AML-955

QuANTUM-Wild: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Quizartinib in Combination With Chemotherapy and as Single-Agent Maintenance in *FLT3*-ITD–Negative Acute Myeloid Leukemia

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SUMMARY

- Quizartinib is an oral, selective, type-II inhibitor of FMS-like tyrosine kinase 3 (FLT3), with potent binding affinity against wild-type (WT) FLT3, FLT3 internal tandem duplications (ITDs), and several FLT3 variants with point mutations within the kinase domain
- FLT3 is overexpressed in the majority of acute myeloid leukemia (AML) cases independent of the presence of a *FLT3* gene mutation, and quizartinib has shown clinical activity in patients with *FLT3*-ITD–negative newly diagnosed (ND) AML
- In the PETHEMA phase 2, placebo-controlled QUIWI trial, quizartinib significantly prolonged overall survival (OS) when used in combination with Induction/Consolidation chemotherapy and as monotherapy Maintenance in patients with ND, *FLT3*-ITD–negative AML
- QuANTUM-Wild is a randomized, double-blind, placebo-controlled, phase 3 trial of quizartinib in combination with chemotherapy and as monotherapy maintenance, in patients with *FLT3*-ITD–negative ND AML
- Approximately 700 patients will be enrolled at sites in North America, South America, Europe, Asia, and Australia
- **If you have a patient that could benefit from participation in QuANTUM-Wild, please contact Daiichi Sankyo for clinical trial information via email at CTRinfo@dsi.com**

BACKGROUND

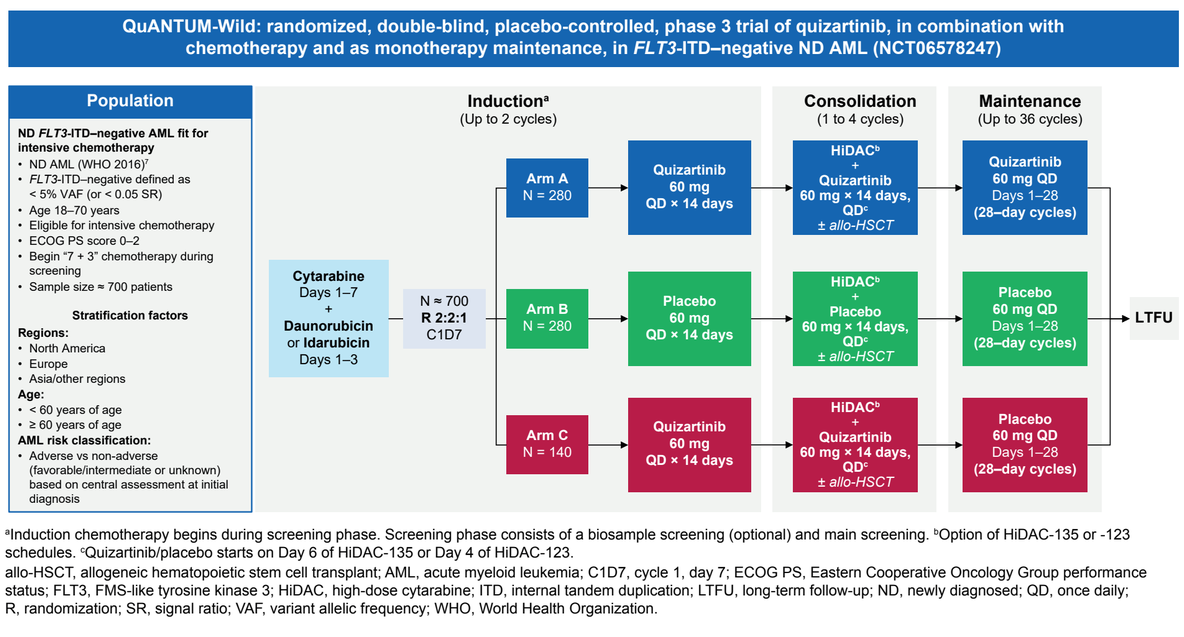
- Approximately 75% of patients with AML do not have a *FLT3*-ITD mutation (*FLT3*-ITD–negative)[1]
  - Patients with *FLT3*-WT AML receiving 7 + 3-based intensive chemotherapy have a poor prognosis and high relapse rates[2]
  - To date, no adjuvant targeted therapies have demonstrated OS improvements in this setting
- Inhibition of FLT3 and other AML-associated kinases could improve standard chemotherapy outcomes for fit patients with *FLT3*-WT AML
- The randomized SORAML trial, which included ND AML patients aged < 60 years with *FLT3*-ITD and *FLT3*-WT, showed that the addition of type II inhibitor sorafenib to 7 + 3 chemotherapy improved leukemia-free survival, but not OS[3]
- Quizartinib is approved in combination with chemotherapy for the treatment of *FLT3*-ITD–positive ND AML based on the phase 3, QuANTUM-First trial (NCT02668653), and has also demonstrated clinical activity in *FLT3*-ITD–negative AML[4–6]
  - In a phase 1 trial (NCT00462761), quizartinib treatment as a single-agent led to responses in patients with *FLT3*-ITD and *FLT3*-WT relapsed/refractory AML[5]
  - Results from the randomized, placebo-controlled, phase 2, QUIWI trial (NCT04107727), by the PETHEMA group showed that adding quizartinib to Induction and Consolidation chemotherapy, followed by up to 12 months of single-agent quizartinib Maintenance for patients achieving complete remission (CR) or CR with incomplete count recovery (CRi), was associated with significantly prolonged OS in patients with ND, *FLT3*-ITD–negative AML[6]
- QuANTUM-Wild is an ongoing, double-blind, randomized, placebo-controlled, phase 3 trial assessing the addition of quizartinib to standard intensive Induction and Consolidation chemotherapy, followed by single-agent quizartinib Maintenance, in patients with *FLT3*-ITD–negative ND AML

METHODS

Study design

- QuANTUM-Wild (ClinicalTrials.gov NCT06578247; EU CT 2023-507936-20-00; jRCT 2061240069) is a phase 3, double-blind, randomized, placebo-controlled trial enrolling patients aged 18–70 years with *FLT3*-ITD–negative ND AML
  - *FLT3*-ITD negativity is defined as a *FLT3*-ITD mutant-to-total variant allele frequency of < 5% by central assessment using a validated *FLT3* assay; patients with *FLT3*-tyrosine kinase domain mutations were not excluded
  - Patients cannot have AML secondary to prior chemotherapy or radiotherapy; AML with known antecedent myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN), or MDS/MPNs including chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML) and others
- Key eligibility criteria and study design elements are illustrated in **Figure 1**

Figure 1. QuANTUM-Wild trial design



[a]Induction chemotherapy begins during screening phase. Screening phase consists of a biosample screening (optional) and main screening. [b]Option of HiDAC-135 or -123 schedules. [c]Quizartinib/placebo starts on Day 6 of HiDAC-135 or Day 4 of HiDAC-123.
allo-HSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukemia; C1D7, cycle 1, day 7; ECOG PS, Eastern Cooperative Oncology Group performance status; FLT3, FMS-like tyrosine kinase 3; HiDAC, high-dose cytarabine; ITD, internal tandem duplication; LTFU, long-term follow-up; ND, newly diagnosed; QD, once daily; R, randomization; SR, signal ratio; VAF, variant allelic frequency; WHO, World Health Organization.

- The trial comprises five consecutive phases: Screening, Induction, Consolidation, Maintenance, and Long-Term Follow-Up
- Eligible patients are randomized in a 2:2:1 ratio into three treatment arms, stratified by region, age, and risk status:
  - **Arm A:** Quizartinib in all phases of treatment, in combination with chemotherapy during the Induction and Consolidation phases, then as monotherapy in the Maintenance phase
  - **Arm B:** Placebo in all phases of treatment, in combination with chemotherapy during the Induction and Consolidation phases, then as monotherapy in the Maintenance phase
  - **Arm C:** Quizartinib in combination with chemotherapy in the Induction and Consolidation phases, followed by placebo monotherapy in the Maintenance phase

Study phases

- In the Induction phase, patients will receive the standard "7 + 3" Induction chemotherapy regimen of continuous infusion of cytarabine on days 1–7 and an anthracycline (either daunorubicin [60 mg/m^2/day] or idarubicin [12 mg/m^2/day], at investigator's discretion) on days 1–3, followed by quizartinib/placebo (60 mg) on days 8–21
  - A second Induction cycle of either "7 + 3" or "5 + 2" chemotherapy is allowed if bone marrow blast count is ≥ 5% after first Induction
- Patients who achieve CR or CRi during Induction will enter the Consolidation phase and receive ≥ 1 to ≤ 4 cycles, per investigator discretion, of high-dose cytarabine (HiDAC-135 or HiDAC-123 schedule) followed by quizartinib/placebo (60 mg) once daily for 14 days in each cycle
  - Patients may receive an allogeneic hematopoietic stem cell transplant (allo-HSCT) at the investigator's discretion after completing ≥ 1 cycle of HiDAC Consolidation
- After Consolidation with HiDAC ± allo-HSCT, eligible patients will enter the Maintenance phase and receive continuous single-agent quizartinib (60 mg) once daily or placebo for up to 36 cycles (28 days per cycle)
  - The Maintenance phase will continue until relapse, start of non-protocol-specified AML treatment, death, unacceptable toxicity, trial closure, or completion of 36 cycles, whichever occurs first
- The Long-Term Follow-Up phase begins upon completion of 36 cycles of quizartinib/placebo in the Maintenance phase or permanent discontinuation of quizartinib/placebo in any phase

Endpoints and statistical considerations

- Primary, secondary, and key exploratory endpoints are detailed in **Table 1**
- The primary endpoint is OS, defined as the time from randomization until death by any cause, between Arm A and Arm B
  - Arm C, which lacks quizartinib maintenance therapy compared to Arm A, is included to investigate the contribution of quizartinib as monotherapy in the Maintenance phase to the overall treatment effect

Table 1. QuANTUM-Wild trial endpoints

Endpoint	Description
Primary endpoint:	
OS, Arm A vs Arm B	**Time from randomization until death**
Secondary endpoints:	
Arm A vs Arm B	
EFS	Time from randomization until failure to achieve CR at the end of Induction, relapse after CR, or death
DOCR	Time from CR until relapse or death
RFS	For patients who achieve CR, time from randomization until relapse or death
CR rate	Proportion of patients who achieve CR by end of Induction
$CR_{MRD(-)}$	MRD negativity by *NPM1*, *CBF*, and *FLT3*-ITD[a]
Safety	Incidence of TEAEs, serious TEAEs, adverse events of special interest, changes in vital signs, ECG, safety laboratory evaluations, and physical examinations
PK of quizartinib and its metabolite, AC886	Plasma concentrations at each time point and PK parameters (AUC_{24h}, C_{max}, C_{min}, T_{max} and accumulation ratio and parent/metabolite ratio)
Arm C vs Arm B	
OS	Time from randomization until death
Key exploratory endpoints: CRc rate and duration; CIR; PROs; biomarkers (assessments of associations of molecular alterations and gene expression profiles with clinical responses); other efficacy outcomes for Arm A vs Arm B and Arm A vs Arm C	

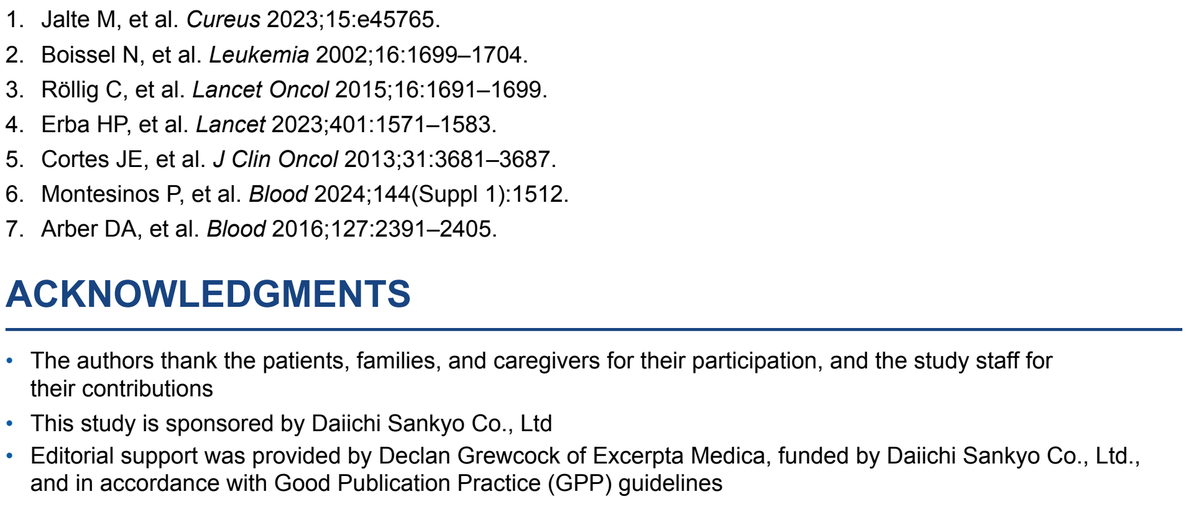
[a]*NPM1* and *CBF* MRD are assessed individually in patients with these mutations present at screening, and *FLT3*-ITD MRD is assessed in all patients.
AUC_{24h}, area under the concentration versus time curve from time 0 to 24 hours; CBF, core binding factor; CIR, cumulative incidence of relapse; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CR, complete remission; CRc, composite CR (CR + CR with incomplete blood count recovery); DOCR, duration of CR; ECG, electrocardiogram; EFS, event-free survival; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; MRD, measurable residual disease; NPM1, nucleophosmin 1; OS, overall survival; PK, pharmacokinetics; PRO, patient reported outcome; RFS, relapse-free survival; TEAE, treatment-emergent adverse event; T_{max}, time to C_{max}.

- The planned sample size is ~700 patients, including ~280 patients each in Arms A and B, and ~140 patients in Arm C
- The trial is powered for the primary analysis of OS between Arm A and Arm B; the planned sample size provides ≥ 90% power to detect an OS hazard ratio of 0.68 at a two sided significance level of 0.05
- The primary OS analysis will be performed when 289 deaths have occurred between Arm A and Arm B, and ≥ 24 months have elapsed since the last patient was randomized
  - An OS interim analysis will be performed when approximately 231 deaths (~80% of target) have occurred and ≥ 15 months have elapsed since the last patient was randomized
  - The study may be stopped at the OS interim analysis if the pre-specified superiority boundary is crossed

Enrollment

- Trial enrollment is currently ongoing
- Approximately 260 sites are planned across North and South America, Europe, Asia, and Australia (**Figure 2**)

Figure 2. QuANTUM-Wild enrolling countries



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