SAMENVATTING HOVON 150

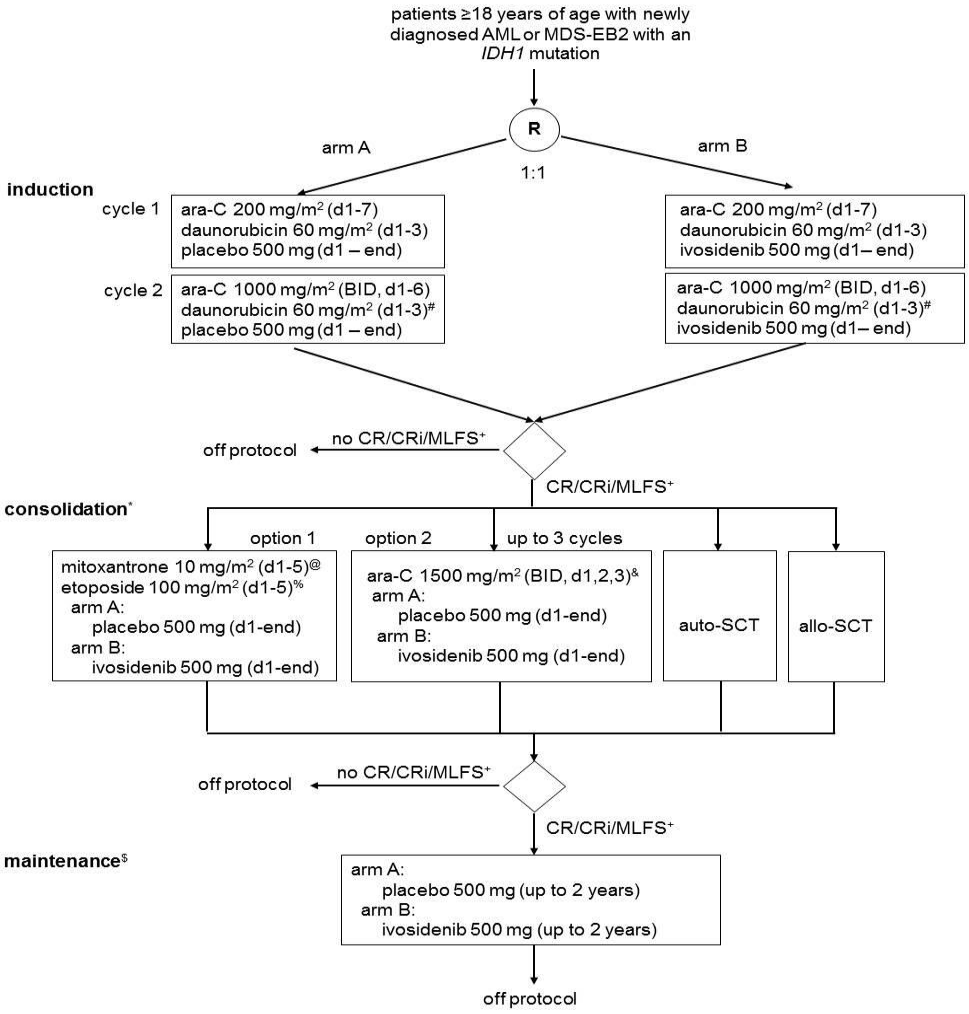
TITEL

A phase 3, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation, respectively, eligible for intensive chemotherapy.

INDICATIE : AML, MDS

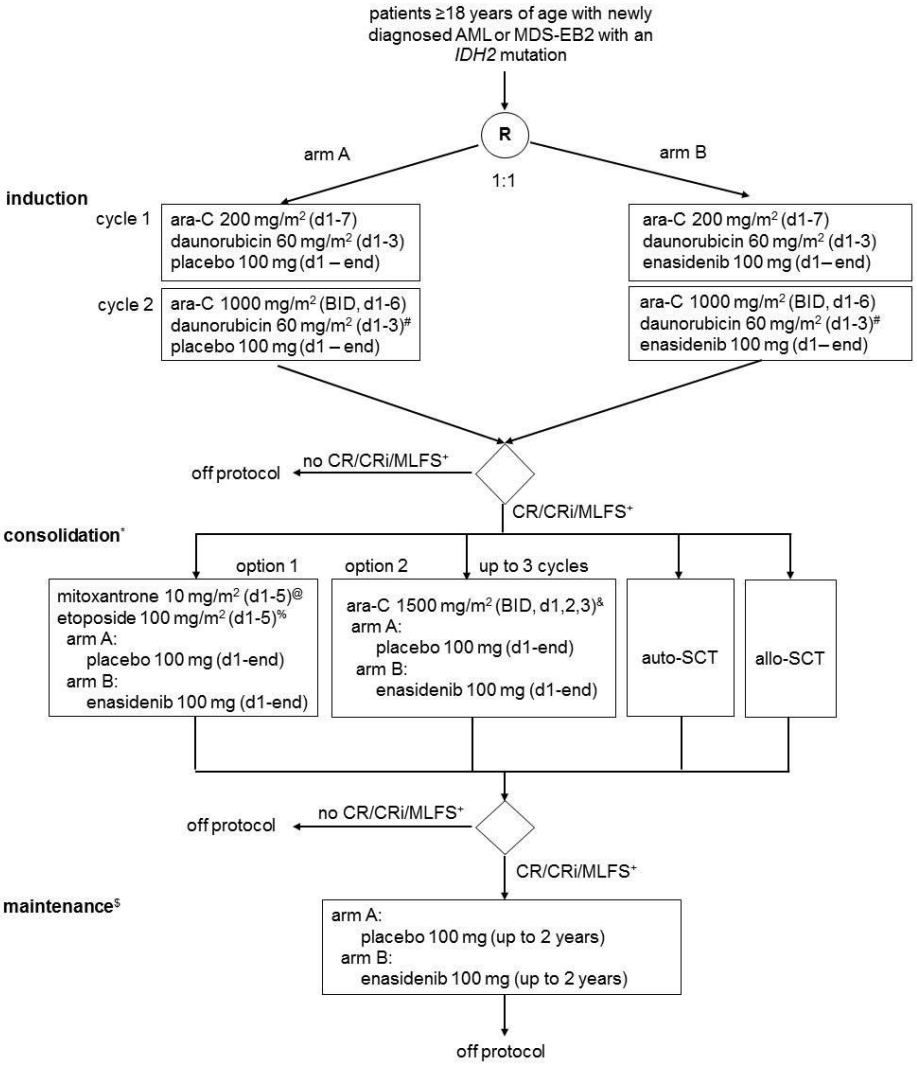
SCHEMA

IDH1 cohort (randomization ivosidenib vs placebo)



patients ≥ 61 years of age will receive induction cycle 2 without daunorubicin
* depending on risk classification and study group
+ note: patients who have no signs of leukemia but do not formally fulfill the criteria of CR/CRi (morphologic leukemia free state (MLFS) according to ELN2017 definition) are also allowed to continue treatment on protocol.
@ patients ≥ 61 years of age will receive consolidation chemo option 1 with dose adjustment of mitoxantrone (days 1-3)
% patients ≥ 61 years of age will receive consolidation chemo option 1 with dose adjustment of etoposide (days 1-3)
& patients ≥ 61 years of age will receive consolidation chemo option 2 with dose adjustment of ara-C to 1000 mg/m²
$ alternatively, patients in CR/CRi/MLFS may proceed directly to maintenance treatment without receiving consolidation treatment

IDH2 cohort (randomization enasidenib vs placebo)



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INCLUSIE CRITERIA

♦ Age ≥18 years
♦ Newly diagnosed AML or MDS-EB2 defined according to WHO criteria, with a documented *IDH1* or *IDH2* gene mutation (as determined by the clinical trial assay) at a specific site (IDH1 R132, IDH2 R140, IDH2 R172). AML may be secondary to prior hematological disorders, including MDS, and/or therapy-related (in which prior disease should have been

documented to have existed for at least 3 months). Patients may have had previous treatment with hypomethylating agents (HMAs) for MDS. HMAs have to be stopped at least four weeks before registration
♦ Patients with dual mutant *FLT3* and *IDH1* or *IDH2* mutations may be enrolled only if, for medical or other reasons, treatment with a FLT3 inhibitor is not considered.
♦ Considered to be eligible for intensive chemotherapy.
♦ ECOG/WHO performance status ≤ 2
♦ Adequate hepatic function as evidenced by:
o Serum total bilirubin ≤ 2.5 × upper limit of normal (ULN) unless considered due to Gilbert's disease (e.g. a mutation in *UGT1A1*) (only for patients in IDH2 cohort), or leukemic involvement of the liver – following written approval by the (Co)Principal Investigator

o Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤ 3.0 × ULN, unless considered due to leukemic involvement of the liver, following written approval by the Principal Investigator.
♦ Adequate renal function as evidenced by creatinine clearance > 40 mL/min based on the Cockroft-Gault formula for glomerular filtration rate (GFR).
♦ Able to understand and willing to sign an informed consent form (ICF).
♦ Written informed consent
♦ Female patients of reproductive potential must undergo a pregnancy test prior to starting study drug and this test must have a negative result. The first pregnancy test will be performed at entry (within 7 days prior to first study drug administration). A pregnancy test should also be repeated within 72 hours before the first study drug administration and confirmed negative prior to dosing. Patients with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy or tubal occlusion or who have not been naturally postmenopausal for at least 24 consecutive months.
♦ Females of reproductive potential as well as fertile men and their partners who are females of reproductive potential must agree to abstain from sexual intercourse or to use a highly effective form of contraception from the time of giving informed consent, during the study, and for 4 months (females and males) following the last dose of ivosidenib/enasidenib or placebo. A highly effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, double-barrier method (e.g., synthetic condoms, diaphragm or cervical cap with spermicidal foam, cream, or gel) or male partner sterilization.
♦ Subject agrees not to participate in another interventional study while on treatment

EXCLUSIE CRITERIA

. ♦ Prior chemotherapy for AML or MDS-EB2 (with the exception of HMA). Hydroxyurea is allowed for the control of peripheral leukemic blasts in patients with leukocytosis (e.g., white blood cell [WBC] counts > 30x109/L).
♦ Dual IDH1 and IDH2 mutations.
♦ Acute promyelocytic leukemia (APL) with PML-RARA or one of the other pathognomonic variant fusion genes/chromosome translocations.
♦ Blast crisis after chronic myeloid leukemia (CML).
♦ Taking medications with narrow therapeutic windows with potential interaction with investigational medication (see Appendix I), unless the patient can be transferred to other medications prior to enrolling or unless the medications can be properly monitored during the

study.
♦ Taking P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transportersensitive substrate medications (see Appendix J) unless the patient can be transferred to other medications within ≥ 5 half-lives prior to administration of ivosidenib or enasidenib, or unless the medications can be properly monitored during the study.
♦ Breast feeding at the start of study treatment.
♦ Active infection, including hepatitis B or C or HIV infection that is uncontrolled at randomization. An infection controlled with an approved or closely monitored antibiotic/antiviral/antifungal treatment is allowed.
♦ Patients with a currently active second malignancy. Patients are not considered to have a currently active malignancy if they have completed therapy and are considered by their physician to be at < 30% risk of relapse within one year. However, patients with the following history/concurrent conditions are allowed:
o Basal or squamous cell carcinoma of the skin
o Carcinoma in situ of the cervix
o Carcinoma in situ of the breast
o Incidental histologic finding of prostate cancer
♦ Significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure (appendix G); myocardial infarction, unstable angina and/or stroke; or left ventricular ejection fraction (LVEF) < 40% by ultrasound or MUGA scan obtained within 28 days prior to the start of study treatment.
♦ QTc interval using Fridericia's formula (QTcF) ≥ 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). Prolonged QTc interval associated with bundle branch block or pacemaking is permitted with written approval of the Principal Investigator.
♦ Taking medications that are known to prolong the QT interval (see Appendix K), unless the patient can be transferred to other medications within ≥ 5 half-lives prior to dosing or unless the medications can be properly monitored during the study.
♦ Dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of orally administered drugs.
♦ Clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid (CSF) during screening is only required if there is a clinical suspicion of CNS involvement by leukemia during screening.
♦ A known medical history of progressive multifocal leukoencephalopathy (PML).
♦ Immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or severe disseminated intravascular coagulation
♦ Any other medical condition deemed by the Investigator to be likely to interfere with a patient's ability to give informed consent or participate in the study.
♦ Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.