Exposure-Overall Survival Analysis for Quizartinib in Newly Diagnosed Patients with FMS-Like Tyrosine Kinase 3-Internal-Tandem-Duplication-Positive Acute Myeloid Leukemia

#S-075

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BACKGROUND

- Quizartinib and its pharmacologically active metabolite AC886 are potent and selective type II FMS-like tyrosine kinase 3 (FLT3) inhibitors. Quizartinib was approved by FDA in 2024 for the treatment of patients with newly diagnosed FLT3-internal tandem duplication (ITD)-positive acute myeloid leukemia (AML) based on the results of the phase 3 clinical trial QuANTUM-First (NCT02668653)[1].
- In QuANTUM-First, patients were randomized to receive 40 mg/day of quizartinib or placebo in combination with standard induction and consolidation chemotherapy. Patients with blood count recovery entered the continuation phase to receive quizartinib or placebo as monotherapy, starting at 30 mg/day and escalating to 60 mg after 15 days. Dose adjustments were based on concomitant administration of strong cytochrome P450 3A (CYP3A) inhibitors and/or QT prolongation.
- Model-informed drug development (MIDD) evidence supporting the adequacy of the dosing regimen evaluated in QuANTUM-First in terms of QT prolongation was generated by Vaddady et al[2].

OBJECTIVE

- The aim of the present analysis was to provide supportive MIDD evidence for the effectiveness of the dosing regimen evaluated in QuANTUM-First.

CONCLUSIONS

- Overall survival (OS) was found to be related to quizartinib steady-state exposure in the induction phase.
- A modest positive trend was shown when evaluating OS from the start of the continuation phase alone.
- These results supported the benefit of achieving higher quizartinib exposure while properly mitigating the risk of QT interval prolongation based on the observed QTcF and concomitant use of strong CYP3A inhibitors.

METHODS

- MIDD evidence generation was underpinned by a parametric time-to-event (TTE) analysis evaluating the effect of quizartinib and AC886 exposure on OS.
- The primary analysis included data from all treatment phases: induction, consolidation and continuation. To better understand the impact of the dose escalation to 60 mg, an additional analysis was conducted using data from the continuation phase only (**Table 1**).
- The evaluated exposure metrics (**Table 2**) were derived for quizartinib, AC886 and their sum based on a previously developed population PK model[3].
- Covariates **(Table 2)** were tested on the baseline hazard using the stepwise covariate modeling (SCM) procedure with adaptive scope reduction[4]. The forward selection and backward elimination p-values were 0.01 and 0.001, respectively.
- Empirical forest plots[5] were used to illustrate hazard ratios for OS in patient subgroups, based on the final model. Parameters uncertainty was generated by drawing 250 samples from the variance-covariance matrix of the parameters.

Table 1. Number of patients and OS events in the analysis data sets

	Number of patients	Events	
		n	%
All treatment phases			
Placebo	268	156	58.2
Quizartinib	259	126	48.6
All	527	282	53.5
Consolidation phase			
Placebo	92	26	28.3
Quizartinib	116	25	21.6
All	207	51	24.6

Table 2. Covariates and exposure metrics evaluated in the analyses

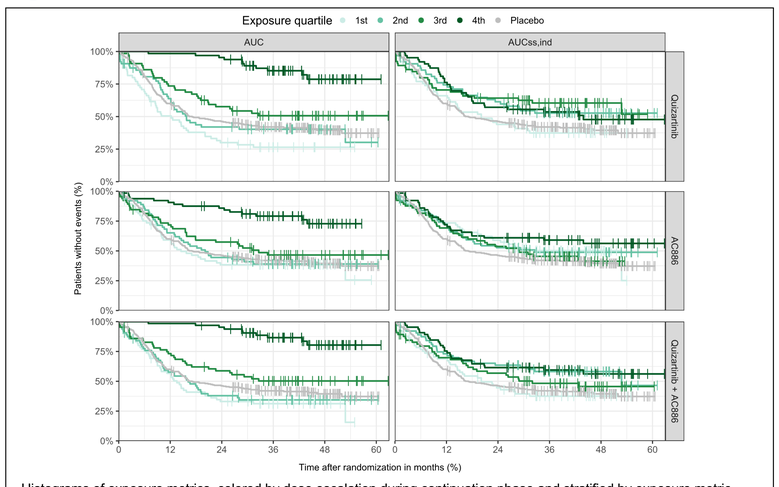
Covariates tested	All treatment phases	Continuation phase
White blood cell (WBC) count at the time of diagnosis (<40x109/L or ≥ 40 x109/L)	✓	✓
FLT3-ITD allelic ratio (3-25%, 26-50% or >50%)	✓	✓
NPM1 mutation	✓	✓
Acute Myeloid Leukemia cytogenetic risk score (AML CRS)	✓	✓
Eastern Cooperative Oncology Group performance status (ECOG) score	✓	✓
Sex	✓	✓
Race	✓	✓
Age at baseline	✓	✓
Body weight at baseline	✓	✓
Haematopoietic stem cell transplantation (HSCT) before initiation of continuation treatment		✓
Treatment arm		✓
Individual average concentration for quizartinib and AC886 on day 1 of the continuation phase		✓
Exposure metrics evaluated	**All treatment phases**	**Continuation phase**
Daily average quizartinib area under the curve (**AUC**) up until time of event/censoring or date of last dose, whichever occurred first	✓	
Steady-state daily quizartinib AUC following 40 mg/day in the induction phase ($\mathbf{AUC_{ss,ind}}$)	✓	
Daily average quizartinib concentration from the first continuation treatment dose up to the time of event/censoring or date of last dose, whichever occurred first ($\mathbf{C_{av,cont}}$)		✓

RESULTS

PRIMARY ANALYSIS CONDUCTED IN ALL TREATMENT PHASES

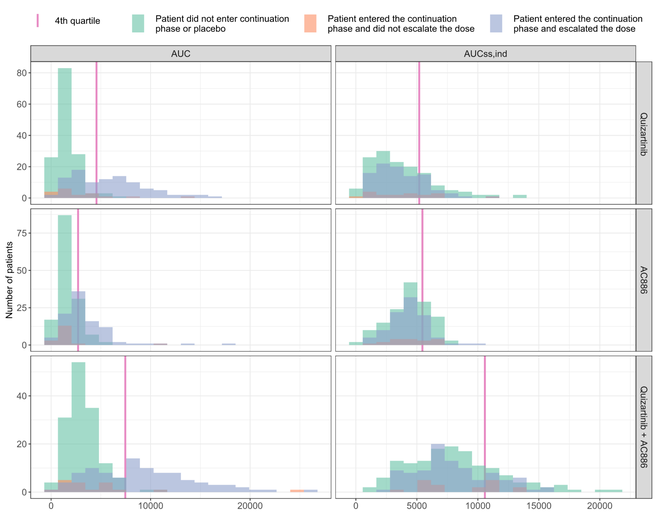
- Kaplan-Meier (KM) curves for OS, stratified by exposure quartiles, indicated that patients with the highest daily average AUC had longer survival compared to placebo and patients with lower drug exposure (**Figure 1**).
- The exposure-response (ER) relationship between daily average AUC and OS was confounded by (i) quizartinib accumulation over time, (ii) escalation to 60 mg in the continuation phase, and (iii) the treatment phase effect observed in quizartinib PK, wherein patients exhibited higher exposure (dose-normalized) during the continuation phase compared to the induction and consolidation[4].
- As shown in **Figure 2**, a large fraction of patients that entered the continuation phase had a daily average AUC larger than the 4th quartile, leading to a bias in the ER relationship. Instead, overlapping distributions of $AUC_{ss,ind}$ were observed in subjects entering or not entering the continuation phase, indicating that it is independent of the above confounding factors. Hence, $AUC_{ss,ind}$ was selected as the exposure metric for the model-based analysis.
- The placebo model was a TTE model with time-varying hazard according to a Gompertz distribution. Age was identified as a statistically significant risk factor on the baseline hazard, with older patients being at higher risk. When data from the quizartinib arm were added to the model, a linear ER relationship with $AUC_{ss,ind}$ was found (final model). The model performed well (**Figure 3**); however, the slope was associated with relatively large uncertainty (RSE 37.2%). The parameter estimates of the final model are presented in **Table 3**.
- Age was identified as a statistically significant risk factor on the baseline hazard, with older patients being at higher risk. Univariate forest plots predicted a median (95% CI) HR of 0.790 (0.690-0.933) at the median $AUC_{ss,ind}$ compared to placebo (**Figure 4a**).
- Empirical forest plots of the hazard ratio (HR) showed that the drug effect was comparable across various patient subgroups (**Figure 4b**).

Figure 1. Percent of patients without an event



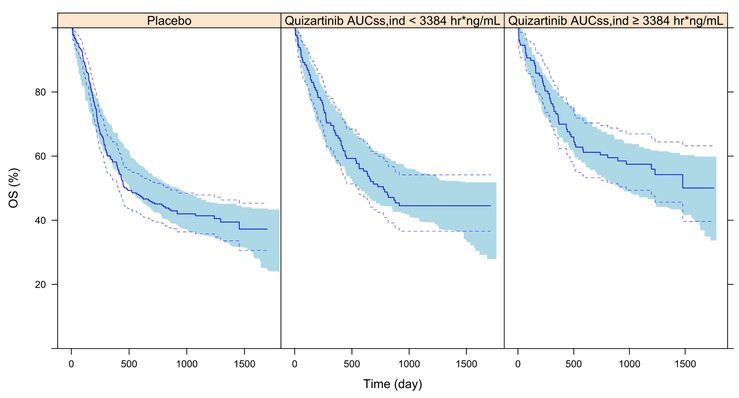
Histograms of exposure metrics, colored by dose escalation during continuation phase and stratified by exposure metric and by analyte.

Figure 2. Distribution of exposure metrics by dose escalation in the continuation phase.



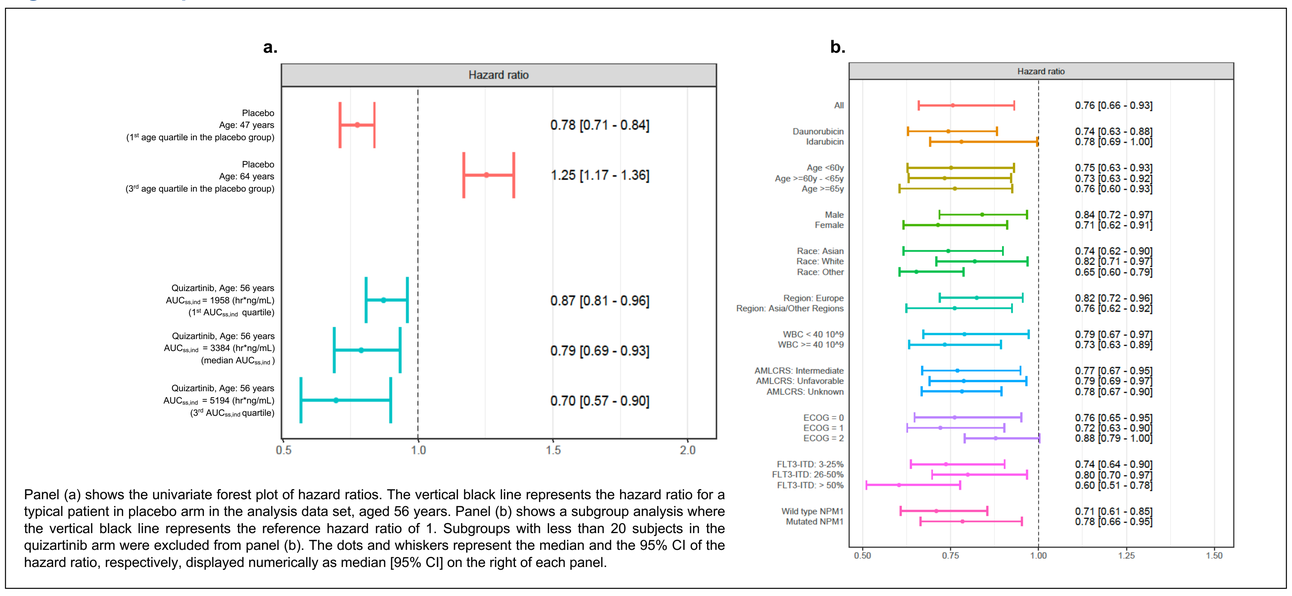
Percent of patients without an event versus time, colored by exposure quartiles and stratified by exposure metric and analyte. Vertical bars indicate where one or multiple subjects have been censored in time.

Figure 3. Visual predictive checks of probability of OS over time



The plots are stratified according to treatment arm and to $AUC_{ss,ind}$ levels below or equal and above the median $AUC_{ss,ind}$. The solid and dashed blue lines represent the Kaplan-Meier point estimate and 95% CI, based on observed data. The shaded areas represent the 95% CI of the Kaplan-Meier point estimate, based on 200 replicate simulations.

Figure 4. Forest plots for the final model



Panel (a) shows the univariate forest plot of hazard ratios. The vertical black line represents the hazard ratio for a typical patient in placebo arm in the analysis data set, aged 56 years. Panel (b) shows a subgroup analysis where the vertical black line represents the reference hazard ratio of 1. Subgroups with less than 20 subjects in the quizartinib arm were excluded from panel (b). The dots and whiskers represent the median and the 95% CI of the hazard ratio, respectively, displayed numerically as median [95% CI] on the right of each panel.

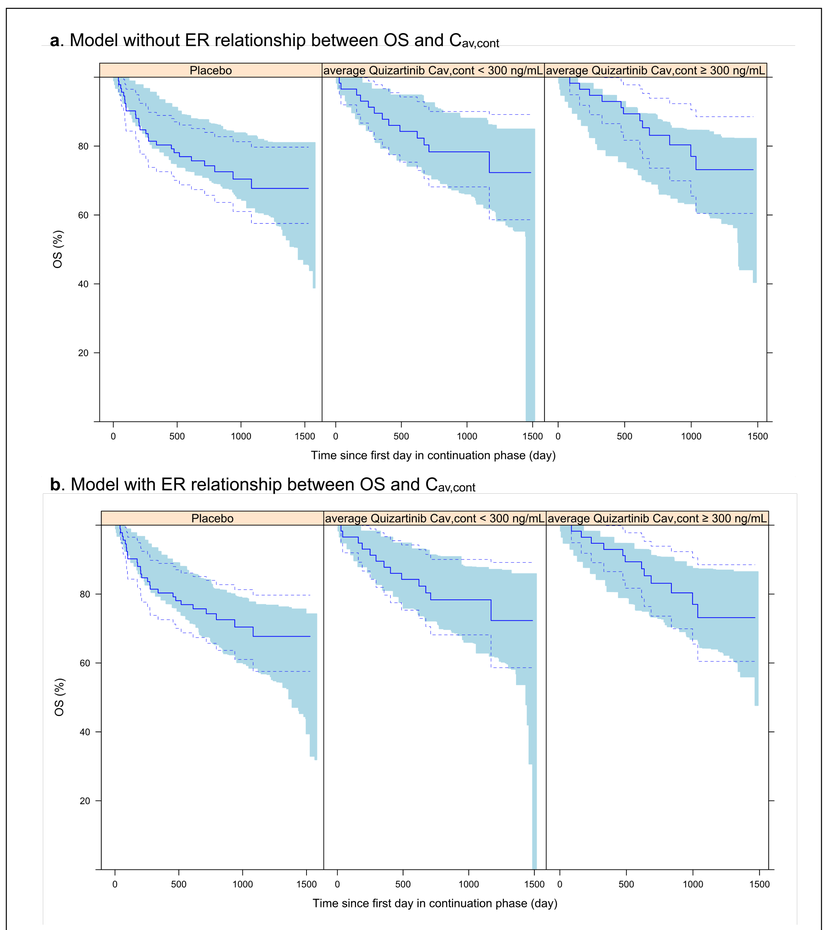
Table 3. Parameter estimates of the final model

Parameter	Unit	Value	RSE (%)
Baseline hazard	$year^{-1}$	0.669	9.13
Gompertz shape parameter	$year^{-1}$	-0.619	11.1
Age on baseline hazard	$year^{-1}$	0.0288	17.2
Slope for linear effect of quizartinib $AUC_{ss,ind}$	$(hr*ng/mL)^{-1}$	-0.0690	37.2
OFV		4467.8	
Condition number		7.7	

ADDITIONAL ANALYSIS CONDUCTED IN THE CONTINUATION PHASE

- The exposure-OS relationship with $C_{av,cont}$ was not expected to be impacted by the aforementioned confounding factors because subjects in the continuation phase are close to steady state.
- Quizartinib $C_{av,cont}$ was not found to be statistically significant. However visual predictive checks of the resulting model showed underprediction of OS at higher exposure levels (**Figure 5a**). A model assuming an ER relationship with $C_{av,cont}$ better described the observed data, suggesting a trend of longer survival with higher quizartinib exposure (**Figure 5b**).

Figure 5. Visual predictive checks of OS for placebo or quizartinib-treated patients in the continuation phase



The plots are stratified according to treatment arm and to daily average quizartinib concentration from the first continuation treatment dose up to the time of event ($C_{av,cont}$) levels below or equal and above the average $C_{av,cont}$. The solid and dashed blue lines represent the Kaplan-Meier point estimate and 95% CI, based on observed data. The shaded areas represent the 95% CI of the Kaplan-Meier point estimate, based on 200 replicate simulations.

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