Quizartinib with reinduction chemotherapy and as single-agent maintenance in children and adolescents with relapsed/refractory *FLT3*-ITD⁺ AML: a phase 1/2 multicenter study

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SUMMARY

- FMS-related tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) mutations occur in approximately 10–15% of pediatric acute myeloid leukemia (AML) cases and are often associated with a poor prognosis and high-risk disease
- Quizartinib is an oral FLT3 inhibitor approved for adult patients with newly diagnosed *FLT3*-ITD⁺ AML, and has demonstrated tolerability and clinical activity in pediatric patients with relapsed/refractory (R/R) AML
- This global, open-label, multicenter, single-arm phase 1/2 trial assessed quizartinib in combination with fludarabine + cytarabine chemotherapy for reinduction, with optional consolidation, and as a single-agent maintenance therapy (after optional allogeneic hematopoietic cell transplantation [allo-HCT]) in pediatric patients with R/R *FLT3*-ITD⁺ AML
- Quizartinib demonstrated a manageable safety profile, consistent with previous findings, and clinical activity in combination with reinduction chemotherapy and as single-agent maintenance in pediatric patients with R/R *FLT3*-ITD⁺ AML

CONCLUSIONS

- This phase 1/2 trial in pediatric patients with *FLT3*-ITD⁺ R/R AML demonstrated that quizartinib, in combination with reinduction chemotherapy and as single-agent maintenance, had a safety profile similar to that observed in adults and demonstrated preliminary clinical efficacy
- Treatment-emergent adverse events (TEAEs) associated with discontinuation of study treatment were low, and no fatal TEAEs were reported
- Of the 13 patients eligible for efficacy evaluation, 3 achieved remission (CRc), 8 achieved a morphologic leukemia-free state (MLFS), and 2 did not respond
- The pharmacokinetics (PK) of quizartinib, and its primary metabolite AC886, was consistent across all age groups and generally comparable to that observed in adult patients

INTRODUCTION

- *FLT3*-ITD mutations occur in approximately 10–15% of pediatric AML cases and are often associated with a poor prognosis and high-risk disease[1-2]
- The presence of *FLT3*-ITD mutations confers increased risk of relapse and decreased survival in childhood AML[3]
- A retrospective study in pediatric patients with de novo AML reported that patients with *FLT3*-ITD mutations had lower remission induction rates (70%, vs 88% without *FLT3*-ITD; $P = 0.01$), and lower 5-year rates of event-free survival (EFS; 29% vs 46%, respectively; $P = 0.0046$) and overall survival (OS; 32% vs 58%; $P = 0.037$)[3]
- Quizartinib is a FLT3 inhibitor with single-agent activity in R/R AML, and is approved in combination with chemotherapy, followed by maintenance monotherapy, for adult patients with newly diagnosed, *FLT3*-ITD⁺ AML[4]
- Quizartinib demonstrated tolerability and activity in pediatric patients with R/R AML in a Children's Oncology Group-sponsored phase 1 trial (NCT01411267), warranting further investigation[5]
- Here, we report findings of quizartinib administered in combination with fludarabine + cytarabine chemotherapy for reinduction, followed by consolidation, including hematopoietic cell transplantation in eligible patients, and as a single-agent maintenance therapy in pediatric patients with R/R *FLT3*-ITD⁺ AML

METHODS

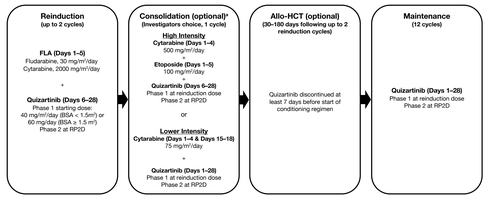
- This global, open-label, multicenter, single-arm phase 1/2 dose-escalation and dose-expansion trial (NCT03793478) enrolled pediatric patients with R/R *FLT3*-ITD⁺ AML aged ≥ 1 year to ≤ 18 years, and young adults up to 21 years of age
  - Key eligibility criteria are presented in **Table 1**
- Phase 1 determined the recommended phase 2 dose (RP2D) of quizartinib (**Figure 1**)
  - Quizartinib doses started at 40 mg/m²/day for patients with a body surface area (BSA) < 1.5m² and 60 mg/day for those with BSA ≥ 1.5 m²
- Phase 2 recruited additional patients to further evaluate the safety, PK, and efficacy of quizartinib at the RP2D
- Patients received 1–2 reinduction cycles of fludarabine 30 mg/m²/day + cytarabine 2000 mg/m²/day + quizartinib (**Figure 1**)
- Following reinduction, patients could receive optional allo-HCT if eligible (or consolidation therapy if allo-HCT was not immediately available), followed by 1 year of single-agent quizartinib maintenance at reinduction dose (**Figure 1**)
- Primary endpoints were the determination of the quizartinib RP2D (phase 1 only), composite complete remission (CRc) rate, safety and tolerability, and the PK of quizartinib and its primary metabolite, AC886
- Safety was assessed in patients who received ≥ 1 dose of quizartinib. Dose-limiting toxicities (DLTs) were evaluated in reinduction Cycle 1 (C1) during phase 1 for the determination of the quizartinib RP2D
- Efficacy assessment included patients with centrally confirmed *FLT3*-ITD⁺ mutation who received ≥ 75% of the prescribed quizartinib doses during reinduction C1 and had ≥ 1 follow-up bone marrow evaluation
  - Response criteria were adapted from Cheson[7] and Creutzig[8]

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
AML diagnosis (WHO 2008[9]) with ≥ 5% blasts in bone marrow	Isolated CNS relapse (CNS2/3 disease allowed if treated with intrathecal chemotherapy)
R/R after first-line high-dose chemotherapy	APL, JMML, or myeloid proliferations related to Down syndrome
Confirmed *FLT3*-ITD⁺ activating mutation in bone marrow or peripheral blood[a]	Uncontrolled cardiovascular disease[b]
Age 1 month to ≤ 21 years	Systemic fungal, bacterial, viral or other active infection without improvement despite appropriate treatment
Karnofsky/Lansky performance status[6] > 50%	Known active hepatitis B or C, or HIV infection
Full recovery from previous chemotherapy toxicity (Grade ≤ 1 or baseline)	Concomitant chemotherapy, radiation, or immunotherapy other than protocol-specified
≥ 90 days since prior HCT (if applicable)	

[a]*FLT3*-ITD/*FLT3*-wildtype allelic ratio ≥ 0.05. [b]Including: congenital long QT syndrome, clinically significant ventricular arrhythmias, QTc > 450 ms, uncontrolled angina/MI within 6 months, second/third degree heart block, heart rate < 50 bpm, uncontrolled hypertension, left bundle branch block, or class 3/4 heart failure.
AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; bpm, beats per minute; CNS, central nervous system; HCT, hematopoietic cell transplantation; HIV, human immunodeficiency virus; ITD, internal tandem duplication; JMML, juvenile myelomonocytic leukemia; MI, myocardial infarction; WHO, World Health Organization.

Figure 1. Study treatment schema



Each cycle consists of 28 consecutive days. [a]Consolidation is allowed only as a bridging therapy for those patients proceeding to transplant. Investigators choose 1 option for consolidation as a bridge-to-transplant or proceed directly to allo-HCT. Patients not proceeding to allo-HCT will qualify to proceed to continuation if they achieved a CR, CRi, PR, or MLFS in reinduction. [b]DLTs will be determined during reinduction Cycle 1 only.
BSA, body surface area; CR, complete remission; CRi, complete remission with incomplete count recovery; DLT, dose-limiting toxicity; FLA, fludarabine and cytarabine; MLFS, morphologic leukemia-free state; PR, partial remission; RP2D, recommended phase 2 dose.

RESULTS

Patient enrollment and demographics

- Overall, 16 patients were enrolled and treated (n = 9 in dose escalation, n = 7 in dose expansion)
- At data cutoff (24 June 2025), all patients except 1 patient in the dose-expansion phase had discontinued study treatment and entered the long-term follow-up period
- All patients received at least 1 reinduction cycle, 6 (38%) patients received 2 cycles of reinduction chemotherapy, 1 (6%) patient received consolidation chemotherapy, and 9 (56%) patients received both allo-HCT and quizartinib maintenance treatment
- Baseline demographics and disease characteristics are presented in **Table 2**
  - The median age was 13.5 (range, 3–17) years; 69% (n = 11) of patients were male and 19% (n = 3) had a prior allogeneic transplant
- The RP2Ds of quizartinib were established as 40 mg/m²/day for BSA < 1.5 m² and 60 mg/day for BSA ≥ 1.5 m²

Table 2. Baseline demographics and disease characteristics

Characteristic	All patients (N = 16)
Age, years, median (range)[a]	13.5 (3–17)
Sex, n (%)	
Male	11 (69)
Female	5 (31)
Race, n (%)	
White	10 (63)
Other	4 (25)
Missing	2 (13)
Weight, kg, median (range)	51.1 (17–84)
BSA, m², median (range)	1.54 (0.7–2)
Relapsed AML, n (%)	5 (31)
Refractory AML, n (%)	11 (69)
Time from AML diagnosis to R/R, weeks, median (range)	7.0 (3–75)
Prior allo-HCT, n (%)	3 (19)
Baseline WBC, × 10⁹/L, median (range)	0.12 (0.05–1.49)
Risk status with specific cytogenetic patterns, n (%)	
Intermediate	1 (6)
Unfavorable	13 (81)
Unknown	2 (13)
AML subtype, n (%)	
AML with recurrent genetic abnormalities	
AML with mutated *RUNX1*	1 (6)
Unknown	1 (6)
AML not otherwise categorized	
AML with minimal differentiation	2 (13)
AML without maturation	2 (13)
AML with maturation	5 (31)
Acute monoblastic/monocytic leukemia	3 (19)
Unknown	2 (13)

[a]Age is collected in the CRF; if it is not available in CRF, it is calculated using the informed consent date and the birth date.
CRF, case report form; WBC, white blood cell count.

Safety

- All patients had ≥ 1 TEAE, most commonly anemia (56%, n = 9) and vomiting (50%, n = 8) (**Table 3**)
- Fourteen patients (88%) experienced a Grade ≥ 3 TEAE, with cytopenias being the most common (thrombocytopenia, 44%, n = 7; anemia, 38%, n = 6; neutropenia, 38%, n = 6) (**Table 4**)
- Two TEAEs were associated with treatment discontinuation: Grade 3 QT prolongation and Grade 2 thrombocytopenia (n = 1 each)
- One patient in phase 1 experienced Grade 3 thrombocytopenia that initially qualified as a DLT, but was later found not to be drug-related
- Serious TEAEs were reported in 63% (n = 10) of patients, most commonly febrile neutropenia (25%, n = 4) and sepsis (13%, n = 2)

Efficacy

- Of the 13 patients that were eligible for efficacy evaluation, the CRc rate was 23%, including 1 patient who achieved complete remission (CR) and 2 achieving CR with incomplete blood count recovery (CRi) after completion of up to 2 reinduction cycles, 8 (62%) achieved a MLFS, and 2 (13%) did not respond (**Table 5**)

Table 3. TEAEs (all grades) occurring in ≥ 20% of all patients

Preferred term, n (%)	Safety analysis set (N = 16)
Anemia	9 (56)
Vomiting	8 (50)
Alanine aminotransferase increased	7 (44)
Aspartate aminotransferase increased	7 (44)
Hypokalemia	7 (44)
Neutropenia	7 (44)
Pyrexia	7 (44)
Thrombocytopenia	7 (44)
Nausea	6 (38)
Blood bilirubin increased	5 (31)
Diarrhea	5 (31)
Febrile neutropenia	5 (31)
Hypoalbuminemia	5 (31)
Pain in extremity	5 (31)
Hypomagnesemia	4 (25)
White blood cell count decreased	4 (25)

Table 4. Grade ≥ 3 TEAEs occurring in ≥ 10% of all patients

Preferred term, n (%)	Safety analysis set (N = 16)
Thrombocytopenia	7 (44)
Anemia	6 (38)
Neutropenia	6 (38)
Febrile neutropenia	5 (31)
White blood cell count decreased	4 (25)
Hypophosphatemia	3 (19)
Leukopenia	3 (19)
Neutrophil count decreased	3 (19)
Alanine aminotransferase increased	2 (13)
Aspartate aminotransferase increased	2 (13)
Bilirubin conjugated increased	2 (13)
Gamma-glutamyltransferase increased	2 (13)
Hypokalemia	2 (13)
Hypoxia	2 (13)
Lymphocyte count decreased	2 (13)
Platelet count decreased	2 (13)
Pulmonary edema	2 (13)
Sepsis	2 (13)

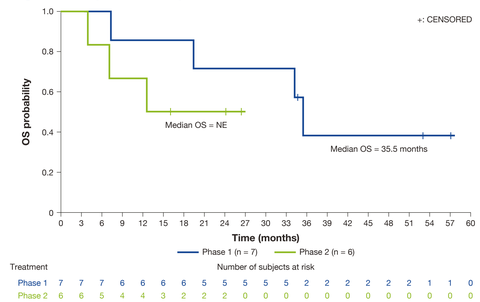
Table 5. Efficacy results

Response parameters	Efficacy analysis set (N = 13)
CRc (CR + CRi),[a] n (%)	3 (23.1)
80% CI[b]	(8.8–44.4)
Best response,[c] n (%)	
CR[c]	1 (7.7)
CRi	2 (15.4)
MLFS	8 (61.5)
PR	0
No response	2 (15.4)
Median EFS (95% CI), months[d]	0.1 (NE–NE)
Median OS (95% CI), months[d]	34.2 (7.3–NE)

[a]Defined as the percentage of participants achieving CR + CRi after completion of up to 2 reinduction cycles. [b]The 2-sided 80% CIs are based on the exact (Clopper–Pearson) binomial distribution. [c]After completion of up to 2 reinduction cycles.
[d]Median estimates from Kaplan–Meier analysis. CI is computed using the Brookmeyer-Crowley method.
CI, confidence interval; EFS, event-free survival; PR, partial remission.

- Durations of remission for the 3 CRc patients were 32.4 months (death after CRi), 22.4 months (relapse after CR), and 13.4 months (relapse after CRi)
- Median overall survival (OS) was 34.2 months (95% confidence interval [CI], 7.3 months–not estimated [NE]) (**Figure 2**)
  - OS rates at 1, 2, and 3 years were 77%, 61%, and 32%, respectively
- Of the 16 patients that were eligible for safety evaluation (including 3 patients whose *FLT3*-ITD mutation status was not confirmed by the central laboratory), 2 (13%) achieved CR and 3 (19%) achieved CRi, (CRc rate 31%, 5/16) after completion of up to 2 reinduction cycles
- Median OS in the safety evaluable population was 35.5 months (95% CI, 12.5–NE)
  - OS rates at 1, 2, and 3 years were 81%, 60%, and 38%, respectively

Figure 2. Kaplan–Meier plot of OS



NE, not estimated.

Pharmacokinetics

- A non-compartmental analysis showed that, compared with adults, quizartinib and AC886 in pediatric patients exhibited maximum (plasma/serum) concentration (C_{max}) values that were 1.03-fold and 1.09-fold of the adult population, respectively. Their area under the (plasma concentration–time) curve during steady state (AUC_{tss}) values were 0.79-fold and 0.88-fold of adult levels, indicating that pediatric exposures are comparable to those in adults (**Table 6**)
- The slightly higher PK variability in pediatric patients may be related to nasogastric administration in 2 patients and concomitant high dose intensity metamizole (a reported moderate cytochrome P450 3A [CYP3A] inducer) use in 1 patient[9]

Table 6. Summary of steady-state NCA result by age groups

		Quizartinib		AC886 metabolite		Metabolite: parent ($AUC_{tau,ss}$)
		$C_{max,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng h/mL)	$C_{max,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng h/mL)	
Current study: Pediatric R/R AML reinduction phase						
Age: 1–5 y (n = 2)	Observations	76.8, 347	1020, 2760	279, 633	5140, 11100	5.03, 4.03
Age: 6–12 y (n = 5)[a]	Geometric Mean (%CV)	281 (85.8%)	4340 (135)	188 (77.1)	3090 (67.4)	0.710 (167)
Age: 13–17 y (n = 9)		199 (107)	3030 (148)	290 (74.3)	5410 (76.9)	1.78 (134)
Overall (N = 16)		216 (97.4)	3150 (133)	265 (75.8)	4740 (77.3)	1.50 (160)
Reference Study: QuANTUM-First ND AML induction Phase Adult PK (PopPK simulated 60 mg)[b]						
60 mg (n = 259)	Geometric Mean (%CV)	209 (71.1)	4010 (84.9)	244 (52)	5390 (51.1)	1.34 (67.6)
GMR (pediatric/ adult)		**1.03**	**0.79**	**1.09**	**0.88**	-

[a]One patient received concomitant high dose intensity metamizole (a reported moderate CYP3A inducer). [b]Adult PK parameters for the 60 mg dose were simulated with patients in the QuANTUM-First study induction phase PK parameters.
AML, acute myeloid leukemia; AUC_{tau}, area under the plasma concentration–time curve from time 0 to tau (24 hours); C_{max}, maximum (plasma/serum) concentration; CV, coefficient of variation; CYP3A, cytochrome P450 3A; GMR, geometric mean ratio; NCA, non-compartmental analysis; ss, steady state.

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