Sponsor:	HOVON foundation
Trial:	HOVON 132 AML
EudraCT:	2013-002843-26
Title of study:	Randomized study with a run-in dose-selection phase to assess the added value of lenalidomide in combination with standard remission-induction chemotherapy and post-remission treatment in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or high risk myelodysplasia (MDS) (IPSS-R risk score > 4.5)
Report date:	25Jun2025

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Function:	Principal Investigator
Date:	17-Jul-25
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Publications:
Löwenberg B, Pabst T, Maertens J, et al. Addition of lenalidomide to intensive treatment in younger and middle-aged adults with newly diagnosed AML: the HOVON-SAKK-132 trial. *Blood Adv*. 2021;5(4):1110-1121. doi:10.1182/bloodadvances.2020003855

Studied period:
24Apr2014 (date of inclusion of first patient) – 19May2020 (primary endpoint/final analysis). Date last patient last visit was 20Dec2024 but no long-term follow up analysis was planned.

Phase of development:
Phase III

Objectives:
Primary study objectives
Part A-run-in:
To select in a randomized approach the feasible dose level of lenalidomide when given orally at three variable dose levels (at 20 mg/day 1-21; 15 mg/day 1-21 or 10 mg/day 1-21) in combination with standard induction cycles I and II in patients with AML/MDS with IPSS-R> 4.5

Part A:
To evaluate the effect of lenalidomide on EFS at the (during Part A run-in) selected feasible dose level when combined with remission induction chemotherapy cycles I and II in a randomized comparison to remission induction cycles I and II without addition of lenalidomide

Part B:
To evaluate the effect on the Cumulative incidence of relapse (CIR) of 6 cycles of maintenance therapy with lenalidomide treatment (10 mg/day for 21 days followed by 14 days rest) after post remission chemotherapy cycle III or autoHSCT versus observation only

Secondary study objectives
Part A: First randomization

- To investigate the efficacy of lenalidomide in combination with remission induction chemotherapy cycles I and II (in comparison with the same treatment without lenalidomide) in all patients with regard to complete remission rate (CR/ CRi), DFS, CIR and OS
- To investigate the efficacy of lenalidomide in combination with remission induction chemotherapy cycles I and II in molecularly and cytogenetically distinguishable subsets with regard to complete remission rate (CR/CRi), DFS, CIR and OS
- To evaluate the treatment effects according to MRD measurements following therapy by standardized sampling of bone marrow/blood following remission induction treatment
- To determine the prognostic value of molecular markers and gene expression profiles of the leukemia cells assessed at diagnosis for both remission induction treatments
- To investigate the toxicities of lenalidomide in combination with remission induction chemotherapy cycles I and II
- To compare CIR after autoHSCT and cycle III according to molecular markers and MRD measurements
- To evaluate the effect of lenalidomide on the feasibility of collecting adequate autologous stem cell grafts and the probability of proceeding to autoHSCT

Part B: Second randomization

- To investigate the efficacy of lenalidomide with regard to DFS and OS measured from 2nd randomization
- To investigate post remission and post-transplant toxicities and need for transfusions when lenalidomide is applied after post remission chemotherapy/autoHSCT
- To evaluate the efficacy of lenalidomide as post-remission therapy to prevent relapse in all randomized patients, but also in relationship with the distinctive risk categories of AML (as based on cytogenetics and molecular genetics) and MRD estimates

Methodology:
Part A Run-in randomized dose-selection study: According to decision rules based on DLT frequency and myelosuppression, in a randomized run-in study the dose level of lenalidomide as an addition to standard induction chemotherapy was established. Treatment with and without lenalidomide added to standard induction chemotherapy consisting of idarubicin/ cytarabine (cycle I) and daunorubicine/ cytarabine (cycle II) was compared.

Part A randomized phase III study: Following the dose-selection phase the study continued as a randomized phase III study with induction treatment with or without lenalidomide.

Part B randomized maintenance study: Subsequently, the effect of 6 cycles lenalidomide treatment (10 mg/day for 21 days followed by 14 days rest) after post-remission chemotherapy cycle III or autoHSCT versus observation only for patients in CR1 was investigated.

In part A (run-in and randomized phase III), eligible patients were randomly assigned in a 1:1 ratio to receive remission induction therapy with or without lenalidomide. Random assignment was performed by using a minimization procedure to ensure balance in the number of patients enrolled to each treatment arm overall, within each registration center and diagnostic subgroup (AML, RAEB, or leukemia with ambiguous lineage). Randomization minimization factors in part B of the trial were registration center, diagnostic subgroup, treatment arm of the induction randomization, and type of consolidation treatment received.

Number of patients:
Planned: 927 (127 patients in Part A run-in, 800 in Part A)
Enrolled: 927 (127 patients in Part A run-in, 800 in Part A)
Analyzed: 780

Enrolled but not analyzed, including reason:

Reason:	Number of patients excluded for this reason:
Not evaluable for primary endpoint	127 (enrolled in run-in at dose level 20mg/m2)
Not eligible	20

Diagnosis and main criteria for inclusion:
Eligibility criteria for registration/randomization 1
Inclusion criteria:

- Age 18-65 years, inclusive
- Patients with
    - a diagnosis of AML and related precursor neoplasms according to WHO 2008 classification (excluding acute promyelocytic leukemia) including secondary AML (after an antecedent hematological disease (e.g. MDS) and therapy-related AML), or
    - acute leukemia's of ambiguous lineage according to WHO 2008 or
    - a diagnosis of refractory anemia with excess of blasts (MDS) and IPSS-R score > 4.5
- WHO performance status 0, 1 or 2
- Sampled bone marrow and/ blood cells for centralized molecular analysis and MRD evaluation, unless in case of a dry marrow tap with no possibility to collect marrow cells. In cases of marrow tap failure only blood cells will be sampled.
- Adequate renal and hepatic functions as indicated by the following laboratory values:
    - Serum creatinine ≤1.0 mg/dL (≤88.7 µmol/L); if serum creatinine >1.0 mg/dL (>88.7 µmol/L), then the estimated glomerular filtration rate (GFR) must be >60 mL/min/1.73 m2 as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 m2) = 186 x (Serum Creatinine in mg/dL)-1.154 x (age in years)-0.203 x (0.742 if patient is female) x (1.212 if patient is black) NOTE: if serum creatinine is measured in umol/L,

recalculate it in mg/dL according to the equation: 1 mg/dL = 88.7 umol/L) and use above mentioned formula.
    - Serum bilirubin ≤2.5 x upper limit of normal (ULN)
    - Aspartate transaminase (AST) ≤ 2.5 x ULN
    - Alanine transaminase (ALT) ≤ 2.5 x ULN
    - Alkaline phosphatase ≤ 2.5 x ULN
- Written informed consent
- Ability and willingness to adhere to the lenalidomide Pregnancy Prevention Program

Exclusion criteria:
- Previous therapy with lenalidomide
- Acute promyelocytic leukemia
- Myeloproliferative neoplasia
- Previous treatment for AML or high risk MDS (IPSS-R > 4.5), except hydroxyurea
- Concurrent history of active malignancy in two past years prior to diagnosis except for:
    - basal and squamous cell carcinoma of the skin
    - in situ carcinoma of the cervix
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etcetera)
- Cardiac dysfunction as defined by:
    - Myocardial infarction within the last 6 months of study entry, or
    - Reduced left ventricular function with an ejection fraction < 50% as measured by MUG scan or echocardiogram or
    - Unstable angina, or
    - Unstable cardiac arrhythmias
- Hypersensitivity to the active substance or to any of the excipients of the drug product
- Pregnant or lactating females
- Unwilling or not capable to use effective means of birth control
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Eligibility criteria for randomization 2a (Part B)
Inclusion criteria:
- CR or Cri
- Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
- Platelet count ≥ 75 x 109/L
- Serum creatinine clearance ≥ 30 ml/min or estimated glomerular filtration rate (GFR) >60 mL/min/1.73 m2
- Total bilirubin ≤ 2.5 x ULN
- AST ≤ 2.5 x ULN
- ALT ≤ 2.5 x ULN

Exclusion criteria:
- Severe cardiac dysfunction (NYHA classification II-IV)

- Severe pulmonary dysfunction (CTCAE grade III-IV)
- Severe neurological or psychiatric disease
- Serious active infections
- Previous serious toxicities related to the use of lenalidomide
- CMV reactivation, which is not responsive to first line valganciclovir

Investigational Medicinal Product(s), dose and mode of administration:
Investigational arm was the standard treatment plus IMP lenalidomide.
Part A run-in: Lenalidomide, 20 mg/day 1-21 in cycles I and II, orally.
Part A: Lenalidomide, 15 mg/day 1-21 in cycles I and II, orally.

Comparator(s), dose and mode of administration:
Comparator arm was the standard treatment:

Cycle I:

Agent	**Dose/day**	**Route of administration**	**Days**
Idarubicin	12 mg/m^2	3 hr infusion	1, 2, 3
Cytarabine (Ara-C)	200 mg/m^2	24 hr infusion	1 thru 7

Cycle II:

Agent	**Dose/day**	**Route of administration**	**Days**
Daunorubicin	60 mg/m^2	1 hr infusion	1, 3, 5
Cytarabine (Ara-C)	1000 mg/m^2 q 12 hrs	3 hr infusion	days 1 thru 6

Criteria for evaluation - Efficacy:
The study began with a dose-selection run-in phase with an initial dose of lenalidomide of 20 mg/day on days 1 to 21 in cycles 1 and 2 and then continued with lenalidomide at 15 mg/day as an open-label phase 3 trial (part A of the trial) which is reported here.

Primary endpoint:
Event-free survival (EFS) is the primary endpoint of part A of the trial. EFS is defined as the time from registration to induction failure, relapse or death, whichever occurs first, where induction failure is defined as failure to reach CR/CRi on induction.

Secondary endpoints:
- Rate of hematologic response during and after induction
- Disease-free survival (DFS). DFS is defined as the time from the date of achievement of first CR/CRi on protocol until relapse or death, whichever comes first.
- Overall survival (OS). OS is defined as the time from the date of registration to the date of death due to any cause.
- MRD negativity rate after induction cycle 2

Criteria for evaluation - Safety:

- Occurrence of toxicities
- Time to hematopoietic recovery (ANC 0.5 and 1.0 x 109/L; platelets 50 and 100 x 109/L) after each treatment cycle
- Number of platelet transfusions and last day of platelet transfusion after each cycle

Statistical methods:

All analyses were performed according to the intention-to-treat principle, irrespective of protocol compliance, but 20 of 800 patients who seemed ineligible after registration were excluded (7 in the control arm and 13 in lenalidomide arm). Cox regression analysis was used to analyze the effect of treatment on EFS, OS, and DFS with and without adjustment for other covariates, and the response rate variables were analyzed with the use of logistic regression. The between-arm difference of the time to recovery after each chemotherapy cycle was tested by means of Fine and Gray regression. All *P* values were 2-sided, and values of $P < .05$ were considered statistically significant. No corrections were made for multiple testing. Data for the final analysis were locked as of May 19, 2020. At that time, no patients were receiving the trial treatment and no patients were awaiting random assignment to maintenance therapy. Median follow-up time for patients still alive at the date of last contact (n = 436) was 41 months.

Summary of efficacy results:

Patients were enrolled between February 2, 2025 and August 9, 2027. Of 780 eligible patients, 777 (99.6%) received induction cycle 1 starting at a median of 1 day after study registration. At a median of 37 days after registration, 666 (85%) of 780 patients began treatment with induction cycle 2. The percentage of patients attaining CR or CRi after induction on protocol was 87% for the control group and 82% for the lenalidomide treatment group, with no statistically significant difference (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.48-1.05; $P = .08$). Subsequently, 59 (8%) of 780 patients received chemotherapy cycle 3, 170 (22%) underwent autoHSCT, and 304 (39%) proceeded to alloHSCT. The percentages of complete responders (CR/CRi) who received cycle 3, autoHSCT, or alloHSCT were 9%, 26%, and 46%, respectively.

For the analysis of EFS, 430 events were observed. The median EFS was 24 months for the control group and 21 months for the lenalidomide treatment group, which corresponds with respective EFS rates at 4 years of 44% ± 3% (standard error [SE]) and 44% ± 3%, which implies no advantage for lenalidomide (HR, 0.99; 95% CI, 0.82-1.20; $P = .96$). The latter conclusion remains unchanged after adjustment for known prognostic factors at diagnosis (WBC [log-transformed], age, 2017 ELN risk group, AML type). When we accounted for alloHSCT and for consolidation treatment in general, no difference in EFS estimates between the control and lenalidomide treatment groups became apparent either. Further, no differential effect of treatment on competing risks of EFS was observed.

Median OS was 56 months for the control treatment, and it was not yet reached in the lenalidomide group. For the combined treatment groups, the 4-year OS was estimated at 54% ± 2% (SE) with no difference between the two arms (HR, 0.98; 95% CI, 0.79-1.21; *P*

= .83). Further adjustment for alloHSCT and for consolidation treatment did not alter the results.

In those with CR or CRi, the 4-year DFS was 50% ± 2% with no difference between the two arms (HR, 0.95; 95% CI, 0.77-1.18; *P* = .66). Nor was a between-arm difference observed for the competing risks of DFS (i.e., relapse and non-relapse mortality).

In an exploratory analysis, the possible differential effect of lenalidomide treatment on EFS and OS was evaluated in a variety of subgroups distinguished by prognostic factors for treatment outcome (patient age at registration, AML type (de novo AML, sAML, tAML), disease type (AML, RAEB), WBC at diagnosis, and 2017 ELN risk group) and also according to molecular genotypes. No convincing indications were found that selected prognostic subgroups benefit from addition of lenalidomide (compared with the control treatment), except for a statistically significant survival advantage for treatment with lenalidomide in 58 patients with *SRSF2*-mutated AML (57% vs 33% EFS at 4 years; HR, 0.47; 95% CI, 0.23-0.96; *P* = .04). This difference is explained by a lower relapse rate in the lenalidomide treatment group (67% vs 42% DFS at 4 years; HR, 0.39; 95% CI, 0.17-0.93; *P* = .03). The advantage of lenalidomide treatment in the *SRSF2*-mutated subset was also apparent regarding OS (68% vs 43% at 4 years; HR, 0.42; 95% CI, 0.19-0.94; *P* = .03). Remarkably, in the current risk-adjusted treatment study without the use of an FLT3 inhibitor, FLT3-internal tandem duplication (FLT-ITD) does not express any prognostic value or for either high or low allelic ratios (EFS: 43% FLT3-ITD+ vs 45% FLT3-ITD- at 4 years; HR, 1.12; 95% CI, 0.88-1.42; *P* = .35; OS: 59% FLT3-ITD+ vs 53% FLT3-ITD- at 4 years; HR, 0.90; 95% CI, 0.68-1.19; *P* = .47).

MRD status after induction cycle 2 was evaluated centrally according to protocol with NPM1 qRT-PCR and MFC in 424 (64%) of 666 patients who had received cycle 2 and continued in CR/CRi. Among these patients, the overall MRD negativity rate after induction cycle 2 was 77% with no difference between the comparative treatment arms (OR, 0.92; 95% CI, 0.59-1.46; *P* = .73). MRD positivity after induction cycle 2 correlated with a significant negative impact on DFS (43% vs 57% at 4 years; HR, 1.75; 95% CI, 1.27-2.40; *P* = .001) and OS (51% vs 66% at 4 years; HR, 1.98; 95% CI, 1.39-2.81; *P* < .001); however, there was no apparent difference in outcome between the control and lenalidomide treatment groups or in MRD-positive patients or in MRD-negative patients.

Summary of safety results:

The 2 treatment arms were compared with respect to AEs, time of neutrophil and platelet recovery, platelet transfusion requirements, and number of nights spent in the hospital. The incidence and severities of AEs were comparable between the arms during induction and maintenance phase with no apparent differences in the frequencies of AEs of special interest (e.g., pulmonary embolism and thrombosis with a frequency of 5% after cycle 1 and 6% after induction cycle 2). The frequencies of patients presenting with second primary malignancies registered during study follow-up was 4% and did not differ between the treatment arms. Time to neutrophil and platelet recovery and platelet transfusion requirements after induction cycle 1 did not differ, but after cycle 2 and cycle 3, both neutrophil and platelet recovery became progressively delayed in patients assigned to lenalidomide treatment. By

comparison, the median number of days to neutrophil and platelet recovery was prolonged by an additional 2 to 4 days after cycle 2, and the median recovery intervals for neutrophils and platelets after chemotherapy in cycle 3 were delayed by an extra 11 and 24 days, respectively. Patients in the lenalidomide treatment group remained dependent on platelet transfusions during prolonged intervals after cycle 2 and cycle 3. Cycle 3 patients who received lenalidomide during induction spent more nights in the hospital. Early mortality rates (at 30 and 60 days) were 4% and 6%, respectively, with no differences between the treatment groups.

Conclusions:
The results of this prospective multicenter phase III study did not provide indications for a benefit as regards the addition of the drug lenalidomide to standard of care intensive therapy in adults with newly diagnosed acute myeloid leukemia (AML). The major endpoints reflective of clinical outcome (EFS, the primary endpoint; and OS) were not different for the two comparative treatment groups. Thus these data do not lend positive support to the further development of the lenalidomide treatment combination for clinical practice.

The study in a uniquely systematic approach also assessed the value of measurable residual disease (MRD) assessments in the marrow responding patients after completion of remission induction therapy and reveals the profound prognostic impact of MRD on leukemia recurrence. Thus MRD furnishes critical information regarding variations in relapse risk that could guide subsequent therapeutic decisions.

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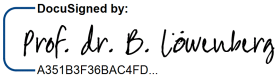
Prof. dr. B. Löwenberg b.lowenberg@erasmusmc.nl prof of hematology, Erasmus University MC Security Level: Email, Account Authentication (None)	DocuSigned by:  A351B3F36BAC4FD... Signature Adoption: Pre-selected Style Using IP Address: 109.36.153.173 Signed using mobile	Sent: 7/17/2025 2:01:17 PM Viewed: 7/17/2025 2:16:46 PM Signed: 7/17/2025 2:17:15 PM
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