Subjects with either an IDH1 or IDH2 mutation will receive azacitidine 75 mg/m2/day SC for 7 days of each 28-day cycle.	Drug: Azacitidine

Outcome Measures

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Primary Outcome Measures :

1. Dose limiting toxicities (DLTs)-Phase 1B [Time Frame: Up to approximately 7 months]

   DLTs will be defined as any of the following events that commence within 28 days of the first dose of IP in a 28-day treatment cycle, constitute a change from baseline irrespective of outcome and are determined by the investigator to be related to treatment.

2. Adverse Events (AEs) in Ph 1b [Time Frame: Up to approximately 4 years]

   Number of participants with adverse events

3. Pharmacokinetics- Cmax [Time Frame: Up to approximately 7 months]

   Maximum observed concentration in plasma

4. Pharmacokinetics- Tmax [Time Frame: Up to approximately 7 months]

   Time to maximum concentration

5. Pharmacokinetics- AUC [Time Frame: Up to approximately 7 months]

   Area under the plasma concentration-time curve

6. Overall response rate (ORR) Ph 2 [Time Frame: Up to approximately 30 months]

   Includes responses of Morphologic complete remission (CR), Morphologic complete remission with incomplete platelet recovery (CRp), morphologic leukemia-free state (MLFS), Morphologic complete remission with incomplete neutrophil recovery (CRi), and Partial remission (PR), according to modified International Working Group (IWG) Acute myeloid leukemia (AML) response criteria.

Secondary Outcome Measures :

1. Overall Response Rate - Phase 1b (Ph 1b) [Time Frame: Up to approximately 13 months]

   Rate of Morphologic complete remission (CR) + Morphologic complete remission with incomplete neutrophil recovery (CRi) + Morphologic complete remission with incomplete platelet recovery (CRp) + Morphologic leukemia-free state (MLFS) + Partial remission (PR) according to modified International Working Group (IWG) Acute myeloid leukemia (AML) response criteria

2. Event-Free Survival - Phase 2 (Ph 2) [Time Frame: Up to approximately 30 months]

   Time from randomization to documented morphologic relapse, progression according to modified International Working Group (IWG) Acute myeloid leukemia (AML) response criteria, or death from any cause, whichever occurs first.

3. Adverse Events (AEs) - Ph 2 [Time Frame: Up to approximately 4 years]

   Number of participants with adverse events

4. Complete remission rate - Ph 2 [Time Frame: Up to approximately 30 months]

   Rate of morphologic complete remission (CR) according to modified International Working Group (IWG) Acute myeloid leukemia (AML) response criteria

5. Hematologic improvement rate - Ph 2 [Time Frame: Up to approximately 30 months]

   Rate of Hematologic improvement - neutrophil response (HI-N) + Hematologic improvement - platelet response (HI-P) + Hematologic improvement - erythroid response (HI-E) according to International Working Group (IWG) Myelodysplastic syndromes (MDS) Hematologic improvement(HI) criteria

6. Duration of Response - Ph 2 [Time Frame: Up to approximately 30 months]

   Time from the first documented MLFS/CR/CRi/CRp/PR to documented morphologic relapse, progression according to modified IWG AML response criteria, or death due to any cause, whichever occurs first

7. Overall Survival - Ph 2 [Time Frame: Up to approximately 30 months]

   Time from randomization to death due to any cause

8. One-year survival- Ph 2 [Time Frame: Up to approximately 12 months]

   The probability of survival at 1 year from randomization

9. Pharmacokinetics- Cmax - Ph 2 [Time Frame: Up to approximately 30 months]

   Maximum observed concentration in plasma

10. Pharmacokinetics- Tmax - Ph 2 [Time Frame: Up to approximately 30 months]

    Time to maximum concentration

11. Pharmacokinetics- AUC - Ph 2 [Time Frame: Up to approximately 30 months]

    Area under the plasma concentration-time curve

12. EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire - Ph 2 [Time Frame: Up to approximately 30 months]

    Is a validated quality-of-life measure applicable to subjects with any cancer diagnosis. It is composed of 30 items that address general physical symptoms, physical functioning, fatigue and malaise, and social and emotional functioning. Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher scores on symptom scales indicating worse symptoms

13. EQ-5D-5L Health Questionnaire - Ph 2 [Time Frame: Up to approximately 30 months]

    Is a standardized instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status, and is applicable to a wide range of health conditions and treatments

14. Overall Response Rate - Phase 1b (Ph 2) [Time Frame: Up to approximately 30 months]

    Rate of Morphologic complete remission (CR) + Morphologic complete remission with incomplete neutrophil recovery (CRi) + Morphologic complete remission with incomplete platelet recovery (CRp) + Morphologic leukemia-free state (MLFS) +Partial remission (PR) according to modified International Working Group (IWG) Acute myeloid leukemia (AML) response criteria

15. Time to Response - Phase 2 [Time Frame: Up to approximately 30 months]

    Time from first dose of study drug to first documented Morphologic complete remission (CR)/ Morphologic complete remission with incomplete neutrophil recovery (CRi)/ Morphologic complete remission with incomplete platelet recovery (CRp)/ Morphologic

leukemia-free state (MLFS)/ Partial remission (PR) according to modified International Working Group (IWG) Acute myeloid leukemia (AML) response criteria

Eligibility Criteria

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Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age 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 with ≥ 20% leukemic blasts in the bone marrow: -Have an Isocitrate dehydrogenase 1 (IDH1) or Isocitrate dehydrogenase 2 (IDH2) gene mutation (R132, R140, or R172)
    - IDH mutational status will be assessed locally; for sites without local testing capabilities, a referral lab will be identified.
        - By the investigator's assessment who are not candidates to receive intensive Inductive chemotherapy (IC).

5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
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 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 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 ** from sexual intercourse or to use 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 at least 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 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 partners 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 at least 4 months following the last study treatment (6 months following 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 Isocitrate dehydrogenase 1 (IDH1) or Isocitrate dehydrogenase 2 (IDH2) mutation.
4. Subject has received prior systemic anticancer therapy, HSCT, or radiotherapy for AML.

   Note: 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 Myelodysplastic syndromes (MDS).

   - Clarification: Subjects with newly diagnosed Acute myeloid leukemia (AML) who are currently receiving their 1st cycle of azacitidine (7 days) can be screened for the study. On study, Cycle 1 must be started at 28 days (+/- 3 days) after initiation of the pre-study azacitidine.
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, Myeloproliferative neoplasm (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.
18. Subject has Heart rate-corrected QT (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.

Contacts and Locations

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Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT02677922***

Contacts

Contact: Associate Director Clinical Trial Disclosure 1-888-260-1599 clinicaltrialdisclosure@

Show 66 Study Locations

Sponsors and Collaborators

Celgene

Investigators

Study Director: Ira Gupta, MD Celgene Corporation

More Information

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Responsible Party:	Celgene
ClinicalTrials.gov Identifier:	NCT02677922 History of Changes
Other Study ID Numbers:	**AG-221-AML-005**
First Posted:	February 9, 2016 Key Record Dates
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Keywords provided by Celgene:
Acute Myeloid Leukemia
Leukemia
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AG-120
AG-221

Additional relevant MeSH terms:
Leukemia
Leukemia, Myeloid
Leukemia, Myeloid, Acute
Neoplasms by Histologic Type
Neoplasms
Azacitidine
Antimetabolites, Antineoplastic
Antimetabolites
Molecular Mechanisms of Pharmacological Action
Antineoplastic Agents
Enzyme Inhibitors