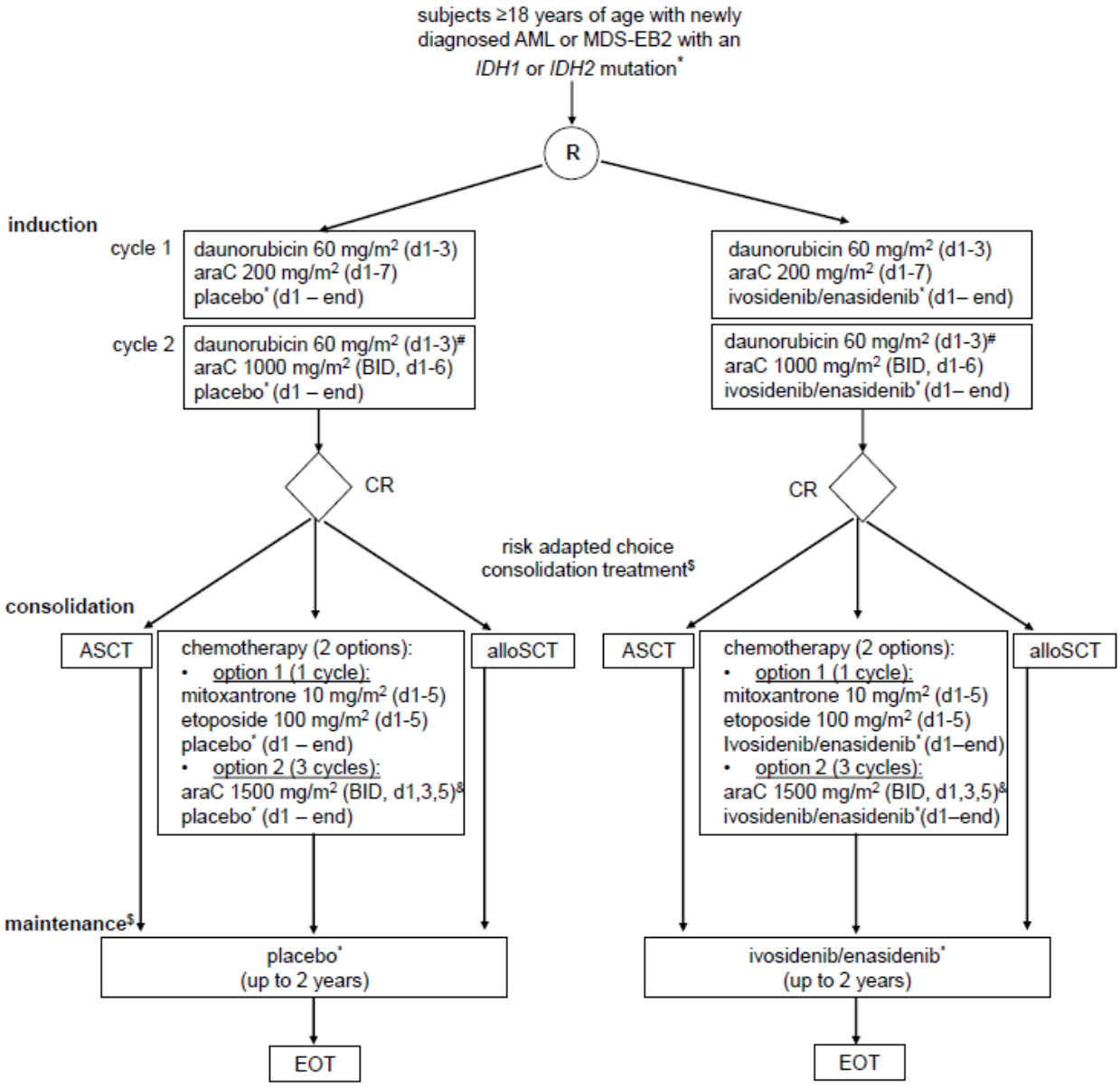
A phase 3, multicenter, double-blind, randomized, placebo-controlled study of AG-120 or AG-221 in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an *IDH1* or *IDH2* mutation, eligible for intensive chemotherapy

HOVON 150 / AMLSG 29-18

EudraCT Nr.: 2018-000451-41

SCHEME OF THE STUDY/ FLOWCHART



* *IDH1* mutation: randomization ivosidenib vs placebo; *IDH2* mutation: randomization enadisenib vs placebo
\# subjects ≥ 61 years of age will receive induction cycle 2 without daunorubicin
$ alternatively, subjects in CR may proceed directly to maintenance treatment without receiving consolidation treatment
& subjects ≥ 61 years of age will receive consolidation chemo option 2 with dose adjustment of araC to 1000 mg/m²

Short title	**HO150 / AMLSG 29-18**
Indication	**AML**
Study objectives	Primary: - To compare event-free survival (EFS) between patients treated with ivosidenib or enasidenib (in combination with induction therapy and consolidation therapy) to patients treated with placebo (in combination with induction therapy and consolidation therapy), and followed by maintenance therapy, in subjects with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) with excess blasts-2 (EB-2), with an isocitrate dehydrogenase 1 (*IDH1*) or isocitrate dehydrogenase 2 (*IDH2*) mutation, eligible for intensive chemotherapy. Key secondary objective: - To determine if treatment including ivosidenib or enasidenib, as compared to placebo, prolongs overall survival (OS). Other secondary objectives: - To compare complete remission (CR/CRi) rates for treatment including ivosidenib/enasidenib vs. placebo. - To compare relapse-free survival (RFS), cumulative incidence of relapse (CIR) and cumulative incidence of death (CID) after CR/CRi between treatment including ivosidenib/enasidenib vs. placebo. - To evaluate minimal residual disease (MRD) levels at sequential time points throughout treatment and CR_{MRD-} rates between treatment including ivosidenib/enasidenib vs. placebo, using molecular and/or flow cytometric techniques. - To assess the safety and tolerability of treatment including ivosidenib /enasidenib vs. placebo. - To compare frequency and severity of adverse events according to CTCAE between treatment including ivosidenib/enasidenib vs. placebo.
Primary endpoint	Primary endpoint: - Event-free survival (EFS), defined as the time from randomization to induction failure, death or relapse after achieving CR or CRi, whichever occurs first.
Secondary endpoints	Key secondary endpoint: - Overall survival (OS), defined as the time from date of randomization to date of death due to any cause. Other secondary endpoints: - Complete remission (CR/CRi) rates - Relapse-free survival (RFS), defined as the time from date of achievement of a remission (CR/CRi) until the date of relapse or death from any cause - Cumulative incidence of relapse (CIR) after CR/CRi

	- Cumulative incidence of death (CID) after CR/CRi, - Complete remission without minimal residual disease (CR_{MRD-}) rate - OS from first CR/CRi - Safety and tolerability of treatment - Frequency and severity of adverse events according to CTCAE - CR/CRi rates, EFS and OS across different patient subgroups, where the groups are defined on basis of prognostic characteristics including age at registration, risk category according to ELN 2017 guidelines as well as cytogenetic and molecular profiles in bone marrow and/or peripheral blood samples.
Study design	Prospective, multicenter, double-blind, randomized, placebo controlled phase 3 clinical study.
Patient population	Newly diagnosed, previously untreated patients ≥18 years of age with AML or MDS-EB-2 with a mutation in either *IDH1* or *IDH2*, considered eligible for intensive treatment.
Planned sample size	968 patients in total (484 patients with *IDH1* mutation and 484 patients with *IDH2* mutation).
Inclusion criteria	1. Newly diagnosed AML or MDS EB-2 defined according to WHO criteria, with a documented *IDH1* or *IDH2* gene mutation at specific sities (IDH1 R132, IDH2 R140, IDH2 R172). AML may be secondary to prior hematological disorders, including MDS, and/or therapy-related. Patients may have had previous treatment with hypomethylating agents (HMAs) for MDS. 2. 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. 3. ≥18 years of age 4. Considered to be eligible for intensive chemotherapy. 5. ECOG/WHO performance status of 0 to 2 6. Adequate hepatic function as evidenced by: a. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) unless considered due to Gilbert's disease (*UGT1A1*28* homozygosity), another mutation in *UGT1A1* (only for patients who will be receiving enasidenib), or leukemic involvement of the liver – this will need to be discussed with the the Medical Monitor. b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤ 3.0 × ULN, unless considered due to leukemic involvement of the liver, following approval by the Medical Monitor. 7. Agree to blood and bone marrow sampling for disease assessment and characterization of response. 8. Be eligible for treatment with the chemotherapeutic agents used in this study for induction and consolidation, as defined in each product's approved labeling. 9. Able to understand and willing to sign an informed consent form (ICF). 10. Female subjects of reproductive potential must undergo a pregnancy test prior to starting study drug. The first pregnancy test will be performed at screening (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. Subjects 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. 11. 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 90 days (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.
Exclusion criteria	1. Prior chemotherapy for AML or MDS-EB2 (with the exception of HMA). Hydroxyurea is allowed for the control of peripheral leukemic blasts in subjects with leukocytosis (e.g., white blood cell [WBC] counts > $30x10^9$/L). 2. Dual *IDH1* and *IDH2* mutations. 3. Acute promyelocytic leukemia (APL) with *PML-RARA* or one of the other pathognomonic variant fusion genes/chromosome translocations. 4. AML with *BCR-ABL1*. 5. Taking medications with narrow therapeutic windows with potential interaction with investigational medication (see Appendix I), unless the subject can be transferred to other medications prior to enrolling or unless the medications can be properly monitored during the study. 6. Taking P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporter-sensitive substrate medications (see Appendix J) unless the subject 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. 7. Breast feeding at of the start of study treatment. 8. Uncontrolled active infection or uncontrolled invasive fungal infection (positive blood or tissue culture). An infection controlled with an approved or closely monitored antibiotic/antifungal treatment is allowed. 9. Subjects 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, subjects with the following history/concurrent conditions are allowed: a. Basal or squamous cell carcinoma of the skin b. Carcinoma in situ of the cervix c. Carcinoma in situ of the breast d. Incidental histologic finding of prostate cancer 10. 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; 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. 11. Inadequate renal function as evidenced by creatinine clearance < 40 mL/min based on the Cockroft-Gault formula for glomerular filtration rate (GFR). 12. 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 approval of the Medical Monitor. 13. Taking medications that are known to prolong the QT interval (see Appendix J), unless the subject can be transferred to other medications within ≥ 5 half-lives prior to dosing. (If equivalent medication is not available, QTc will be closely monitored.) 14. Active hepatitis B or C or HIV at the start of study treatment. 15. Dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of orally administered drugs. 16. 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. 17. Immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or severe disseminated intravascular coagulation 18. Any other medical or psychological condition deemed by the Investigator to be likely to interfere with a subject's ability to give informed consent or participate in the study.
Study medication	AG-120 (ivosidenib) + AG-221 (enasidenib)
Timelines	Start of recruitment: Q4 2018 End of recruitment: Q4 2022 For EFS, two interim analyses are planned. The first interim analysis, for futility, is planned at 94 (33%) EFS events at approximately 26 months after the randomization of the first patient. The second interim analysis, for efficacy, is planned after 189 (67%) EFS events have been observed at approximately 42 months after the first subject is randomized. An interim safety analysis will be performed after 100 patients (50 per treatment arm) have completed induction treatment phase of the trial.
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Sponsor	**HOVON (Hemato-Oncologie voor Volwassenen Nederland)**
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