Synopsis

Sponsor	Technische Universität Dresden (TUD) 01062 Dresden, Germany
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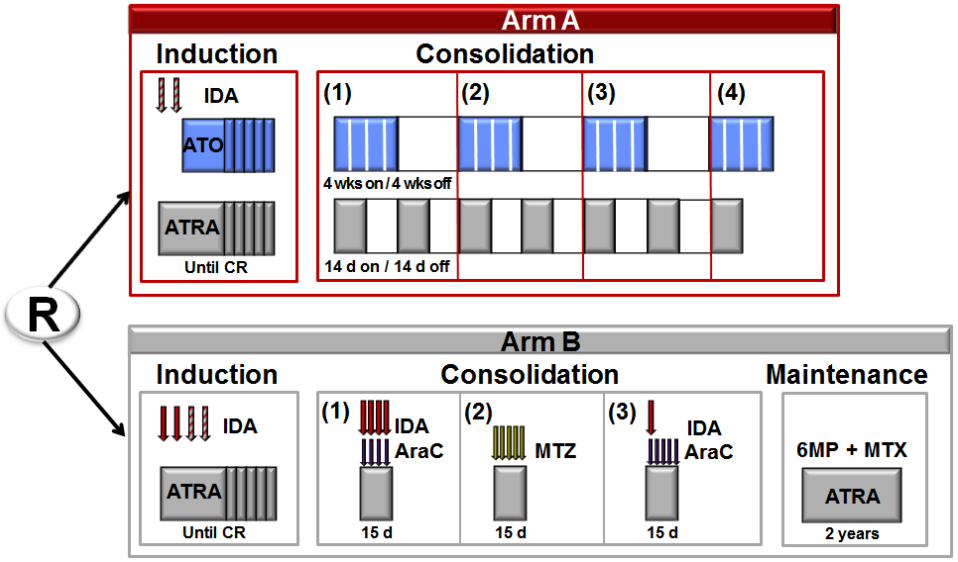
Co-Principal Investigator	Prof. Dr. Francesco Lo-Coco University of Tor Vergata Rome, Italy Francesco.lo.coco@uniroma2.it
Title	**A** randomized **P**hase III study to compare arsenic trioxide (AT**O**) combined to ATRA and idarubicin versus standard ATRA and anthracyc**L**ine-based chemotherapy (AIDA regimen) for patients with new**L**y diagnosed, high-risk acute pr**O**myelocytic leukemia
Short Title	APOLLO-TRIAL
EudraCT	2015-001151-68
Study groups	Prof. Dr. U. Platzbecker, for the SAL group *email: Uwe.Platzbecker@uniklinikum-dresden.de* Prof. Dr. E. Lengfelder, for the AML-CG group *email: Eva.Lengfelder@umm.de* Prof. Dr. R. F. Schlenk, for the AML-SG group *email: Richard.Schlenk@uniklinik-ulm.de* Prof. Dr. D. Niederwieser, for the OSHO group *email: Dietger.Niederwieser@medizin.uni-leipzig.de* Prof. Dr. M. Sanz, Dr. P. Montesinos, for the PETHEMA group *email: sanz_mig@gva.es ; montesinos_pau@gva.es* Prof. Dr. P. Fenaux, Dr. L. Ades, for the French-Belgian-Swiss APL group *email: pierre.fenaux@avc.ap-hop-paris.fr ; lionel.ades@sls.aphp.fr* Prof. Dr. E. Vellenga, for the HOVON group *email: e.vellenga@umcg.nl* Prof. Dr. F. Lo-Coco, Prof. Dr. G. Avvisati for the GIMEMA group *email: Francesco.lo.coco@uniroma2.it ; G.Avvisati@unicampus.it*
Target population	Patients with newly diagnosed high-risk acute promyelocytic leukemia (APL/AML M3) at the age of 18 to 65
Study design	Open label, randomized, prospective multicenter, multinational phase III trial
Objectives of the Trial	To compare event-free survival (EFS) of the experimental treatment arm including ATO/ATRA and idarubicin with standard treatment based on ATRA plus chemotherapy (AIDA regimen)
Endpoints of the Trial	Primary efficacy endpoint: - Event-free survival Key secondary endpoint(s): - CR, OS and CIR rates - Cumulative incidence of secondary MDS or AML - Early death during induction - Quality of life - Toxicity profile - Kinetics of MRD - Duration of in-patient treatment - Health economics
Sample Size	To be assessed for eligibility: n = 280 To be allocated to trial: n = 280 To be analyzed: n = 280 overall including 8% dropout (including 150 pts. in Germany)

Anticipated Duration	First patient in to last patient out (months): 66 (5 ½ years) Duration of the entire trial (months): 66 (5 ½ years) Recruitment period (months): 36 (3 years) Duration of intervention per patient: 9 months vs. 2.5 years (Arm A vs. B) Min. follow-up per patient: 2.5 years after randomization Max. follow-up per patient: until end of entire trial (LPLV) Time schedule: First patient first visit (FPFV): 01/2016 Last patient first visit (LPFV): 12/2018 Last patient last visit (LPLV): anticipated Q3/2021 Study begin is generally the first visit of the first subject. Study end is generally the last visit of the last subject.
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: o Post-menopausal (12 months of natural amenorrhea or 6 months of amenorrhea with Serum FSH > 40 U/ml) o Postoperative (i.e. 6 weeks) after bilateral ovariectomy with or without hysterectomy o Continuous and correct application of a contraception method with a Pearl Index of <1% (e.g. implants, depots, oral contraceptives, intrauterine device – IUD). o Sexual abstinence o 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 of APL at genetic level (*see above) - 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 infection - active multiple sclerosis (patients with inactive MS can be included) - 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

Trial drug

Active pharmaceutical ingredient: Arsenic trioxide
Trade name: Trisenox®
Manufacturer: TEVA Pharmaceuticals Europe B.V.

Treatment



Experimental intervention (Arm A): ATO/ATRA and idarubicin

The 1st day of idarubicin administration counts as the 1st day of induction therapy.

Induction:

IDA	12 mg/m^2	i.v.	day 1, 3 *(day 2 instead of day 3 is also allowed; administration of max. two doses IDA during pre-randomization phase are allowed; **total amount of idarubicin should not exceed 2 doses**)*
ATO	0.15 mg/kg	i.v.	day 5-28 max. up to day 60 after start of IDA
ATRA	45 mg/m^2	p.o.	day 1-28 max. up to day 60; start on day 1 of induction therapy is mandatory

ATRA can be started max. three days before randomization

Consolidation I-IV:

ATO	0.15 mg/kg	i.v.	day 1-5 *(4wks on/ 4wks off for a total of 4 courses)*
ATRA	45 mg/m^2	p.o.	day 1-14 *(14d on/ 14d off for a total of 7 courses)*

At the discretion of the investigator ATRA reduction to 25 mg/m^2 should be done for patients <20 years.

Control intervention (Arm B): AIDA regimen for high-risk (ATRA plus chemotherapy)

The 1st day of idarubicin administration counts as the 1st day of induction therapy.

Induction:

IDA	12 mg/m^2	i.v.	day 1, 3, 5, 7 *(day 2 instead of day 3 is also allowed; administration of max. two doses IDA during pre-randomization phase are allowed; **total amount of idarubicin should not exceed 4 doses**)*
ATRA	45 mg/m^2	p.o.	day 1-28 max. up to day 60; start on day 1 of induction therapy is mandatory

ATRA can be started max. three days before randomization.

Consolidation I:

IDA	5 mg/m^2	i.v.	day 1-4
Ara-C	1000 mg/m^2/3h	i.v.	day 1-4
ATRA	45 mg/m^2	p.o.	day 1-15

Consolidation II:

MTZ	10 mg/m^2	i.v.	day 1-5
ATRA	45 mg/m^2	p.o.	day 1-15

Consolidation III:

IDA	12 mg/m^2	i.v.	day 1
Ara-C	150 mg/m^2/8h	i.v.	day 1-5
ATRA	45 mg/m^2	p.o.	day 1-15

Maintenance (duration 7 cycles = 2 years; one cycle lasts 106 days):

6-MP	50 mg/m^2	p.o.	**Cycle 1-7:** day 1-91 (followed by 15 days of ATRA on days 92-106)
MTX	15mg/m^2	i.m./p.o.	**Cycle 1-7:** once weekly for 91 days (followed by 15 days of ATRA on days 92-106)
ATRA	45 mg/m^2	p.o.	**Cycle 1–6:** day 92-106 **Cycle 7:** without ATRA administration *(treatment break of 6-MP and MTX during ATRA administration)*

At the discretion of the investigator ATRA reduction to 25 mg/m^2 should be done for patients <20 years.

<u>Urgent pre-randomization management of eligible patients:</u>

As high risk APL is a medical emergency requiring immediate start of therapy a certain treatment is allowed before randomization. This is possible since the first four days of therapy are identical in both arms. Treatment will have to be started immediately and patient pre-registered based on morphologic suspicion of high risk APL with no need of waiting for genetic diagnosis confirmation.

In case of suspected high-risk APL, oral ATRA should be started together with up to two administrations of idarubicin (max. 3 days before randomization) to control leukocytosis. A maximum of two doses of idarubicin before randomization is allowed. The day of the first dose of idarubicin counts as the first day of induction therapy. Total idarubicin doses given for induction should not exceed 2 doses at 12 mg/m^2 each in Arm A and 4 doses at 12 mg/m^2 each in Arm B.

ATRA	45 mg/m^2	p.o.	allowed for up to 3 days prior to randomization
IDA	12 mg/m^2	i.v.	allowed for up to 2 injections within 3 days prior to randomization

For a better understanding of the procedure the following two graphics demonstrate the different scenarios in both arms in case of prior treatment with idarubicin or no prior treatment:

Figure 1: Potential scenarios (no pre-treatment and pre-treatment with idarubicin) followed by randomization in Arm A:

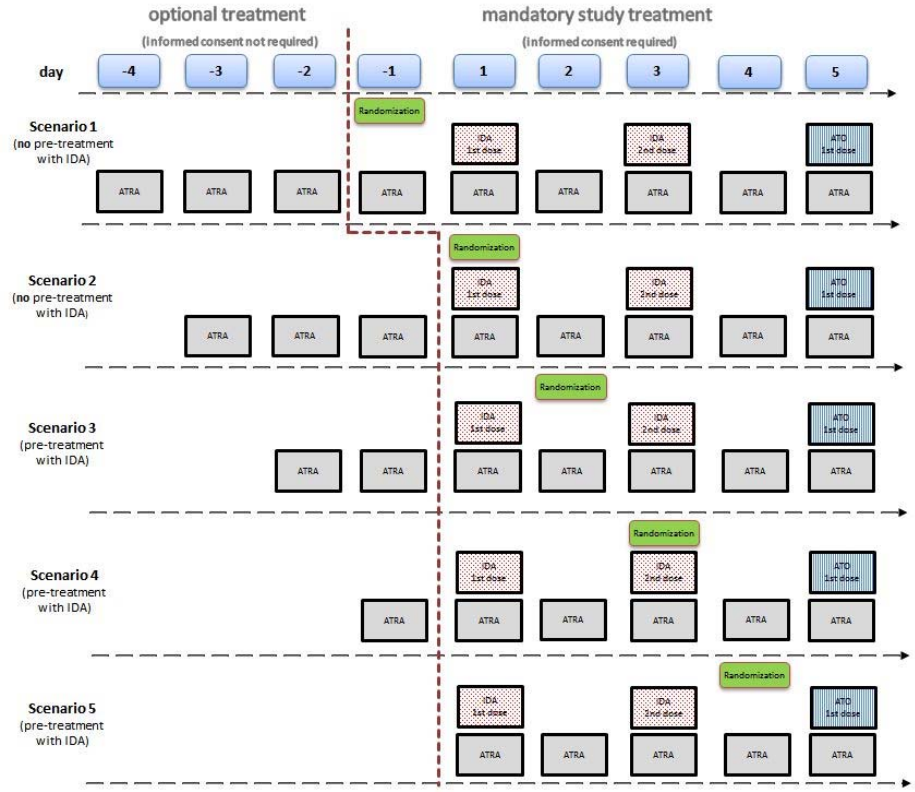
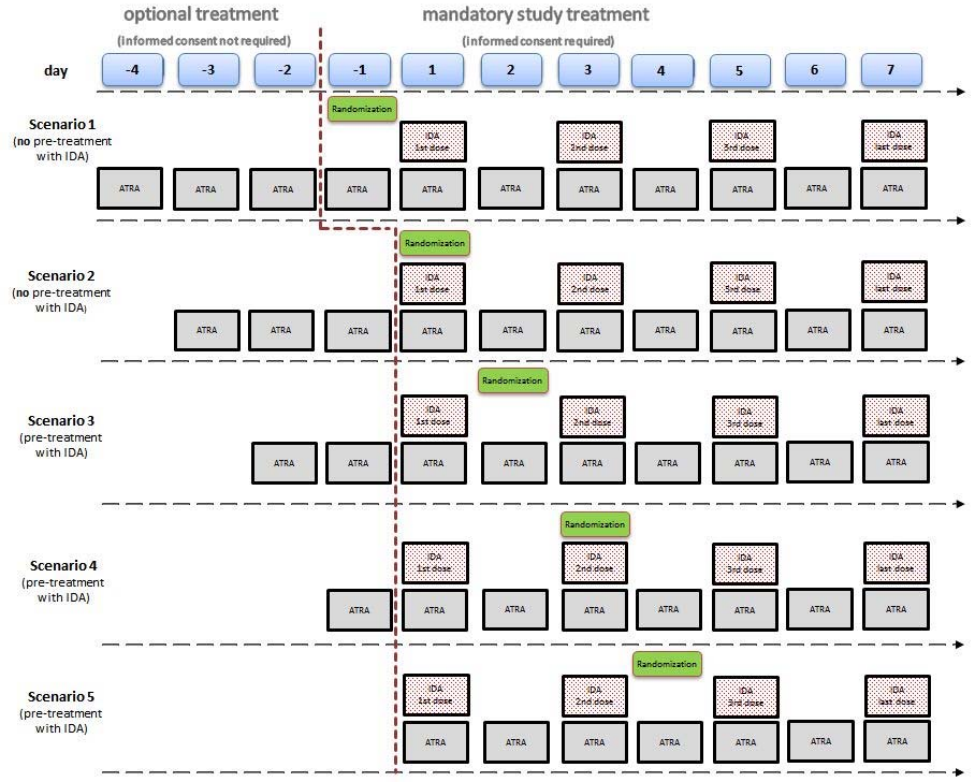


Figure 2: Potential scenarios (no pre-treatment and pre-treatment with idarubicin) followed by randomization in Arm B:



Statistical Considerations	Efficacy / test accuracy: The primary endpoint of the study is event-free survival. This is a time to event endpoint. This cumulative endpoint includes the following events: no achievement of hematological complete remission after induction therapy; no achievement of molecular remission after the last consolidation course (Arm A after 4 courses; Arm B after 3 courses) (molecular resistance); relapse (hematological/molecular); death including early death (within 30 days after randomization) or development of secondary myelodysplasia or leukemia. Description of the primary efficacy / test accuracy analysis and population: The goal is to demonstrate superiority of the experimental treatment. The primary efficacy analysis will be performed on an intent-to-treat basis. Secondary endpoints: - Rate of hematological CR after induction - Rate of early death during induction - Rate of overall survival (OS) at 2 years - Rate of cumulative incidence of secondary MDS or AML - Rate of cumulative incidence of relapse (CIR) at 2 years - Incidence of hematological and non-hematological toxicity - Rate of molecular remission after last consolidation cycle - Assessment of *PML/RARA* transcript level reduction during treatment - To investigate differences in the following a priori Quality of Life selected scales: physical and cognitive functioning as well as fatigue, nausea and vomiting, constipation and appetite loss - To investigate differences in the immune reconstitution between the two arms - Total hospitalization days during therapy and health economic impact