A Study of Safety, Efficacy and Pharmacodynamics of Azacitidine in Children and Young Adults With Acute Myeloid Leukemia.

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2016 by Celgene Corporation

Sponsor:
Celgene Corporation

Information provided by (Responsible Party):
Celgene Corporation

ClinicalTrials.gov Identifier:
NCT02450877

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History of Changes

Purpose

This study is a randomized, multicenter, open-label, Phase 2 study that will be run in 2 parts: a safety run-in part to determine the dose of azacitidine and then a second part to determine the efficacy of that dose in children and young adults with acute myeloid leukemia in molecular relapse after their first complete remission.

Indication Treatment of children and young adults with molecular relapse of acute myeloid leukemia (AML) after first complete remission (CR1).

Objectives Primary Objectives Safety Run-in Part To establish a safe and tolerable dose of azacitidine to be used in the randomized part of the study.

Randomized Part To evaluate the effect of azacitidine treatment in AML subjects at molecular relapse after CR1 when compared to no treatment with regard to the progression-free rate (PFR) at Day 84 (±4 days) post randomization.

Secondary Objectives Safety Run-in Part To establish azacitidine plasma pharmacokinetic (PK) parameters in subjects with molecular relapse AML after CR1 and to assess efficacy.

Randomized Part To evaluate the safety, pharmacodynamics (PD), and efficacy of azacitidine treatment in subjects with molecular relapse AML after CR1.

Study Design The population of this trial consists of children and young adults with AML who achieved a complete response (CR) with molecular remission, defined as Minimal Residual Disease (MRD) less than 5 x 10-4, following their initial induction therapy and who subsequently have a molecular relapse (defined as increase in MRD level by at least 1 log [10-fold] to a level greater than or equal to 5 x 10-4 despite a normal percentage [<5%] of myeloblasts in the bone marrow [BM] aspirate and peripheral blood [PB], and in the absence of proven histological extramedullary relapse). Eligible subjects have a documented diagnosis of AML with at least one of the following molecular aberrations t(8;21), RUNX1-RUNX1T1, inv(16), CBFb/MYH11, t(9;11), MLL-AF9, NPM1 mutation, or FLT3-ITD mutation. Enrolled/randomized pediatric subjects will be followed with regular MRD testing in order to detect a molecular relapse.

In the safety run-in part, up to 12 subjects aged 3 months to less than 18 years will be enrolled. Six subjects will be enrolled in the first cohort of 100 mg/m2 azacitidine administered intravenously (IV) on Days 1 to 7 of a 28-day cycle. Six additional subjects could be enrolled into a second cohort of 75 mg/m2 azacitidine administered IV on Days 1 to 7 of a 28-day cycle depending on the safety and tolerability results of the 100 mg/m2 cohort.

In the randomized part of the study at least 68 subjects will be randomized (or more depending on whether at least 64 subjects are evaluable for the primary endpoint), with at least 60 of the subjects being less than 18 years of age.

Both parts of the study, the safety run-in part and the randomized part, will contain 3 periods: the screening period, the treatment period and the follow-up period. The screening period will last no more than 10 days in the safety run-in part after which the subjects may be enrolled and treated. In the randomized part, the screening period will last an indefinite amount of time until detection of a molecular relapse in the PB followed by confirmation of the relapse in both PB and BM aspirate, at which point the subject may then be randomized. Subjects will be treated with azacitidine (safety run-in part) or in accordance to their assigned treatment arm (randomized part). Upon discontinuation from the treatment period, subjects will enter into the follow-up period which will last up to 2 years from last patient enrolled/randomized.

Condition	Intervention	Phase
Leukemia, Myeloid, Acute	Drug: Azacitidine Other: Control Arm	Phase 2

Study Type: Interventional
Study Design:

Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Randomized, Multicenter, Open-label, Phase 2 Study, With a Safety Run-in Part to Evaluate Safety, Pharmacodynamics and Efficacy of Azacitidine Compared to No Anticancer Treatment in Children and Young Adults With Acute Myeloid Leukemia in Molecular Relapse After First Complete Remission

Resource links provided by 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

U.S. FDA Resources

Further study details as provided by Celgene Corporation:

Primary Outcome Measures:

- Adverse Events (AEs) [Time Frame: Up to Day 28] [Designated as safety issue: Yes]

  All reported adverse events during the first treatment cycle

- Dose-limiting toxicities (DLTs) [Time Frame: up to Day 28] [Designated as safety issue: Yes]

  Number of participant with DLT The rate of the following treatment-related DLTs as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAEs) version 4.0, occurring during Cycle 1 only will be considered in determining the tolerability of the 100 mg/m2 dose of azacitidine:

  - Grade 4 nonhematologic toxicity (excluding transient transaminase elevation)
  - Grade 3 nonhematological toxicity lasting more than 7 days despite optimal treatment with standard supportive measures
  - Grade 3 or 4 hematologic toxicity requiring treatment delay greater than 21 days (disease-related Grade 3 or 4 hematologic toxicity will not be counted as a DLT)

- Progression-free rate at Day 84 post randomization [Time Frame: up to Day 84] [Designated as safety issue: No]

  Proportion of subjects free from clinical progression (clinical relapse and death from any cause) and from molecular progression (defined as lack of stabilization or lack of decrease in molecular aberrations concerning FLT3-ITD mutated, CBF leukemias (eg, t(8;21) and/or inv(16)), MLL-gene rearrangements or NPM1-mutations using central assessment of BM samples by the central laboratories identified for the study, obtained at time points identically prespecified in both randomization arms) at Day 84 (±4 days) post randomization.

Secondary Outcome Measures:

- Pharmacokinetics - Cmax [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Maximum observed concentration in plasma

- Pharmacokinetics - Tmax [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Observed time to maximum plasma concentration

- Pharmacokinetics - AUCt [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Area under the plasma concentration-time curve from time zero to the last quantifiable time point

- Pharmacokinetics - AUC∞ [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Area under the plasma concentration-time curve from time zero to infinity

- Pharmacokinetics - λz [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Terminal phase rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve

- Pharmacokinetics - t½ [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Terminal phase half-life, will be calculated according to the following equation:t½ = 0.693/λz

- Pharmacokinetics - CL [Time Frame: Up to Day 7] [Designated as safety issue: No]

  Total clearance, calculated as Dose/AUC∞

- Pharmacokinetics - Vz [Time Frame: Up to Day 7] [Designated as safety issue: No]

  volume of distribution will be calculated according to the equation: Vz = (CL)/λz

- Changes in DNA methylation (assessments of BM samples using Nano-HELP assay) [Time Frame: up to Day 60] [Designated as safety issue: No]

  Descriptive analyses if the level of DNA methylation at certain CpG loci may predict the response or resistance to azacitidine with regard to the following efficacy endpoints: response, LFS, and OS.

- Leukemia-free survival (LFS) [Time Frame: Up to 9 years] [Designated as safety issue: No]

  Leukemia-free survival is defined as the time from study enrollment (safety run-in part) or randomization (randomized part) until transition to leukemia progression or death.

- Minimal residual disease pre-, and 3 and 6 months post-HSCT [Time Frame: up to 9 years] [Designated as safety issue: No]

  Minimal residual disease levels will be assessed across time points

- Overall survival [Time Frame: up to 9 years] [Designated as safety issue: No]

  Overall survival is the time from study enrollment (safety run-in part) or randomization (randomized part) until death from any cause.

- Proportion treated with HSCT [Time Frame: Up to 9 years] [Designated as safety issue: No]

  The proportion of subjects undergoing HSCT during the conduct of this study over the total number of subjects enrolled into this study.

- Molecular response [Time Frame: up to Day 84] [Designated as safety issue: No]

  Molecular response is the number of subjects with molecular response (1 log or more decrease in defined MRD molecular markers from baseline) divided by the number of subjects within the analysis population.

- Treatment-related mortality/morbidity [Time Frame: up to 9 years] [Designated as safety issue: No]

  All reported SAEs and Deaths during the duration of the study conduct.

- Toxicity after HSCT [Time Frame: up to 9 years] [Designated as safety issue: Yes]

  All reported SAEs and deaths post HSCT during the duration of the study conduct

- Adverse Events (AEs) [Time Frame: up to 9 years] [Designated as safety issue: Yes]

  All reported adverse events during the duration of the study conduct

Estimated Enrollment:	80
Study Start Date:	August 2015
Estimated Study Completion Date:	March 2020
Estimated Primary Completion Date:	August 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Azacitidine Treatment : Subjects randomized to the experimental arm will receive up to 3 cycles of IV azacitidine on Days 1 through 7 at the dose selected from the safety run-in part.	Drug: Azacitidine
Control Arm: 'Watch and Wait' Subjects randomized to the control arm will undergo 'watch and wait' until clinical relapse (defined as at least 5% blasts in PB (peripheral blood) and/or BM (bone marrow) and/or proven histological extramedullary relapse).	Other: Control Arm

Show Detailed Description

Eligibility

Ages Eligible for Study:	3 Months to 21 Years (Child, Adult)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

Safety Run-in Part:

1. Understand and voluntarily provide permission (subjects and when applicable, parental/legal representative(s)) to the informed consent/assent form (ICF/IAF) prior to conducting any study related assessments/procedures.
2. Able to adhere to the study visit schedule and other protocol requirements.
3. Male or Female subjects aged 3 months to less than 18 years old at the time of informed consent/assent.
4. Documented diagnosis of Acute myeloid leukemia (AML) according to World Health Organization (WHO) classification with at least one of the following molecular aberrations below:
    a. t(8;21), RUNX1-RUNX1T1
    b. inv(16), CBFb/MYH11
    c. t(9;11), MLL-AF9
    d. NPM1 mutation
    e. FLT3-ITD mutation.
5. Documentation of molecular remission (MRD less than 5 x 10-4) confirmed at the start of last consolidation course or within 1 month after completion of consolidation treatment.
6. Detection of molecular relapse in the Peripheral Blood (PB) by real-time quantitative polymerase chain reaction (RQ-PCR) within the 7 days prior to signing informed consent/assent form and confirmation of relapse during the screening period. Molecular relapse is defined as an increase in molecular remission (MRD) level of a subject-specific fusion gene or aberration by at least 1 log (10-fold) to a level of at least 5 x 10-4. For subjects who are MRD negative, the rise should be at least 1 log (10-fold) greater than previous sensitivity to a level of 5 x 10-4 or above. An increase in PB must be confirmed in PB and bone marrow (BM) aspirate by RQ-PCR. Confirmation of a molecular relapse is given if the MRD positivity is at the same level or higher in the PB and BM sample compared to the PB MRD levels at the detection of the relapse and in the absence of clinical relapse (defined as at least 5% blasts in PB and/or BM and/or proven histological extramedullary relapse).
7. Lansky play score at least equal to 50; or Karnofsky performance status at least equal to 50, whichever is applicable.
8. Females of Childbearing Potential and male subjects that have reached puberty and are younger than 18 years of age must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction with parent/parents and/or guardian/guardians.
9. Females of Childbearing Potential, defined as females who have achieved menarche and/or 8 years or older and have not undergone a hysterectomy or bilateral oophorectomy, must meet the following conditions below.
    a. Have a negative serum pregnancy test within 72 hours prior to starting study therapy as verified by the study doctor. Agree to ongoing pregnancy testing during the course of the study and after end of study therapy at the 28-day follow-up visit. This applies even if the subject practices true abstinence* from heterosexual contact.
    b. Female subjects must, as appropriate to age and the discretion of the study physician,either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) and/or agree to the use of approved contraceptive method (eg, oral,injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; or vasectomized partner) while on azacitidine; and for 3 months following the last dose.
10. Male subjects must as appropriate to age and the discretion of the study physician:
    a. Agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 3 months following azacitidine discontinuation, even if he has undergone a successful vasectomy.

Randomized Part (at the time of signing ICF/IAF):

1. Understand and voluntarily provide permission (subjects and when applicable,parental/legal representative(s)) to the ICF/IAF prior to conducting any study related assessments/procedures.
2. Able to adhere to the study visit schedule and other protocol requirements.
3. Male or female subjects aged 3 months to less than 21 years old at the time of informed consent/assent. Note: Minimum of 60 subjects less than 18 years of age must be included. The remainder of the randomized subjects may be greater than or equal to 18 but less than 21 years of age.
4. Documented diagnosis of AML, according to WHO classification with at least one of the following molecular aberrations below that is determined by the central laboratory to be present using BM aspirate from initial diagnosis,:
    a. t(8;21), RUNX1-RUNX1T1
    b. inv(16), CBFb/MYH11
    c. t(9;11), MLL-AF9
    d. NPM1 mutation
    e. FLT3-ITD mutation.
5. Documentation of molecular remission (MRD less than 5 x 10-4) confirmed at the start of last consolidation course or within 1 month after completion of consolidation treatment.

Randomized Part (criteria must be checked at Predrug Verification Visit and re-checked at randomization):

1. Predrug verification visit should occur within 7 days of detection of molecular relapse in the PB by RQ-PCR during the screening period. Molecular relapse is defined as an increase in MRD level of a subject-specific fusion gene or aberration by at least 1 log (10-fold) to a level of at least 5 x 10-4. For subjects who are MRD negative, the rise should be at least 1 log (10-fold) greater than previous sensitivity to a level of 5 x 10-4 or above. An increase in PB must be confirmed in PB and BM aspirate by RQ-PCR. Confirmation of a molecular relapse is given if

the MRD positivity is at the same level or higher in the PB and BM sample compared to the PB MRD levels at the detection of the relapse and in the absence of clinical relapse (defined as at least 5% blasts in PB and/or BM and/or proven histological extramedullary relapse).

2. Lansky play score at least equal to 50; or Karnofsky performance status at least equal to 50, whichever is applicable.
3. Females of Childbearing Potential and male subjects that have reached puberty and are:
    a. Younger than 18 years of age must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction with parent/parents and/or guardian/guardians.
    b. Between 18 and 21 years of age must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction with the study physician.
4. Females of Childbearing Potential, defined as females who have achieved menarche and/or 8 years or older and have not undergone a hysterectomy or bilateral oophorectomy, must meet the following conditions below.
    a. Have a negative serum pregnancy test within 72 hours prior to randomization as verified by the study doctor. Agree to ongoing pregnancy testing during the course of the study and after end of study therapy at the 28-day follow-up visit. This applies even if the subject practices true abstinence* from heterosexual contact.
    b. Female subjects must, as appropriate to age and the discretion of the study physician, either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) and/or agree to the use of approved contraceptive method (eg, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; or vasectomized partner) while on azacitidine; and for 3 months following the last dose.
5. Male subjects must as appropriate to age and the discretion of the study physician:
    a. Agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 3 months following azacitidine discontinuation, even if he has undergone a successful vasectomy.
        - True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception].

Exclusion Criteria:

Safety Run-in Part (criteria must be checked at Screening and re-checked on Cycle 1 Day

The presence of any of the following will exclude a subject from enrollment:

Concomitant Treatment

1. Concomitant treatment with any other anticancer therapy except those specified in protocol.
2. Received maintenance therapy after end of consolidation therapy and CR1. Prior Treatment
3. HSCT (hematopoietic stem cell transplantation) within previous 3 months.
4. Treated by any investigational agent in a clinical study within previous 4 weeks. Medical Condition/Laboratory
5. Pregnant or lactating.
6. Symptomatic central nervous system (CNS)-involvement or isolated extramedullary disease at initial diagnosis.
7. FAB (French-American-British) type M3 leukemia (acute promyelocytic leukemia)
8. Therapy-related AML
9. AML of Down syndrome or other congenital syndromes giving rise to leukemia or treatment complications.
10. Symptomatic cardiac disorders (CTCAE (Common Terminology Criteris for Adverse Events) Grade 3 or 4).
11. Evidence of invasive fungal infection or other severe systemic infection requiring treatment doses of systemic/parenteral therapy including known active viral infection with human immunodeficiency virus (HIV) or Hepatitis type B and C.
12. Any other organ dysfunction (NCI CTCAE v4 (National Cancer Institute Common Terminology Criteria for Adverse Events Grade 4) that will interfere with the administration of the therapy according to this protocol.
13. Acute effects of prior chemotherapy/stem cell transplantation.
14. Hypersensitivity to azacitidine.
15. Serum Bilirubin above 1.5 x ULN.
16. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) above 3 x ULN.
17. Any significant medical condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or that would prevent the subject from participating in the study.

Randomized Part (at the time of signing ICF/IAF):

The presence of any of the following will exclude a subject from enrollment:

Concomitant Treatment

1. Concomitant treatment with any other anti-cancer therapy except those specified in protocol.
2. Received maintenance therapy after end of consolidation therapy and CR1. Prior Treatment
3. HSCT within previous 3 months.
4. Treated by any investigational agent in a clinical study within previous 4 weeks. Medical Condition/Laboratory
5. Symptomatic CNS-involvement or isolated extramedullary disease at initial diagnosis.
6. FAB type M3 leukemia (acute promyelocytic leukemia)
7. Therapy-related AML
8. AML of Down syndrome or other congenital syndromes giving rise to leukemia or treatment complications.

9. Acute effects of prior chemotherapy/stem cell transplantation.
10. Hypersensitivity to azacitidine.

Randomized Part (criteria must be checked at Predrug Verification Visit and re-checked at randomization):

The presence of any of the following will exclude a subject from randomization:

Prior Treatment

1. Treated by any investigational agent in a clinical study within previous 4 weeks. Medical Condition/Laboratory
2. Pregnant or lactating.
3. Symptomatic cardiac disorders (CTCAE Grade 3 or 4).
4. Evidence of invasive fungal infection or other severe systemic infection requiring treatment doses of systemic/parenteral therapy including known active viral infection with human immunodeficiency virus (HIV) or Hepatitis type B and C.
5. Any other organ dysfunction (NCI CTCAE v4.0 Grade 4) that will interfere with the administration of the therapy according to this protocol.
6. Serum bilirubin above 1.5 x ULN.
7. AST/ALT above 3 x ULN.
8. Any significant medical condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or that would prevent the subject from participating in the study.

Contacts and Locations

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, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02450877

Contacts

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

Locations

Denmark

Rigshospitalet Copenhagen, Denmark, DK-2100	**Recruiting**

Germany

Charite Berlin Berlin, Germany, 13353	**Recruiting**
Universitatsklinikum Essen Essen, Germany, 45147	**Recruiting**
Klinikum der Johann Wolfgang Goethe-Universität Frankfurt/Main Frankfurt am Main, Germany, 60596	**Recruiting**
Universitatsklinik Freiburg, Germany, 79106	**Recruiting**
Medical School of Hannover Hannover, Germany, 30625	**Recruiting**

Netherlands

VU University Medical Center Amsterdam, Netherlands, 1081 HV	**Recruiting**
Erasmus MC Rotterdam, Netherlands, 3015 GJ	**Recruiting**

Sponsors and Collaborators

Celgene Corporation

Investigators

Study Director: Bouchra Benettaib, MD Celgene Corporation

More Information

Responsible Party:	Celgene Corporation
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Keywords provided by Celgene Corporation:

Children
Young Adults
Azacitidine
Acute Myeloid Leukemia
Molecular Relapse
Vidaza
AZA-AML-004

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

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