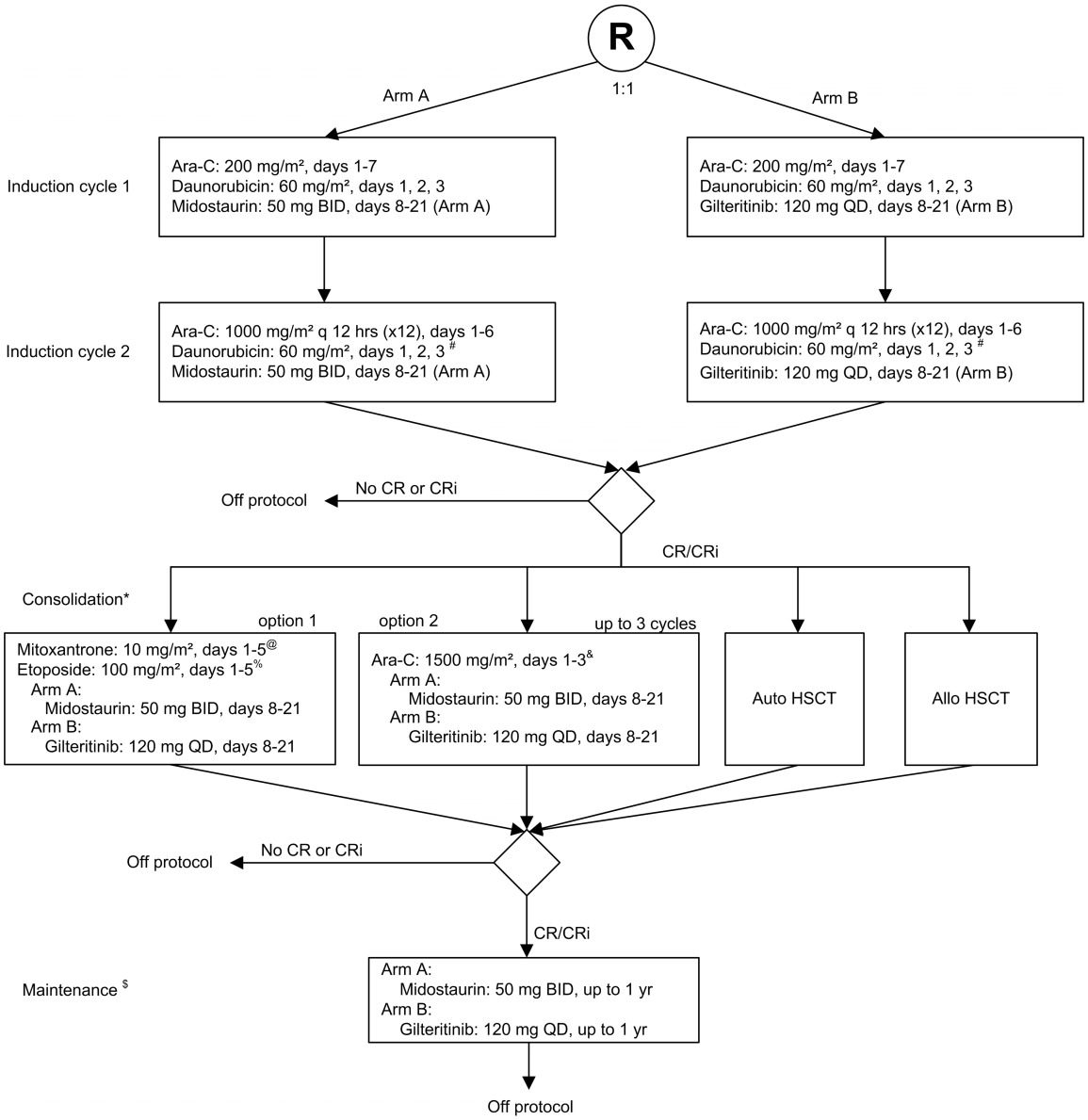
A Phase 3, Multicenter, open-label, Randomized, Study of Gilteritinib versus Midostaurin in Combination with Induction and Consolidation Therapy followed by one-year maintenance in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) or myelodysplastic syndromes with excess blasts-2 (MDS-EB2) with *FLT3* Mutations Eligible for Intensive Chemotherapy

HOVON 156 AML / AMLSG 28-18
EudraCT Nr.: 2018-000624-33

SCHEME OF THE STUDY/ FLOWCHART

Patients with newly diagnosed *FLT3*-mutated AML / MDS-EB2 (age ≥18 yrs)



* depending on risk classification and study group
# 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 1 with dose adjustment of mitoxantrone (days 1-3)
% subjects ≥ 61 years of age will receive consolidation chemo option 1 with dose adjustment of etoposide (days 1-3)
& subjects ≥ 61 years of age will receive consolidation chemo option 2 with dose adjustment of ara-C to 1000 mg/m^2

SYNOPSIS STUDY

Short title	HOVON 156 AML / AMLSG 28-18
Indication	Newly diagnosed patients ≥18 years of age with AML or MDS-EB2 with a mutation in FLT3 (either internal tandem duplication (ITD) or tyrosine kinase domain (TKD), considered eligible for intensive treatment.
Study objectives	Primary objective: • To compare event-free survival (EFS) between Gilteritinib and Midostaurin in combination with induction therapy and consolidation therapy followed by one-year maintenance therapy in subjects with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) with excess blasts-2 (EB2) with a FLT3 gene mutation eligible for intensive chemotherapy. Secondary objectives: • To determine if treatment including Gilteritinib, as compared to Midostaurin, prolongs overall survival (OS). • To compare the complete remission (CR/CRi) rates for treatment including Gilteritinib vs. Midostaurin. • To compare relapse-free survival (RFS), cumulative incidence of relapse (CIR) and death (CID) for treatment including Gilteritibib vs. Midostaurin. • To evaluate minimal residual disease (MRD) levels at sequential time points throughout treatment and CRMRD− rates between treatment including Gilteritinib vs. Midostaurin, using molecular and/or flow cytometric techniques. • To assess the safety and tolerability of treatment including Gilteritinib vs. Midostaurin.
Primary endpoint	Event-free survival (EFS), defined as the time from randomization to treatment failure, death or relapse after achieving CR or CRi, whichever occurs first.
Secondary endpoints	• Overall survival (OS), defined as the time from date of randomization to date of death due to any cause. • 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 (CRMRD−) rate • Frequency and severity of adverse events according to CTCAE • Time to hematopoietic recovery after each treatment cycle
Study design	Prospective, multicenter, open-label, randomized, phase III clinical study.
Patient population	Newly diagnosed patients ≥18 years of age with AML or MDS-EB2 with a mutation in FLT3 (either internal tandem duplication (ITD) or tyrosine kinase domain (TKD), considered eligible for intensive treatment.
Planned sample size	768 (384 patients per arm)
Inclusion criteria	♦ Age ≥18 years

	♦ Newly diagnosed AML or MDS with excess of blasts-2 (EB2) defined according to WHO criteria (appendix A), with centrally documented FLT3 gene mutation (either TKD or ITD or both). AML may be secondary to prior hematological disorders, including MDS, and/or therapy-related. Patients may have had previous treatment with erythroid stimulating agents (ESA) and/or hypomethylating agents (HMAs) for MDS. ESA and HMAs have to be stopped at least four weeks before registration ♦ *FLT3* mutation as assessed by DNA fragment analysis PCR for *FLT3*-ITD and sequencing for *FLT3*-TKD. *FLT3*-ITD positivity is defined as a *FLT3*-ITD / *FLT3*-WT ratio of ≥ 0.05 (5%). *FLT3*-TKD positivity is defined as a variant allelele frequency (VAF = *FLT3* TKD / (*FLT3* WT + *FLT3* TKD)) ≥ 0.05 (5%)) ♦ Considered to be eligible for intensive chemotherapy ♦ Subject is suitable for oral administration of study drug ♦ WHO/ECOG performance status ≤ 2 ♦ Adequate hepatic function as evidenced by o Serum total bilirubin ≤ 2.5 × upper limit of normal (ULN) unless considered due to leukemic involvement following approval by the Principal Investigator o Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤ 3.0 × ULN, unless considered due to leukemic involvement following approval by the Principal Investigator ♦ Adequate renal function as defined by creatinine clearance > 40 mL/min based on the Cockroft-Gault glomerular filtration rate (GFR) ♦ Written informed consent ♦ Patient is capable of giving informed consent ♦ Female subject must either: o Be of nonchildbearing potential: ▪ Postmenopausal (defined as at least 1 year without any menses) prior to screening, or ▪ Documented surgically sterile or status posthysterectomy (at least 1 month prior to screening) o Or, if of childbearing potential,

	▪ Agree not to try to become pregnant during the study and for 6 months after the final study drug administration ▪ And have a negative urine or serum pregnancy test at screening ▪ And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after the final study drug administration. • *Highly effective forms of birth control include: • Consistent and correct usage of established hormonal contraceptives that inhibit ovulation, • Established intrauterine device (IUD) or intrauterine system (IUS), • Bilateral tubal occlusion, • Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.) • Male is sterile due to a bilateral orchiectomy. • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. • *List is not all inclusive. Prior to enrollment, the investigator is responsible for confirming subject will utilize highly effective forms of birth control per locally accepted standards during the protocol defined period. o Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 2

	months and 1 week after the final study drug administration. o Female subject must not donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration. ♦ Male subject and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 4 months and 1 week after the final study drug administration. ♦ Male subject must not donate sperm starting at screening and throughout the study period and for 4 months and 1 week after the final study drug administration. ♦ Subject agrees not to participate in another interventional study while on treatment Waivers to inclusion criteria will NOT be allowed.
Exclusion criteria	♦ Prior chemotherapy for AML or MDS-EB2 (with the exception of ESA and HMA). Hydroxyurea is allowed for the control of peripheral leukemic blasts in subjects with leukocytosis (e.g., white blood cell [WBC] counts > 30 x 10^9/L) ♦ Acute promyelocytic leukemia (APL) with PML-RARA or one of the other pathognomonic variant fusion genes/chromosome translocations ♦ Blast crisis after CML ♦ Taking medications with narrow therapeutic windows listed in Appendix I, unless they can be transferred to other medications prior to registration or unless the medications can be properly monitored during the study ♦ Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A (Appendix I) ♦ Breast feeding as of the start of study treatment ♦ Uncontrolled active infection. An infection controlled with an approved or closely monitored antibiotic/antifungal treatment is allowed ♦ Active hepatitis B or C or HIV infection at randomization ♦ 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

	less than 30% risk of relapse within one year. However, subjects 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: o New York Heart Association (NYHA) Class III or IV congestive heart failure; o Myocardial infarction; o Unstable angina and/or stroke; o Left ventricular ejection fraction (LVEF) < 40% by ECHO or MUGA scan obtained within 28 days prior to the start of study treatment ♦ QTc interval using Fridericia's formula (QTcF) ≥ 450 msec (average of triplicate determinations) or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, family history of long QT interval syndrome). ♦ Subject with hypokalemia and hypomagnesemia at screening (defined as values below LLN) ♦ 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 ♦ Immediate life-threatening, severe complications of leukemia such as uncontrolled bleeding and/or disseminated intravascular coagulation ♦ Any other medical or psychological 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
Study medication	Gilteritinib (120 mg QD PO) - test IMP

	Midostaurin (50 mg BID) - comparator IMP
Timelines	Start of recruitment: Q3/2018 End of recruitment: Q3/2021 Last patient out of treatment: Q3/2023 End of observation: Q3/2033 Duration of the entire trial: 15 years Interim analysis: safety interim analysis will be performed after the first 150 patients completed cycle 1 and cycle 2 of the induction therapy
Principal Investigator	M. Raaijmakers
Sponsor	**HOVON (Hemato-Oncologie voor Volwassenen Nederland)**
Co-investigator	B. Löwenberg G. Ossenkoppele H. Döhner P. Paschka