Study for Patients With Newly Diagnosed, High-risk Acute Promyelocytic Leukemia (TUD-APOLLO-064)

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

Verified July 2016 by Technische Universität Dresden

Sponsor:
Technische Universität Dresden

Collaborators:
Gruppo Italiano Malattie EMatologiche dell'Adulto
Groupe Francophone des Myelodysplasies
Haemato Oncology Foundation for Adults in the Netherlands
Programa para el Tratamiento de Hemopatías Malignas
German Federal Ministry of Education and Research
Teva Pharmaceuticals Europe

Information provided by (Responsible Party):
Technische Universität Dresden

ClinicalTrials.gov Identifier:
NCT02688140

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History of Changes

Purpose

Acute promyelocytic leukemia (APL) is a rare subtype of **acute myeloid leukemia** (**AML**) characterized by consistent clinical, morphologic, and genetic features. According to the FAB classification APL is designated as"M3 leukemia" and assigned to the WHO defined type of **AML** with recurrent cytogenetic abnormalities, "acute promyelocytic leukemia with t(15;17)(q22;q12), (PML/RARα) and variants".

Despite the dramatic progress achieved in frontline therapy of APL with ATRA plus anthracycline-based regimens, relapses still occur in approximately 20% of patients. Moreover, these regimens are associated with significant toxicities due to severe myelosuppression frequently associated with life-threatening infections and potentially serious late effects including development of secondary MDS/**AML**. In a recent randomized clinical trial in low/intermediate-risk APL (WBC ≤ 10 GPt/l APL0406 trial) a combination of arsenic trioxide (ATO) and ATRA has been shown to result into better survival with significantly lower toxicity rates compared to the standard ATRA + idarubicin (AIDA) therapy. Inspired by the results of this trial the investigators intend to perform a randomized study in high-risk APL (WBC at diagnosis > 10 GPt/l) comparing standard AIDA-based treatment with ATO/ATRA combination including low-doses idarubicin during induction. The investigators propose a modified ATO/ATRA protocol with the addition of two doses of IDA (50% compared to standard AIDA induction) for induction because of the anticipated need of adding anthracyclines to control hyperleukocytosis and to achieve long-term disease control in this high-risk APL population. This is followed by 4 cycles of ATO/ATRA consolidation therapy. As in the APL0406 study for low/intermediate-risk patients the investigators expect less severe hematologic toxicity and treatment-related mortality resulting in an improved outcome for patients in the experimental arm. Furthermore, from the start of consolidation, these patients (in contrast to the standard arm) can be treated on an outpatient basis, which is also considered to be associated with an improved quality of life. The study will be conducted as a European intergroup study.

Condition	Intervention	Phase
Acute Promyelocytic Leukemia	Drug: Arsenic trioxide Drug: Idarubicin Drug: Cytarabine Drug: Tretinoin Drug: Mitoxantrone Drug: Mercaptopurine Drug: Methotrexate	Phase 3

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

Official Title: A Randomized Phase III Study to Compare Arsenic Trioxide (ATO) Combined to ATRA and Idarubicin Versus Standard ATRA and Anthracyclines-based Chemotherapy (AIDA Regimen) for Patients With Newly Diagnosed, High-risk Acute Promyelocytic Leukemia

Resource links provided by NLM:

Genetics Home Reference related topics: acute promyelocytic leukemia core binding factor acute myeloid leukemia cytogenetically normal acute myeloid leukemia familial acute myeloid leukemia with mutated CEBPA

MedlinePlus related topics: Arsenic Leukemia

Drug Information available for: Mercaptopurine Methotrexate Cytarabine Tretinoin Arsenic trioxide Arsenic Methotrexate sodium Idarubicin hydrochloride Idarubicin Mitoxantrone Mitoxantrone hydrochloride

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

U.S. FDA Resources

Further study details as provided by Technische Universität Dresden:

Primary Outcome Measures:

- Event-free survival [Time Frame: From date of randomization until the date of first documented event, assessed up to 66 months] [Designated as safety issue: No]

  events are: no achievement of haematological complete remission after induction therapy; no achievement of molecular remission after the last consolidation course; relapse; death including early death or development of secondary AML or MDS

Secondary Outcome Measures:

- Rate of hematological complete remission [Time Frame: up to 60 days, from date of randomization until end of induction therapy] [Designated as safety issue: No]
- Rate of early death within 30 days after randomization [Time Frame: up to 30 days after randomization] [Designated as safety issue: Yes]
- Rate of overall survival (OS) [Time Frame: at 2 years] [Designated as safety issue: No]
- Rate of cumulative incidence of secondary MDS or **AML** [Time Frame: assessed up to 66 months, from date of randomization until occurance of secondary AML or MDS] [Designated as safety issue: No]
- Rate of cumulative incidence of relapse (CIR) [Time Frame: at 2 years] [Designated as safety issue: No]
- Incidence of hematological and non-hematological toxicity [Time Frame: assessed up to 30 months after randomization] [Designated as safety issue: Yes]
- Rate of molecular remission after the last consolidation cycle [Time Frame: up to 256 days after randomization] [Designated as safety issue: No]
- Assessment of acute promyelocytic leukemia/RARa transcript level reduction after induction therapy until end of study [Time Frame: assessed up to 30 months after randomization] [Designated as safety issue: No]
- Quality of Life at the end of induction therapy until the end of study [Time Frame: assessed up to 30 months after randomization] [Designated as safety issue: No]
- To investigate differences in the immune reconstitution between the two arms [Time Frame: assessed up to 30 months after randomization] [Designated as safety issue: No]
- Total hospitalization days during therapy [Time Frame: assessed up to 30 months after randomization] [Designated as safety issue: No]

Estimated Enrollment:	280
Study Start Date:	June 2016
Estimated Study Completion Date:	January 2022
Estimated Primary Completion Date:	November 2021 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Arm A Induction therapy: Patients receive idarubicin i.v. over 20 minutes on day 1 and 3, oral tretinoin twice daily on day 1-28 (max. up to day 60) and arsenic trioxide i.v. over 2 hours on day 5-28 (max. up to day 60). In case of morphological CR and regenerated blood counts, consolidation therapy should be started within 2-4 weeks after documented CR. Consolidation therapy: Patients receive oral tretinoin twice daily on day 1-14. Treatment with tretinoin repeats every 4 weeks for up to 7 courses. Patients also receive arsenic trioxide i.v. over 2 hours on days 1-5 in week 1-4. Treatment with arsenic trioxide repeats every 8 weeks for up to 4 courses.	Drug: Arsenic trioxide Other Names: • ATO • Trisenox (R) • As2O3 Drug: Idarubicin Other Name: IDA Drug: Tretinoin Other Names: • all-trans retinoic acid • ATRA
Active Comparator: Arm B (standard chemotherapy)	Drug: Idarubicin Other Name: IDA Drug: Cytarabine

Induction therapy: Patients receive idarubicin i.v. over 20 minutes on day 1,3,5 and 7 and oral tretinoin twice daily on day 1-28 (max. up to day 60). In case of morphological CR and regenerated blood counts, consolidation therapy should be started within 2-4 weeks after documented CR Consolidation therapy: Patients receive oral tretinoin twice daily on day 1-45, idarubicin i.v. over 20 minutes on day 1-4 and day 31, cytarabine i.v. over 3 hours on day 1-4, over 8 hours on day 31-35, mitoxantrone i.v. over 30 minutes on day 16-20. Maintenance therapy (only for PML-RARa negative patients): Patients receive oral mercaptopurine once daily and methotrexate i.m./p.o. once weekly for 3 months. Treatment with mercaptopurine and methotrexate repeats every 3 months for 7 courses. After completion of course 1 of mercaptopurine and methotrexate, patients receive oral tretinoin once daily on days 1-15. Treatment with tretinoin repeats every 3 months for 6 courses	Other Name: Ara-C Drug: Tretinoin Other Names: • all-trans retinoic acid • ATRA Drug: Mitoxantrone Other Name: MTZ Drug: Mercaptopurine Other Names: • 6-Mercaptopurine • 6-MP Drug: Methotrexate Other Name: MTX

Eligibility

Ages Eligible for Study: 18 Years to 65 Years (Adult)
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Informed consent
- Women or men with a newly diagnosed APL by cytomorphology, confirmed by molecular analysis*
- Age ≥ 18 and ≤ 65 years
- ECOG performance status 0-3
- WBC at diagnosis > 10 GPt/l
- Serum total bilirubin ≤ 3.0 mg/dl (≤ 51 µmol/l)
- Serum creatinine ≤ 3.0 mg/dl (≤ 260 µmol/l)
- Women must fulfill at least one of the following criteria in order to be eligible for trial inclusion:
- Post-menopausal (12 months of natural amenorrhea or 6 months of amenorrhea with Serum FSH > 40 U/ml)
- Postoperative (i.e. 6 weeks) after bilateral ovariectomy with or without hysterectomy
- Continuous and correct application of a contraception method with a Pearl Index of <1% (e.g. implants, depots, oral contraceptives, -intrauterine device - IUD)
- Sexual abstinence
- Vasectomy of the sexual partner
    - The confirmation of diagnosis at genetic level (microspeckled PML nuclear distribution by PGM3 monoclonal antibody and/or PML/RARa fusion by RT-PCR or fluorescence in situ hybridization (FISH) and/or demonstration of t(15;17) at karyotyping) will be mandatory for patient eligibility. However, in order to avoid delay in treatment initiation, patients can be randomized on the basis of morphologic diagnosis only and before the results of genetic tests are available

Exclusion Criteria:

- Patients who are not eligible for chemotherapy as per discretion of the treating physician
- APL secondary to previous radio- or chemotherapy for non-APL disease
- Other active malignancy at time of study entry (exception: basal-cell carcinoma)
- Lack of diagnostic confirmation at genetic level
- Significant arrhythmias, ECG abnormalities:
- Congenital long QT syndrome;
- History or presence of significant ventricular or atrial tachyarrhythmia;
- Clinically significant resting bradycardia (<50 beats per minute)
- QTc >500msec on screening ECG for both genders (using the QTcF formula detailed on protocol)
- Right bundle branch block plus left anterior hemiblock, bifascicular block
- Other cardiac contraindications for intensive chemotherapy (L-VEF <50%)
- Uncontrolled, life-threatening infections
- Severe non controlled pulmonary or cardiac disease
- Severe hepatic or renal dysfunction
- HIV and/or active hepatitis C infection
- Pregnant or breast-feeding patients
- Allergy to trial medication or excipients in study medication
- Substance abuse; medical, psychological or social conditions that may interfere with the patients participation in the study or evaluation of the study results

- Use of other investigational drugs at the time of enrolment or within 30 days before study entry

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: NCT02688140

Contacts

Contact: Uwe Platzbecker, Prof. Dr. +49 351 458 ext 3192 uwe.platzbecker@uniklinikum-dresden.de

Contact: Michaela Sauer +49 351 458 ext 3192 michaela.sauer@uniklinikum-dresden.de

Locations

France

French-Belgian-Swiss APL study group — **Not yet recruiting**
All Participating Sites, France
Contact: Pierre Fenaux, Prof. Dr. pierre.fenaux@avc.ap-hop-paris.fr
Contact: Lionel Ades, Dr. lionel.ades@sls.aphp.fr

Germany

AML-CG study group — **Not yet recruiting**
All Participating Sites, Germany
Contact: Eva Lengfelder, Prof. Dr. Eva.Lengfelder@umm.de

AML-SG study group — **Recruiting**
All Participating Sites, Germany
Contact: Richard F. Schlenk, Prof. Dr. Richard.Schlenk@uniklinik-ulm.de

OSHO study group — **Not yet recruiting**
All Participating Sites, Germany
Contact: Dietger Niederwieser, Prof. Dr. Dietger.Niederwieser@medizin.uni-leipzig.de

SAL study group — **Recruiting**
All Participating Sites, Germany
Contact: Uwe Platzbecker, Prof. Dr. +49 351 458 ext 3192 uwe.platzbecker@uniklinikum-dresden.de
Contact: Michaela Sauer +49 351 458 ext 3192 michaela.sauer@uniklinikum-dresden.de

Italy

GIMEMA study group — **Not yet recruiting**
All Participating Sites, Italy
Contact: Francesco Lo-Coco, Prof. Dr. Francesco.lo.coco@uniroma2.it
Contact: Fabio Efficace, Dr. f.efficace@gimema.it

Netherlands

HOVON study group — **Not yet recruiting**
All Participating Sites, Netherlands
Contact: Edo Vellenga, Prof. Dr. e.vellenga@umcg.nl

Spain

PETHEMA study group — **Not yet recruiting**
All Participating Sites, Spain
Contact: Miguel A. Sanz, Prof. Dr. sanz_mig@gva.es
Contact: Pau Montesinos, Prof. Dr. montesinos_pau@gva.es

Sponsors and Collaborators

Technische Universität Dresden

Gruppo Italiano Malattie EMatologiche dell'Adulto

Groupe Francophone des Myelodysplasies

Haemato Oncology Foundation for Adults in the Netherlands

Programa para el Tratamiento de Hemopatías Malignas

German Federal Ministry of Education and Research

Teva Pharmaceuticals Europe

Investigators

Principal Investigator: Uwe Platzbecker, Prof. Dr. Technische Universität Dresden (TUD)

More Information

Responsible Party:	Technische Universität Dresden
ClinicalTrials.gov Identifier:	NCT02688140 History of Changes
Other Study ID Numbers:	TUD-**APOLLO**-064
Study First Received:	February 11, 2016
Last Updated:	July 7, 2016
Health Authority:	Germany: Federal Institute for Drugs and Medical Devices Germany: Ethics Commission

Keywords provided by Technische Universität Dresden:

APL	**acute myeloid leukemia** with t(15;17)(q22;q12)
acute promyelocytic leukemia (M3)	newly diagnosed
high-risk acute promyelocytic leukemia (APL/**AML** M3)	high-risk

Additional relevant MeSH terms:

Leukemia	Reproductive Control Agents
Leukemia, Promyelocytic, Acute	Physiological Effects of Drugs
Neoplasms by Histologic Type	Antimetabolites, Antineoplastic
Neoplasms	Antimetabolites
Leukemia, Myeloid, Acute	Molecular Mechanisms of Pharmacological Action
Leukemia, Myeloid	Antineoplastic Agents
Methotrexate	Dermatologic Agents
Cytarabine	Enzyme Inhibitors
6-Mercaptopurine	Folic Acid Antagonists
Tretinoin	Immunosuppressive Agents
Idarubicin	Immunologic Factors
Mitoxantrone	Antirheumatic Agents
Arsenic trioxide	Nucleic Acid Synthesis Inhibitors
Abortifacient Agents, Nonsteroidal	Antiviral Agents
Abortifacient Agents	Anti-Infective Agents

ClinicalTrials.gov processed this record on October 07, 2016