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Bleximenib or Placebo in Combination With Standard Induction and Consolidation Therapy Followed by Maintenance for the Treatment of Patients With Newly Diagnosed *KMT2A*-Rearranged or *NPM1*-Mutant Acute Myeloid Leukemia Eligible for Intensive Chemotherapy: A Double-Blind Phase 3 Study (HOVON 181 AML / AMLSG 37-25)

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Key Takeaway

HOVON 181 AML / AMLSG 37-25 is a phase 3 prospective, global, multicenter, double-blind, placebo-controlled, randomized study evaluating the efficacy and safety of bleximenib versus placebo in combination with SoC remission induction and consolidation IC followed by maintenance therapy in adults with ND AML harboring *KMT2A* rearrangements or *NPM1* mutations

Registration Information

This study is registered with EUclinicaltrials.eu (EU CT number: 2025-522767-15) and with ClinicalTrials.gov (NCT number: NCT07223814)

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Abbreviations

AML, acute myeloid leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplant; CNS, central nervous system; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; IDAC, intermediate dose cytarabine; *KMT2A*, lysine methyltransferase 2A gene; *KMT2Ar*, *KMT2A* rearranged; *NPM1*, nucleophosmin 1 gene; *NPM1m*, *NPM1* mutated; QTc, corrected QT interval; SoC, standard of care.

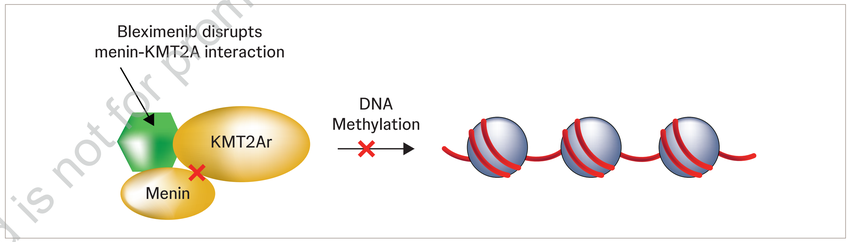
Background

- Newly diagnosed (ND) acute myeloid leukemia (AML) is a genetically heterogeneous disease with a 5-year overall survival rate of ~30%[1,2]
- In AML, *KMT2A* rearrangements (*KMT2Ar*) are associated with poor treatment outcomes, while *NPM1* mutations (*NPM1m*) are generally associated with favorable risk[3,4]
- Treatment with cytarabine + anthracycline (daunorubicin or idarubicin) ('7+3') with cytarabine consolidation remains the standard of care (SoC) for patients eligible for intensive chemotherapy (IC)[3]
- Bleximenib is a potent menin inhibitor with activity in *KMT2Ar* and *NPM1m* AML (**Figure 1**).[5] No menin inhibitors are currently approved for patients with ND *KMT2Ar* or *NPM1m* AML who are eligible for IC
- In the phase 1b ALE1002 study (NCT05453903), high rates of response were observed with bleximenib in combination with '7+3' in participants with ND *KMT2Ar* or *NPM1m* AML eligible for IC[6]
  - The safety profile of bleximenib in combination with '7+3' was consistent with the '7+3' backbone, with no differentiation syndrome or QTc prolongation signal identified
  - No drug-drug interactions with '7+3' were observed

Objective

- To evaluate the efficacy and safety of bleximenib versus placebo in combination with SoC remission induction and consolidation IC followed by maintenance therapy in adults with ND *KMT2Ar* or *NPM1m* AML who are eligible for IC

Figure 1: Mechanism of action of bleximenib

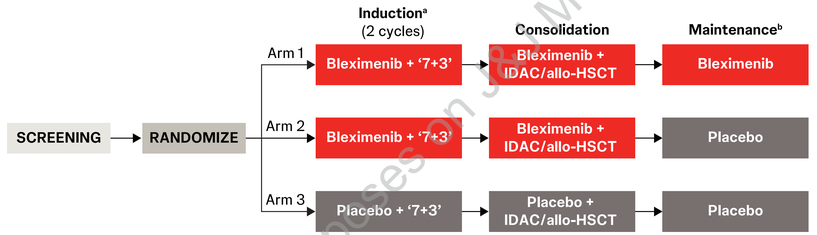


Methods

Study design

- HOVON 181 AML / AMLSG 37-25 (EU CT number: 2025-522767-15, NCT number: NCT07223814) is a prospective, global, multicenter, double-blind, placebo-controlled, randomized, phase 3 clinical study
- 875 participants will be randomly assigned to 1 of 3 study arms (**Figure 2**)

Figure 2: HOVON 181 AML / AMLSG 37-25 study design



[a]Second induction cycle: IDAC ± anthracycline.
[b]All participants eligible for maintenance, regardless of allo-HSCT status.

Endpoints

Primary endpoint	
Event-free survival	• Defined as time from randomization to failure to achieve complete remission (CR) after remission induction, hematologic relapse after achieving CR, or death
Secondary endpoints	
Key secondary endpoint	• Overall survival
Additional secondary endpoints	• Duration of CR • Rate of CR • Incidence of adverse events

Eligibility criteria

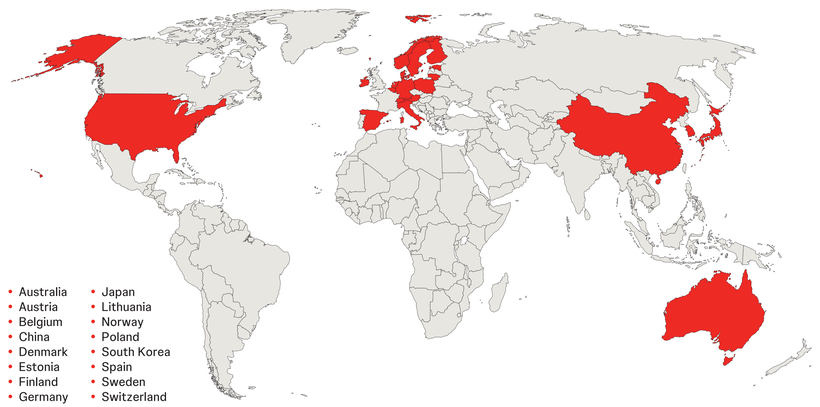
Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • ND *KMT2Ar* or *NPM1m* AML[a] • Eligible for IC • ECOG PS ≤2 • Adequate hepatic and renal function	• Prior chemotherapy for AML • Known active leukemic involvement of the CNS • Prior solid organ transplantation • Active infectious hepatitis • Significant cardiac disorder ≤6 months prior to randomization

[a]≥10% blasts in peripheral blood per 2022 International Consensus Classification criteria.

Study enrollment

- Global enrollment is planned to begin in late 2025 (**Figure 3**)

Figure 3: Countries participating in the trial



- Australia
- Austria
- Belgium
- China
- Denmark
- Estonia
- Finland
- Germany
- Ireland
- Italy
- Japan
- Lithuania
- Norway
- Poland
- South Korea
- Spain
- Sweden
- Switzerland
- The Netherlands
- United States

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