Study of AG-120 (Ivosidenib) vs. Placebo in Combination With Azacitidine in Patients With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation (AGILE)

ClinicalTrials.gov Identifier: NCT03173248

Recruitment Status : Recruiting
First Posted : June 1, 2017
Last Update Posted : May 29, 2020

See **Contacts and Locations**

Sponsor:
Agios Pharmaceuticals, Inc.

Information provided by (Responsible Party):
Agios Pharmaceuticals, Inc.

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

How to Read a Study Record

Study Description

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Brief Summary:

Study AG120-C-009 is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of AG-120 (ivosidenib) + azacitidine vs placebo + azacitidine in adult participants with previously untreated IDH1m AML who are considered appropriate candidates for non-intensive therapy. The primary endpoint is event-free survival (EFS). The key secondary efficacy endpoints are overall survival (OS), rate of complete remission (CR), rate of CR and complete remission with partial hematologic recovery (CRh), and overall response rate (ORR). Participants eligible for study treatment based on Screening assessments will be randomized 1:1 to receive oral AG-120 or matched placebo, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine. An estimated 200 participants will take part in the study.

Condition or disease	Intervention/treatment	Phase
Newly Diagnosed Acute Myeloid Leukemia (AML) Untreated AML AML Arising From Myelodysplastic Syndrome (MDS) Leukemia, Myeloid, Acute	Drug: AG-120 (ivosidenib) with Azacitidine Drug: Placebo with Azacitidine	Phase 3

Study Design

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Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	200 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Treatment
Official Title:	A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination With Azacitidine in Subjects ≥ 18 Years of Age With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation
Actual Study Start Date :	June 26, 2017
Estimated Primary Completion Date :	October 31, 2021
Estimated Study Completion Date :	October 31, 2021

Resource links provided by the National Library of Medicine NIH NLM

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
Myelodysplastic Syndromes

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: AG-120 (ivosidenib) with Azacitidine	Drug: AG-120 (ivosidenib) with Azacitidine Continuous 28-day cycles of AG-120 (ivosidenib) 500 mg orally (PO) once daily (QD) in combination with azacitidine 75 mg/m2/day SC or IV for the first week of each cycle
Placebo Comparator: Placebo with Azacitidine	Drug: Placebo with Azacitidine Continuous 28-day cycles of Placebo orally (PO) once daily (QD) in combination with azacitidine 75 mg/m2/day SC or IV for the first week of each cycle

Outcome Measures

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Primary Outcome Measures :

1. Event-Free Survival (EFS) [Time Frame: Up to approximately 52 months]

   EFS is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve complete remission (CR) by Week 24.

Secondary Outcome Measures :

1. Complete Remission Rate (CR Rate) [Time Frame: Up to approximately 52 months]

   CR rate is defined as the proportion of participants who achieve a CR. A Cochran-Mantel-Haenszel (CMH) test will be used to compare CR rate between the 2 treatment arms.

2. Overall Survival (OS) [Time Frame: Up to approximately 52 months]

   OS is defined as the time from date of randomization to the date of death due to any cause. Kaplan-Meier (KM) curves and KM estimates of OS will be presented for each treatment arm.

3. CR + Complete Remission With Partial Hematologic (CRh) Rate [Time Frame: Up to approximately 52 months]

   CR + CRh rate is defined as the proportion of participants who achieve a CR or CRh. CRh is defined as a CR with partial recovery of peripheral blood counts (less than 5% bone marrow blasts, absolute neutrophil count (ANC) greater than 0.5 × 10^9/liter (L) 500/microliter (µL)], and platelets greater than 50 × 10^9/L [50,000/µL]). A CMH test will be used to compare the CR + CRh rate between the 2 treatment arms.

4. Objective Response Rate (ORR) [Time Frame: Up to approximately 52 months]

   ORR is defined as the rate of CR, CR with incomplete hematologic recovery (CRi) (including CR with incomplete platelet recovery [CRp]), partial remission (PR), and morphologic leukemia-free state (MLFS). The best response is calculated using the following hierarchy: CR, followed by CRi (including CRp), followed by PR and MLFS. A summary of best response by treatment arm will be produced. A CMH test will be used to compare ORR between the 2 treatment arms.

5. CR + CRi (Including CRp) Rate [Time Frame: Up to approximately 52 months]

   The CR + CRi (including CRp) rate is defined as the proportion of participants who achieve a CR or CRi (including CRp). A CMH test will be used to compare the CR + CRi (including CRp) rate between the 2 treatment arms.

6. Duration of CR (DOCR) [Time Frame: Up to approximately 52 months]

   DOCR will be calculated as the date of the first occurrence of CR to the date of first documented disease relapse, or death. DOCR is only defined for participants who achieve a CR.

7. Duration of CRh (DOCRh) [Time Frame: Up to approximately 52 months]

   DOCRh will be calculated as the date of the first occurrence of CR or CRh to the date of first documented disease relapse or death. DOCRh is only defined for participants who achieve a CR or CRh.

8. Duration of Response (DOR) [Time Frame: Up to approximately 52 months]

   DOR will be calculated as the date of the first response to the date of first documented disease relapse, disease progression, or death. DOR is only defined for participants who achieve a CR, CRi (including CRp), PR, and/or MLFS.

9. Duration of CRi (DOCRi) [Time Frame: Up to approximately 52 months]

   DOCRi will be calculated as the date of the first occurrence of CR or CRi (including CRp) to the date of the first documented relapse or death. DOCRi is only defined for participants who achieve a CR or CRi (including CRp).

10. Time to CR (TTCR) [Time Frame: Up to approximately 52 months]

    TTCR will be assessed from the date of randomization to the date of first occurrence of CR. TTCR is only defined for participants who achieve a CR.

11. Time to CRh (TTCRh) [Time Frame: Up to approximately 52 months]

    TTCRh will be assessed from the date of randomization to the date of first occurrence of CR or CRh. TTCRh is only defined for participants who achieve a CR or CRh.

12. Time to Response (TTR) [Time Frame: Up to approximately 52 months]

    TTR will be assessed from the date of randomization to the date of the first response. TTR is only defined for participants who achieve a CR, CRi (including CRp), PR, and/or MLFS.

13. Time to CRi (TTCRi) [Time Frame: Up to approximately 52 months]

    TTCRi will be assessed from the date of randomization to the date of first occurrence of CR or CRi (including CRp). TTCRi is only defined for participants who achieve a CR or CRi (including CRp).

14. Percentage of Participants with Abnormalities in Vital Sign Measurements [Time Frame: From Baseline up to approximately 1 week after last dose of treatment (up to a maximum of 52 months)]

    Vital signs will include body temperature, respiratory rate, blood pressure, and heart rate.

15. Percentage of Participants with Abnormalities in Eastern Cooperative Oncology Group Performance Status (ECOG PS) [Time Frame: From Baseline up to approximately 1 week after last dose of treatment (up to a maximum of 52 months)]
16. Percentage of Participants with Abnormalities in 12-lead Electrocardiograms (ECGs) [Time Frame: From Baseline up to approximately 1 week after last dose of treatment (up to a maximum of 52 months)]
17. Percentage of Participants with Abnormalities in Echocardiogram (ECHO) or Multi-Gated Acquisition (MUGA) for Left Ventricular Ejection Fraction (LVEF) [Time Frame: From Baseline up to approximately 1 week after last dose of treatment (up to a maximum of 52 months)]

    LVEF is determined by ECHO or MUGA scan in participants.

18. Percentage of Participants with Abnormalities in Clinical Laboratory Tests [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    Clinical laboratory assessments will include hematology, serum chemistry, coagulation.

19. Percentage of Participants with Adverse Events (AEs) [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a investigational medicinal product; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

20. Percentage of Participants with AEs of Special Interest (AESIs) [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    AESIs are AEs that are not solicited local or systemic AEs, they are predefined AEs that required close monitoring and prompt reporting to the sponsor. AESIs include protocol-specified QT prolongation, isocitrate dehydrogenase (IDH) differentiation syndrome and

leukocytosis.

21. Percentage of Participants with Serious Adverse Events (SAEs) [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    An SAE is defined as an untoward medical occurrence, significant hazard, contraindication, side effect or precaution that at any dose: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant.

22. Percentage of Participants Using Concomitant Medications [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    Participants receiving concomitant medications will be adequately monitored by ECG controls, drug concentration (where applicable), and serum electrolytes (ie, potassium and magnesium).

23. Units of Platelets and Red Blood Cells (RBC) Infused [Time Frame: Up to approximately 52 months]

    All measures that are indicative of clinical benefit are measured like number of units of platelet and RBC infused.

24. Rate of Infection [Time Frame: Up to approximately 52 months]
25. Days Spent Hospitalized [Time Frame: Up to approximately 52 months]
26. Change From Baseline in the European Organisation for Research and Treatment of Cancer (EORTC) QLC-C30 Questionnaire [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    The EORTC QLQ-C30 questionnaire measures quality of life and consists of 30 questions that are incorporated into 5 functional domains (physical, role, cognitive, emotional, and social); a global health status/global quality of life; 3 symptom scales (fatigue, pain, and nausea and vomiting); and 6 single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment experienced by participants with cancer.

27. Change From Baseline in the EORTC EQ-5D-5L Questionnaire [Time Frame: From Baseline up to approximately 4 weeks after last dose of treatment (up to a maximum of 52 months)]

    The EORTC EQ-5D-5L questionnaire measures quality of life and spans 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which

are used to build a composite of the participant's health status.

28. Percentage of Participants With CR With IDH1 Mutation Clearance (MC) [Time Frame: Up to approximately 52 months]

    CR with IDH1 MC is defined as a response of CR where there is no evidence of the IDH1 mutation by molecular techniques to below the level of detection (0.02%-0.04%) for ≥1 on-treatment time point. A CMH test will be used to compare the rate of CR between 2 treatment arms.

29. Percentage of Participants With Drug Exposure, Dose Modifications and Dose Intensities [Time Frame: From Baseline up to the last dose of treatment (up to a maximum of 52 months)]

    The number of doses administered, total dose, duration of treatment, dose intensity, and the proportion of participants with dose modifications, will be summarized by treatment arm.

30. Circulating Plasma Concentration of AG-120 and 2-HG [Time Frame: From Baseline up to the last dose of treatment (up to a maximum of 52 months)]

    Serial blood samples will be drawn before and after dosing of study treatment in order to determine circulating plasma concentrations.

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, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. Be ≥ 18 years of age and meet at least 1 of the following criteria defining ineligibility for intensive induction chemotherapy (IC): ≥ 75 years old, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 2, severe cardiac disorder (eg, congestive heart failure requiring treatment, LVEF, ≤50%, or chronic stable angina), severe pulmonary disorder (eg, diffusing capacity of the lungs for carbon monoxide ≤65% or forced expiratory volume in 1 second ≤65%), creatinine clearance <45 mL/minute, bilirubin >1.5 times the upper limit of normal (× ULN) and/or have any other comorbidity that the Investigator judges to be incompatible with intensive IC and must be reviewed and approved by the Medical Monitor before study enrollment.
2. Have previously untreated AML, defined according to World Health Organization (WHO) criteria, with ≥ 20% leukemic blasts in the bone marrow. Participants with extramedullary disease alone (ie, no detectable bone marrow and no detectable peripheral blood AML) are not eligible for the study.
3. Have an isocitrate dehydrogenase 1 (IDH1) mutation.
4. Have an ECOG PS score of 0 to 2.
5. Have adequate hepatic function.
6. Have adequate renal function.
7. Have agreed to undergo serial blood and bone marrow sampling.
8. Be able to understand and willing to sign an informed consent form (ICF).
9. Be willing to complete Quality of Life assessments during the study
10. If female with reproductive potential, must have a negative serum pregnancy test prior to the start of study therapy. Females of reproductive potential, as well as fertile men and their female partners of reproductive potential, must agree to use 2 effective forms of contraception.

Exclusion Criteria:

1. Are candidates for and willing to receive intensive induction chemotherapy (IC) for their AML.
2. Have received any prior treatment for AML with the exception of hydroxyurea.
3. Have received a hypomethylating agent for myelodysplastic syndrome (MDS).
4. Participants who had previously received an experimental agent for MDS may not be randomized until a washout period has elapsed since the last dose of that agent.
5. Have received prior treatment with an IDH1 inhibitor.
6. Have a known hypersensitivity to any of the components of AG-120, matched placebo, or azacitidine.
7. Are female and pregnant or breastfeeding.
8. Have an active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement

despite appropriate antibiotics, antiviral therapy, and/or other treatment.

9. Have a prior history of cancer other than MDS or myeloproliferative disorder, unless the participant has been free of the disease for ≥ 1 year prior to the start of study treatment.
10. Have had significant active cardiac disease within 6 months prior to the start of the study treatment.
11. Have any condition that increases the risk of abnormal ECG or cardiac arrhythmia.
12. Have a condition that limits the ingestion or absorption of drugs administered by mouth.
13. Have uncontrolled hypertension (systolic blood pressure [BP] > 180 mmHg or diastolic BP > 100 mmHg).
14. Have clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia.
15. Have immediate, life-threatening, severe complications of leukemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.
16. Have any other medical or psychological condition deemed by the Investigator to be likely to interfere with the participant's ability to give informed consent or participate in the study.
17. Are taking medications that are known to prolong the QT interval unless they can be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications can be properly monitored during the study. (If equivalent medication is not available, heart rate corrected QT interval [QTc] will be closely monitored.)
18. Have a known medical history of progressive multifocal leukoencephalopathy.

Contacts and Locations

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Information from the National Library of Medicine

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): ***NCT03173248***

Contacts

Contact: Medical Affairs Agios Pharmaceuticals, Inc. 1.833.228.8474 medinfo@agios.com

Locations

▸ Show 201 study locations

Sponsors and Collaborators

Agios Pharmaceuticals, Inc.

More Information

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Responsible Party: Agios Pharmaceuticals, Inc.
ClinicalTrials.gov Identifier: NCT03173248 History of Changes
Other Study ID Numbers: AG120-C-009
First Posted: June 1, 2017 Key Record Dates
Last Update Posted: May 29, 2020
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Individual Participant Data (IPD) Sharing Statement:
Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: Yes
Studies a U.S. FDA-regulated Device Product: No

Keywords provided by Agios Pharmaceuticals, Inc.:
Acute Myeloid Leukemia
Leukemia
Azacitidine
AG-120
ivosidenib

Additional relevant MeSH terms:

Leukemia	Azacitidine
Leukemia, Myeloid	Ivosidenib
Leukemia, Myeloid, Acute	Antimetabolites, Antineoplastic
Myelodysplastic Syndromes	Antimetabolites
Neoplasms by Histologic Type	Molecular Mechanisms of Pharmacological Action
Neoplasms	Antineoplastic Agents
Bone Marrow Diseases	Enzyme Inhibitors
Hematologic Diseases	