Trial of Intensive Chemotherapy With or Without Volasertib in Patients With Newly Diagnosed High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

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

Verified October 2016 by University of Ulm

Sponsor:
University of Ulm

Information provided by (Responsible Party):
Prof. Dr. Hartmut Doehner, University of Ulm

ClinicalTrials.gov Identifier:
NCT02198482

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History of Changes

Purpose

Randomized Phase II Trial of Intensive Chemotherapy With or Without Volasertib (BI 6727) in Patients With Newly Diagnosed High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

Condition	Intervention	Phase
Acute Myeloid Leukemia (AML) High-risk Myelodysplastic Syndrome (MDS)	Drug: Volasertib Drug: Cytarabine Drug: Daunorubicin Drug: Mitoxantrone	Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Dose Finding Safety Run-in Phase Followed by a Randomized Phase II Trial of Intensive Chemotherapy With or Without Volasertib (BI 6727) Administered Prior or After Chemotherapy in Patients With Newly Diagnosed High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

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 Myelodysplastic Syndromes

Drug Information available for: Cytarabine Daunorubicin Mitoxantrone

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

U.S. FDA Resources

Further study details as provided by University of Ulm:

Primary Outcome Measures:

- Rate of complete remission (CR) and CR with incomplete blood count recovery (CRi) [Time Frame: 2 months] [Designated as safety issue: No]

Secondary Outcome Measures:

- Cumulative incidence of relapse [Time Frame: 4 years] [Designated as safety issue: No]
- Cumulative incidence of death [Time Frame: 4 years] [Designated as safety issue: Yes]
- Relapse-free survival [Time Frame: 4 years] [Designated as safety issue: No]
- Event-free survival [Time Frame: 4 years] [Designated as safety issue: Yes]
- Overall survival [Time Frame: 4 years] [Designated as safety issue: Yes]
- Incidence and intensity of adverse events [Time Frame: 8 months] [Designated as safety issue: Yes]

Estimated Enrollment:	264
Study Start Date:	February 2016
Estimated Study Completion Date:	August 2021
Estimated Primary Completion Date:	August 2017 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: Daunorubicin, Cytarabine (DA) DA Induction I: • Daunorubicin 60 mg/m² i.v., d 1-3 • Cytarabine 100 mg/m² cont. i.v., d 1-7 Induction II: • Daunorubicin 50 mg/m² i.v. d 1-3 • Cytarabine 100 mg/m² cont. i.v., d 1-5 Consolidation therapy: Patients with genetic favourable risk and those patients not eligible for allogeneic HSCT due to comorbidities, high HCT-CI or patient wish will proceed to 3 cycles of age-adapted consolidation therapy with mitoxantrone and intermediate-dose cytarabine (MiDAC). • Mitoxantrone Younger adults (18 to 60 yrs): 10 mg/m2 by i.v. on day 1. Elderly patients (>60 yrs): 8 mg/m2 by i.v. infusion on day 1. • Intermediate-dose cytarabine: Younger adults (18 to 60 yrs): 1500 mg/m2 q12h on days 1-3 Elderly patients (>60 yrs): 1000 mg/m2 q12h on days 1-3 An allogeneic HSCT is intended for patients with intermediate I/II and adverse-risk genetics. Optionally, one cycle of consolidation with MiDAC may be given prior to alloHSCT.	Drug: Cytarabine Other Name: ARA-cell Drug: Daunorubicin Other Name: Daunoplastin Drug: Mitoxantrone Other Name: Novantron
Experimental: Volasertib, Daunorubicin, Cytarabine VDA Induction I • Volasertib i.v., d1 • Daunorubicin 60 mg/m² i.v., d 2-4 • Cytarabine 100 mg/m² cont. i.v., d 2-8 Induction II • Volasertib i.v., d1 • Daunorubicin 50 mg/m² i.v. d 2-4 • Cytarabine 100 mg/m² cont. i.v., d 2-6 Consolidation therapy: Patients with genetic favourable risk and those patients not eligible for allogeneic HSCT will proceed to 3 cycles of age-adapted consolidation therapy with mitoxantrone and intermediate-dose cytarabine in combination with Volasertib (V-MiDAC). • Volasertib i.v., d1 • Mitoxantrone Younger adults (18 to 60 yrs): 10 mg/m2 by i.v. on day 2. Elderly patients (>60 yrs): 8 mg/m2 by i.v. on day 2. • Intermediate-dose cytarabine: Younger adults (18 to 60 yrs): 1500 mg/m2 q12h on days 2-4 Elderly patients (>60 yrs): 1000 mg/m2 q12h on days 2-4 An allogeneic HSCT is intended for patients with intermediate I/II and adverse-risk genetics. Optionally, one cycle of consolidation with V-MiDAC may be given prior to alloHSCT.	Drug: Volasertib Drug: Cytarabine Other Name: ARA-cell Drug: Daunorubicin Other Name: Daunoplastin Drug: Mitoxantrone Other Name: Novantron
Experimental: Daunorubicin, Cytarabine, Volasertib DAV Induction I • Volasertib i.v., d7 • Daunorubicin 60 mg/m² i.v., d 1-3	Drug: Volasertib Drug: Cytarabine Other Name: ARA-cell Drug: Daunorubicin

• Cytarabine 100 mg/m² i.v., d 1-7 Induction II • Volasertib i.v., d5 • Daunorubicin 50 mg/m² i.v. d 1-3 • Cytarabine 100 mg/m² cont. i.v., d 1-5 Consolidation therapy: Patients with genetic fav. risk and those patients not eligible for alloHSCT will proceed to 3 cycles of age-adapted consolidation therapy with mitoxantrone and intermediate-dose cytarabine in combination with Volasertib (MiDAC-V). • Volasertib i.v., d4 • Mitoxantrone Younger adults (18 to 60 yrs): 10 mg/m2 by i.v. on day 1. Elderly patients (>60 yrs): 8 mg/m2 by i.v. on day 1. • Intermediate-dose cytarabine: Younger adults (18 to 60 yrs): 1500 mg/m2 q12h on days 1-3 Elderly patients (>60 yrs): 1000 mg/m2 q12h on days 1-3 An allogeneic HSCT is intended for patients with intermediate I/II and adverse-risk genetics. Optionally, one cycle of consolidation with MiDAC-V may be given prior to alloHSCT.	Other Name: Daunoplastin Drug: Mitoxantrone Other Name: Novantron

Detailed Description:

The trial is a randomized, Phase II, open label multi-center trial in adult patients with newly diagnosed AML or high-risk MDS as defined in the inclusion/exclusion criteria.

An initial safety run-in study will be performed administering intensive induction therapy consisting of daunorubicin and cytarabine with the study drug volasertib administered prior or after chemotherapy, as well as consolidation therapy consisting of intermediate-dose cytarabine with the study drug volasertib administered prior or after chemotherapy. After establishing the volasertib dose, the randomized Phase II portion of the trial will begin:

Patients will be equally randomized to DA (daunorubicin, cytarabine), V-DA (volasertib administered prior to daunorubicin, cytarabine), and DA-V (volasertib administered after daunorubicin, cytarabine). All patients will receive a second induction cycle with reduced daunorubicin and cytarabine doses. Patients refractory to the first induction cycle and patients not achieving a CR/CRi after two induction cycles will be off-study and followed up.

Patients in CR/CRi after induction therapy will proceed to consolidation therapy. Consolidation will be stratified based on the genetic risk profile (according to ELN criteria) and patient-related factors (e.g., age, HCT-CI, comorbidities, patient wish). Patients with a favorable genetic risk profile and those patients considered ineligible for allogeneic HCT will receive repetitive cycles of consolidation according to initial randomization, either MiDAC, V-MiDAC (volasertib administered prior to cytarabine), or MiDAC-V (volasertib administered after cytarabine). All other patients are assigned to allogeneic HCT.

Eligibility

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

Criteria

Inclusion Criteria:

- Patients with confirmed diagnosis of acute myeloid leukemia (AML) or related precursor neoplasm, or acute leukemia of ambiguous lineage according to the current World Health Organization (WHO) classification, or patients with myelodysplastic syndrome (MDS) classified as refractory anemia with excess blasts-2 (RAEB-2)
- Consent for a genetic assessment in AMLSG central laboratory
- Patients considered eligible for intensive chemotherapy
- ECOG performance status of ≤ 2
- Age >= 18; there is no upper age limit
- No prior chemotherapy for acute leukemia except hydroxyurea for up to 5 days during the diagnostic screening phase; patients may have received prior therapy for myelodysplastic syndrome.
- Non-pregnant and non-nursing. Due to the teratogenic potential of volasertib in humans, pregnant or nursing patients may not be enrolled. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to registration. Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control - one highly effective method (e.g., IUD, hormonal, tubal ligation, or partner's vasectomy), and one additional effective method (e.g., latex condom, diaphragm, or cervical cap) for 6 months after therapy is stopped. "Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months.
- Men must agree not to father a child and must use a latex condom during any sexual contact with women of childbearing potential while receiving therapy and for 6 months after therapy is stopped, even if they have undergone a successful vasectomy
- Signed written informed consent

Exclusion Criteria:

- Patients with acute promyelocytic leukemia exhibiting t(15;17)(q22;q12); PML-RARA, or with variant translocations
- Prior treatment with volasertib or any other PLK1 inhibitor

- Performance status WHO >2 (see Appendix I)
- Patients with ejection fraction <50% by echocardiography within 14 days of day 1
- QTcF prolongation >470 ms or QT prolongation deemed clinically relevant by the investigator (e.g., congenital long QT syndrome). The QTcF will be calculated as the mean of 3 ECGs taken at screening.
- Any clinically significant, advanced or unstable disease or history of that may interfere with primary or secondary variable evaluations or put the patient at special risk, such as:
  - creatinine >1.5x upper normal serum level;
  - total bilirubin, AST or AP >2.5x upper normal serum level;
  - heart failure NYHA III/IV,
  - uncontrolled hypertension,
  - unstable angina,
  - serious cardiac arrhythmia;
  - severe obstructive or restrictive ventilation disorder
  - uncontrolled infection
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy, if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.
- Severe neurological or psychiatric disorder interfering with ability of giving an informed consent
- Known or suspected active alcohol or drug abuse
- Known positive for HIV, active HBV, HCV, or hepatitis A infection
- Hematologic disorder independent of leukemia
- No consent for registration, storage and processing of the individual disease characteristics and course as well as information of the family physician and/or other physicians involved in the treatment of the patient about study participation.
- No consent for biobanking.
- Current participation in any other interventional clinical study within 30 days before the first administration of the investigational product or at any time during the study
- Breast feeding women or women with a positive pregnancy test at Screening visit

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: NCT02198482

Contacts

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Sponsors and Collaborators

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Investigators

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More Information

Responsible Party:	Prof. Dr. Hartmut Doehner, Prof. Dr., University of Ulm
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Keywords provided by University of Ulm:
Acute Myeloid Leukemia (AML)
Volasertib
High-risk Myelodysplastic Syndrome (MDS)

Additional relevant MeSH terms:

Leukemia
Syndrome
Leukemia, Myeloid
Leukemia, Myeloid, Acute
Myelodysplastic Syndromes
Preleukemia
Neoplasms by Histologic Type
Neoplasms
Disease
Pathologic Processes
Bone Marrow Diseases
Hematologic Diseases
Precancerous Conditions
Cytarabine
Mitoxantrone
Daunorubicin
Antimetabolites, Antineoplastic
Antimetabolites
Molecular Mechanisms of Pharmacological Action
Antineoplastic Agents
Antiviral Agents
Anti-Infective Agents
Immunosuppressive Agents
Immunologic Factors
Physiological Effects of Drugs
Analgesics
Sensory System Agents
Peripheral Nervous System Agents
Topoisomerase II Inhibitors
Topoisomerase Inhibitors

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