SAMENVATTING HOVON 138

TITEL

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

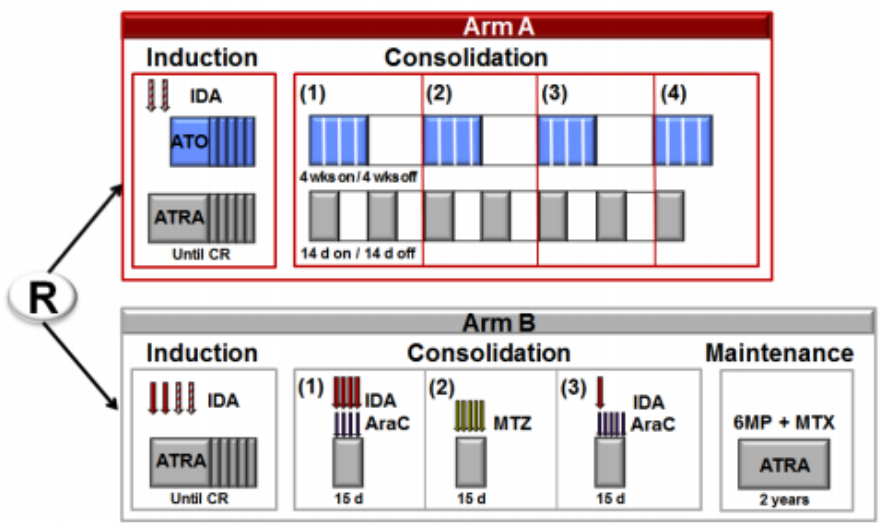
Open label, randomized, prospective multicenter, multinational phase III trial

Short Title: **APOLLO-TRIAL**

INDICATIE

Patients with newly diagnosed high-risk actute promyelotic leukemia (APL/AML M3) at the age of 18 to 65

SCHEMA



Flow chart of treatment plan for experimental (Arm A) and control (Arm B) arm
(Ara-C = cytarabine; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; IDA = idarubicin; MTZ = mitoxantrone; 6-MP = 6-mercaptopurine; MTX = methotrexate)

4.1.1 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.*

4.1.2 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 5.5.6)
    - 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
- 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