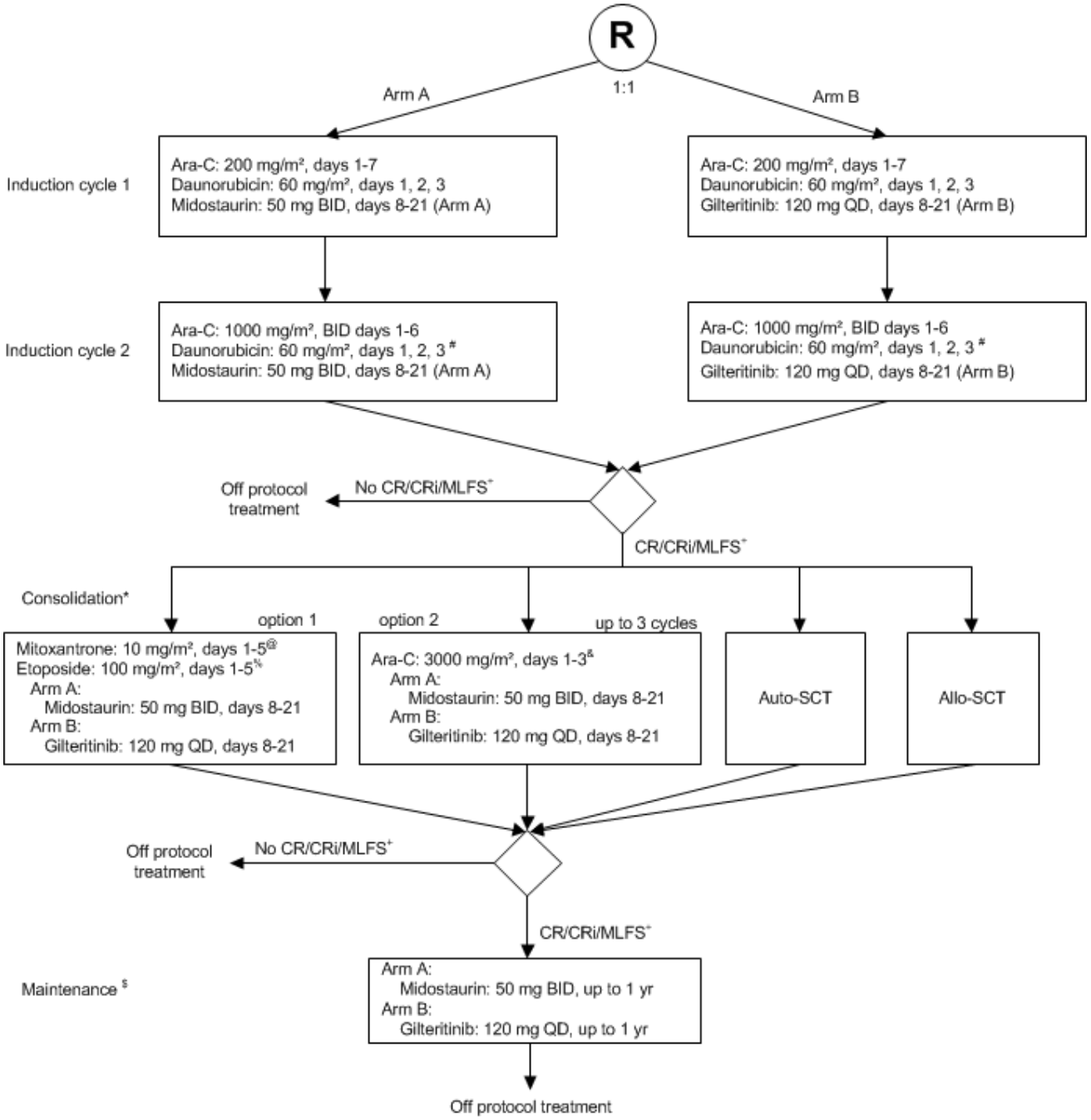
HOVON 156 AML
SYNOPSIS

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

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



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 2000 mg/m²
$ alternatively, patients in CR may proceed directly to maintenance treatment without receiving consolidation treatment

HOVON 156 AML
SYNOPSIS

Short title	HOVON 156 AML
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 patients with newly diagnosed acute myeloid leukemia (AML) with a *FLT3* gene mutation eligible for intensive chemotherapy. Key secondary objectives: • To determine if treatment with gilteritinib, as compared to midostaurin, prolongs overall survival (OS) in the AML patient group. • To compare the complete remission (CR) rate after induction therapy (i.e., CR as best response during or at completion of induction) for treatment including gilteritinib vs. midostaurin in the AML patient group. Other secondary objectives: • To compare CR and CR with incomplete hematologic recovery (CRi) rates after induction cycle 1 and after induction cycle 2 for treatment including gilteritinib vs. midostaurin in the AML patient group. • To compare relapse-free survival (RFS), cumulative incidence of relapse (CIR) and death (CID) for treatment including gilteritibib vs. midostaurin in the AML patient group. • To evaluate minimal residual disease (MRD) levels at sequential time points throughout treatment and CR_{MRD-} rates between treatment including gilteritinib vs. midostaurin, using molecular and/or flow cytometric techniques in the AML patient group. • To assess the safety and tolerability of treatment including gilteritinib vs. midostaurin in the AML patient group. • To assess the time to hematopoietic recovery (ANC 0.5 and $1.0x10^9$/L; platelets 50 and $100x10^9$/L) after each chemotherapy treatment cycle in the AML patient group. • To assess the percentage of patients undergoing an allogeneic stem cell transplant (allo-SCT) in the AML patient group. • To determine quality of life (QoL) during maintenance treatment with gilteritinib vs. midostaurin in the AML patient group.

	Exploratory objectives: • To compare the above mentioned endpoints between gilteritinib and midostaurin in combination with induction and consolidation therapy followed by one-year maintenance therapy in patients with Myelodysplastic Syndromes (MDS) with excess blasts-2 (EB2) with a *FLT3* gene mutation eligible for intensive chemotherapy.
Primary endpoint	Primary endpoint: - Event-free survival (EFS)
Secondary endpoints	Key secondary endpoints: - Overall survival (OS) - Complete remission (CR) rate after induction (i.e., best response of CR during or at completion of induction) Other secondary endpoints: - CR and CRi rates after induction cycle 1 and after induction cycle 2 - Relapse-free survival (RFS) after CR - Cumulative incidence of relapse (CIR) after CR - Cumulative incidence of death (CID) after CR - Complete remission without minimal residual disease (CR_{MRD-}) rate - Frequency and severity of adverse events according to CTCAE - Time to hematopoietic recovery after each chemotherapy treatment cycle.
Study design	Prospective, multicenter, open-label, randomized, phase 3 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 AML patients (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, 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) for MDS. ESA have to be stopped at least four weeks before registration • *FLT3* mutation as assessed by DNA fragment analysis PCR for *FLT3*-ITD and *FLT3*-TKD mutation. Positivity is defined as a *FLT3*-ITD or *FLT3*-TKD / *FLT3*-WT ratio of ≥ 0.05 (5%). • Considered to be eligible for intensive chemotherapy • Patient 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 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

following written approval by the (co) 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 patient must either:
  - 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)
  - 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 patient.

      *List is not all inclusive. Prior to enrollment, the investigator is responsible for confirming patient will utilize highly effective forms of birth control per locally accepted standards during the protocol defined period.
  - Female patient 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.
  - Female patient must not donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration.
- Male patient 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 patient 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. • Patient agrees not to participate in another interventional study while on treatment
Exclusion criteria	• Prior chemotherapy for AML or MDS-EB2, including prior treatment with hypomethylating agents. Hydroxyurea is allowed for the control of peripheral leukemic blasts in patients 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 • Patient requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A (Appendix I) • Breast feeding at start of study treatment • Active, uncontrolled infection, including hepatitis B or C or HIV infection at randomization. An infection controlled with an approved or closely monitored antibiotic/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 less than 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: 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). Prolonged QTc interval associated with bundle branch block or pacemaking is permitted with written approval of the (co) Principal Investigator. • Patient with hypokalemia and/or hypomagnesemia at screening (defined as values below LLN) Note: electrolyte suppletion is allowed to correct LLN values before screening. • 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 (IMP)	Gilteritinib (120 mg QD PO) Midostaurin (50 mg BID)
Timelines	Start of recruitment: Q4/2019 End of recruitment: Q4/2022 Last patient out of treatment: Q4/2024 End of observation: Q4/2032
Principal Investigator	M. Raaijmakers
Co-Principal Investigator	H. Döhner
Sponsor	**HOVON**
Co-sponsor(s)	German-Austrian AML Study Group (AMLSG), Swiss Group for Clinical Cancer Research (SAKK)
Co-investigator	B. Löwenberg G. Ossenkoppele
Monitoring	PPD (study specific)
Data management	e-CRF, via HDC
Trial locations	• Australia (AU) • Austria (AT) • Belgium (BE) • Finland (FI) • France (FR) • Germany (DE) • Ireland (IE) • Lithuania (LT) • Luxembourg (LU) • Netherlands (NL) • Norway (NO) • Spain (ES) • Sweden (SE) • Switzerland (CH)
Number of sites	200 sites in total