Population Pharmacokinetic (PopPK) and Concentration-QTc Analysis of Quizartinib in Patients (pts) With *FLT3*-ITD–Positive Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

Dongwoo Kang,[1] Elizabeth Ludwig,[2] David Jaworowicz,[2] Hannah Huang,[2] Jill Fiedler-Kelly,[2] Jorge Cortes,[3] Siddhartha Ganguly,[4] Samer Khaled,[5] Alwin Krämer,[6] Mark Levis,[7] Giovanni Martinelli,[8] Alexander Perl,[9] Nigel Russell,[10] Malaz Abutarif,[1] Youngsook Choi,[1] Ken Kobayashi,[1] Jeanne Mendell,[1] Ophelia Yin[1]

[1]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [2]Cognigen Corporation, a Simulations Plus company, Buffalo, NY, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]University of Kansas Cancer Center, Fairway, KS, USA; [5]City of Hope, Arcadia, CA, USA; [6] Universität Heidelberg and German Cancer Research Center, Heidelberg, Germany; [7] The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [8]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [9]University of Pennsylvania, Philadelphia, PA, USA; [10]Centre for Clinical Haematology, Nottingham University Hospital, Nottingham, UK

BACKGROUND

- Fms-related tyrosine kinase 3 (*FLT3*) is expressed in hematopoietic progenitor cells; signaling through FLT3 promotes their proliferation and differentiation. *FLT3* is mutated in approximately 30% of patients with AML[1,2]
- The *FLT3*–internal tandem duplication (ITD) mutation represents the most common type of *FLT3* mutation and is associated with high relapse rates, decreased response to salvage therapy, and shorter overall survival (OS)[1-4]
- Quizartinib is an oral, once-daily, highly potent and selective, next-generation, type II FLT3 inhibitor that has shown high clinical activity in patients with *FLT3*-ITD positive R/R AML[5,6]
- Single-agent quizartinib demonstrated a clinically meaningful OS benefit in patients with R/R *FLT3*-ITD AML vs salvage chemotherapy, with a 24% reduction in the risk of death in the phase 3 QuANTUM-R (AC220-007) trial[7]

OBJECTIVES

- The objectives of the current analyses were:
  - To develop PopPK models for quizartinib and its major metabolite (AC886) in a pooled analysis of 7 trials
  - To evaluate the exposure-response relationship between quizartinib concentration and the QT interval by electrocardiogram (ECG) corrected for heart rate (QTc) in patients in the QuANTUM-R study

METHODS

PopPK Analysis

- The PopPK analysis included data from 5 phase 1 studies, 1 phase 2 study (2689-CL-2004), and 1 phase 3 study (QuANTUM-R) (**Table 1**)
- Quizartinib was given as single or multiple doses of 20, 30, 60, and 90 mg (17.7, 26.5, 53.0, 79.5 mg free base). In QuANTUM-R, the starting dose was 30 mg/day, followed by an increase to 60 mg/day after 2 weeks if the QT interval corrected using Fridericia's formula (QTcF) was < 450 ms. Patients receiving a concurrent strong cytochrome P450 3A isozyme (CYP3A) inhibitor initiated quizartinib at 20 mg/day, with an increase to 30 mg/day after 2 weeks if QTcF was < 450 ms
- For the PopPK model, a base model was selected first, after consideration of various compartment structure models. Once a base model was selected, the effects of candidate covariates on exposure were tested within the model. Forward addition (α = .01) followed by backward elimination (α = .001) was then used to build the covariate model. A parent PK model for quizartinib was built. Next, a sequential metabolite PK model for AC886 was developed based on post hoc parameter values of the quizartinib PK model. The final population PK model was used to generate quizartinib exposures to assess the clinical significance of covariate effects and to evaluate the exposure-response relationship between quizartinib and QTc

Exposure-response QTc Analysis

- Concentration-QTc (C-QTc) model development included only data from the QuANTUM-R study
- PK samples were obtained at matched time points at which ECGs were taken: predose; 2, 4, and 6 hours postdose on PK visit days; then less frequently on other visit days
  - Observed ECG data were corrected with heart rate using Fridericia's calculation
- For the C-QTc model, various structure models were considered as the base model, including linear and nonlinear models. Forward addition (α = .01) followed by backward elimination (α = .001) was used to build the covariate model. Thorough evaluation of the model was considered, including circadian rhythm correction, evaluation of parameter distributions, test for hysteresis, and incorporation of effect from the AC886 metabolite
- Nonlinear mixed-effects modeling in NONMEM version 7.3 (ICON Development Solutions) was used for PopPK and C-QTc analyses. SAS version 9.4 (SAS Institute), R software version 3.1.2 (The R Foundation), and KIWI version 2 (Cognigen Corporation, a Simulations Plus company) were used for data manipulation and plotting, respectively

Table 1. Summary of Clinical Studies Included in PopPK Pooled Data Set

Study	Phase	N	No. of PK Samples		Dose Regimen	Participant Population	Description
			Quizartinib	AC886			
AC220-014	1	80	1528	1439	Single dose of 60 mg solution or 30, 60, or 90 mg tablets	Healthy volunteer	Relative bioavailability and dose proportionality
AC220-015	1	89	1970	1543	Single dose of 30 mg	Healthy volunteer	Drug-drug interaction with ketoconazole, fluconazole
AC220-016	1	30	686	654	Single dose of 30 mg	Healthy volunteer	Hepatic impairment study
AC220-018	1	62	1422	1338	Single dose of 30 mg	Healthy volunteer	Drug-drug interaction with lansoprazole
2689-CL-011	1	13	243	239	Multiple daily doses of 30, 40, 60, or 90 mg	Patients with AML	Maintenance dosing following transplant for R/R AML[8]
2689-CL-2004	2b	72	1090	1070	Multiple daily doses of 30 or 60 mg	Patients with AML	Dose-ranging study in AML[8]
QuANTUM-R (AC220-007)	3	239	3457	3346	Multiple daily doses of 20, 30, or 60 mg	Patients with AML	Phase 3 study in R/R AML[7]
Total		**585**	**10,396**	**9629**			

RESULTS

PopPK

- The PopPK analysis included quizartinib and AC886 concentration data from 585 participants (**Table 2**)

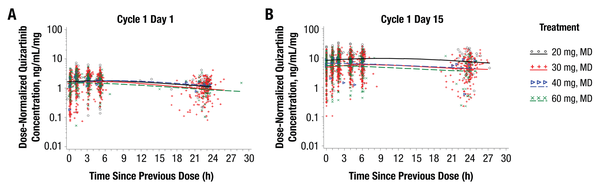
Table 2. Participant Characteristics in the PopPK Data Set

Characteristic	Healthy (n = 261)	Patients (n = 324)	Total (N = 585)
Age, median (range), years	33 (18, 66)	55 (19, 81)	46 (18, 81)
Sex, n (%)			
Male	168 (64.4)	160 (49.4)	328 (56.1)
Female	93 (35.6)	164 (50.6)	257 (43.9)
Race, n (%)			
White	179 (68.6)	247 (76.2)	426 (72.8)
Black or African American	62 (23.8)	12 (3.7)	74 (12.6)
Asian	4 (1.5)	27 (8.3)	31 (5.3)
American Indian or Alaska Native	5 (1.9)	1 (0.3)	6 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)
Other	10 (3.8)	8 (2.5)	18 (3.1)
Unknown	0	29 (9.0)	29 (5.0)
BSA, median (range), m^2	1.9 (1.4, 2.5)	1.9 (1.3, 2.8)	1.9 (1.3, 2.8)
Weight, median (range), kg	76.0 (48.1, 112)	72.0 (39.5, 153)	73.9 (39.5, 153)
Red blood cell count, median (range), 10^{12}/L	4.8 (3.5, 6.1)	3.0 (0.4, 5.1)	3.7 (0.4, 6.1)
Liver function variables, median (range)			
Albumin, g/dL	4.4 (3.3, 5.2)	3.7 (2.1, 4.8)	4.1 (2.1, 5.2)
ALP, U/L	64.0 (31.0, 221)	86.0 (28.0, 507)	74.0 (28.0, 507)
ALT, U/L	16.0 (6.0, 201)	23.5 (1.5, 224)	19.0 (1.5, 224)
AST, U/L	19.0 (10.0, 261)	24.0 (3.0, 688)	21.0 (3.0, 688)
Total bilirubin, mg/dL	0.4 (0.1, 3.4)	0.5 (0.1, 1.6)	0.4 (0.1, 3.4)
eGFR, median (range), mL/min/1.73 m^2	92.0 (49.1, 379)	94.3 (21.2, 256)	92.9 (21.2, 379)
Concomitant CYP3A inhibitor, n (%)			
Strong CYP3A inhibitors	29 (11.1)	92 (28.4)	121 (20.7)
Moderate CYP3A inhibitors	30 (11.5)	107 (33.0)	137 (23.4)
Weak or no CYP3A inhibitors	202 (77.4)	125 (38.6)	327 (55.9)

Summary of demographics and covariates for PopPK data set. All factors were tested for covariate effects on PK parameters
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; eGFR, estimated glomerular filtration rate.

- **Figure 1** shows the concentration profiles of quizartinib in patients with AML
- A 3-compartment model best described quizartinib PK, and a 2-compartment model best described AC886
- Model-predicted typical values for apparent clearance (CL), apparent central volume of distribution (V_c), apparent intercompartmental clearance between the central compartment and peripheral compartment 1 (Q_1), apparent volume of the first peripheral compartment (V_{p1}), apparent intercompartmental clearance between the central compartment and peripheral compartment 2 (Q_2), volume of the second peripheral compartment (V_{p2}), first-order absorption rate constant (k_a), and duration of zero-order input (D_1) for quizartinib in a patient with AML not receiving a strong CYP3A inhibitor in the final model were 6.07 L/h, 276 L, 31.6 L/h, 319 L, 0.591 L/h, 53.3 L, 0.855 h^{-1}, and 1.17 h, respectively

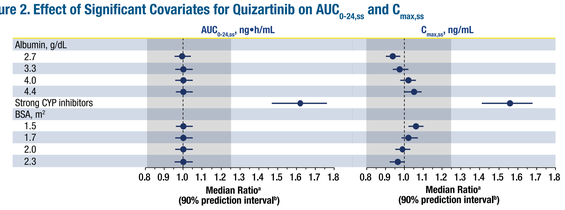
Figure 1. Dose-Normalized Quizartinib Concentrations vs Time From Multiple-Dose Patient Studies in Semi-Log Scale



The lines represent smoothing splines to fit the data.
MD, multiple dose.

- Strong CYP3A inhibitor use was identified as a statistically significant covariate on CL and bioavailability (F1), with quizartinib CL estimated to be 48.7% lower and F1 estimated to be 18% higher with concomitant strong CYP3A inhibitor use, resulting in a 62% increase in the area under the plasma concentration-time curve from time 0 to 24 hours at steady state ($AUC_{0\text{-}24,ss}$) and a 56% increase in peak plasma drug concentration after dosing at steady state ($C_{max,ss}$) of quizartinib (**Figure 2**)
  - The most common concomitant strong CYP3A inhibitors were voriconazole, posaconazole, itraconazole, clarithromycin, and ketoconazole. All other strong CYP3A inhibitors were used in < 0.17% of the analysis population
- Albumin and BSA were statistically significant covariates on quizartinib V_c. However, the magnitude of these effects on the quizartinib $AUC_{0\text{-}24}$,ss and $C_{max,ss}$ was within the 0.8- to 1.25-fold range
- Age, body weight, sex, race, eGFR, hepatic impairment (including AST, ALT, ALP, and total bilirubin), renal impairment, and concomitant use of acid-reducing agents (including proton pump inhibitors, H_2-receptor blockers, and antacids) were not found to be significant predictors of quizartinib PK

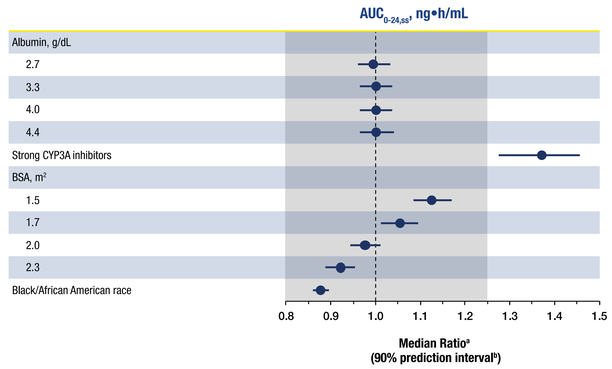
Figure 2. Effect of Significant Covariates for Quizartinib on $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$



[a] Ratio of quizartinib exposure to reference patient (with albumin of 3.7 g/dL and BSA of 1.9 m^2).
[b] Based on 1000 simulations.

- BSA and black/African American race were statistically significant covariates on AC886 apparent clearance of the metabolite (CL_m); however, the magnitude of these effects on the sum of quizartinib and AC886 exposure was within the 0.8- to 1.25-fold range (**Figure 3**)
- Typical values for AC886 PK parameters in a patient with AML not receiving a strong CYP3A inhibitor and of non–black/African American race were as follows: CL_m, 4.91 L/h; apparent central volume of distribution of the metabolite (V_{cm}), 7.37 L; volume of the peripheral compartment of the metabolite (V_{pm}), 60.8 L; and apparent intercompartmental clearance of the metabolite (Q_m), 3.45 L/h

Figure 3. Effect of Significant Covariates on $AUC_{0\text{-}24,ss}$ of Quizartinib and AC886



[a] Ratio of quizartinib and AC886 exposure to reference patient (with albumin of 3.7 g/dL and BSA of 1.9 m^2).
[b] Based on 1000 simulations.

Exposure-Response C-QTc Analysis

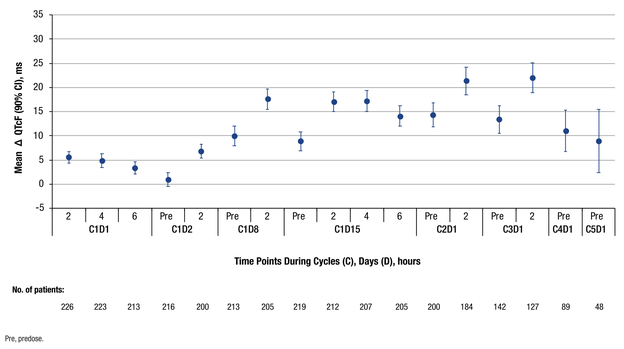
- A total of 2842 PK-matched mean QTcF samples were available from 226 participants for the C-QTc analysis (**Table 3, Figure 4**)
  - A 30-minute window was used to match PK and QTcF samples, except for 24-hour samples, for which a 90-minute window was used

Table 3. Patient Characteristics for the C-QTc Data Set at Baseline

Characteristic	N = 226
Age, median (range), years	55 (19, 81)
Sex, n (%)	
Male	104 (46.0)
Female	122 (54.0)
Race, n (%)	
White	168 (74.3)
Black or African American	8 (3.5)
Asian	24 (10.6)
American Indian or Alaska Native	1 (0.4)
Other	7 (3.1)
Unknown	18 (8.0)
Weight, median (range), kg	70.0 (39.5, 147)
QTcF, median (range), ms	414 (364, 471)
Hypocalcemia, n (%)	97 (42.9)
Hypokalemia, n (%)	35 (15.5)
Hypomagnesemia, n (%)	63 (27.9)
QT-prolonging drug use, n (%)	66 (29.2)

Summary of demographics and covariates for C-QTc data set. All factors were tested for covariate effects on slope and intercept except for baseline QTcF, which was tested for slope only.

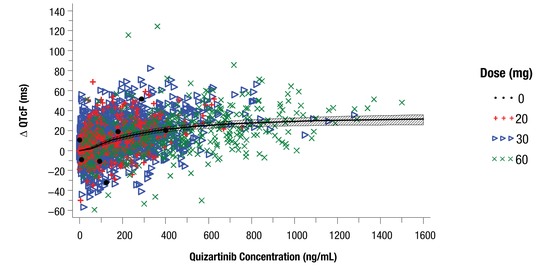
Figure 4. Observed Change in QTcF Data With Respect to Visit Days



Pre, predose.

- An exposure-response model described the relationship between quizartinib and AC886 concentrations and C-QTc: The model was parameterized in terms of baseline QTcF, fixed time effect parameters for the circadian rhythm correction of baseline QTcF, and separate sigmoid maximum pharmacologic effect (E_{max}) functions for quizartinib and AC886. The choice of E_{max} functions was driven by the observed data in QuANTUM-R and, hence, serves as "fit for purpose" (**Figure 5**)
- QTc shows an exposure-dependent increase with respect to quizartinib and AC886 concentrations; the relative contribution from quizartinib and AC886 is ≈ 12:1
- Hypokalemia (serum potassium < 3.5 mmol/L) was a statistically significant covariate on baseline QTcF but not on E_{max}. In patients with hypokalemia, baseline QTcF was predicted to be prolonged by 6.15 ms compared with the population mean of 413 ms. At the same quizartinib and AC886 concentrations, Δ QTcF would be expected to be the same in patients with or without hypokalemia

Figure 5. Scatterplot of Δ QTcF vs Quizartinib by Dose, With Mean (90% CI) Δ QTcF (black)



The solid line represents the model-predicted mean drug effect. Shaded area represents the 90% uncertainty around median drug effect predictions. Predicted ΔQTcF represents contributions of quizartinib and AC886.

- The predicted mean Δ QTcF at the geometric mean C_{max} of quizartinib (and the corresponding AC886 concentration) following 28 days of 60 mg once-daily dosing in the actual study population is 21.1 ms (90% CI, 18.3-23.6 ms) (**Table 4**)
- The predicted mean Δ QTcF at $C_{max,ss}$ of 60 mg was 22.1 ms (90% CI, 18.0-26.1 ms)
- The predicted mean Δ QTcF for nominal dosing of 60 mg once daily without dose adjustment and without the use of strong CYP3A inhibitors is higher, 22.4 ms (90% CI, 19.5-24.9 ms)

Table 4. Predicted Δ QTcF at Geometric Mean C_{max} of Quizartinib and Corresponding AC886 Concentrations by Dose (nominal and actual dosing records)

Dose	Mean Δ QTcF, ms	90% CI, ms
30 mg[a]	14.6	(12.3-17.0)
60 mg[b]	21.1	(18.3-23.6)
60 mg[a]	22.4	(19.5-24.9)

[a] 30 days of nominal dosing without the use of strong CYP3A inhibitors (n = 226).
[b] On day 28 following actual dosing used in the QuANTUM-R study, based on QT-based and other dose modifications (n = 109).

CONCLUSIONS

- Strong CYP3A inhibitor use was the only clinically meaningful factor affecting quizartinib PK exposure
- QTcF showed an exposure-dependent increase with respect to quizartinib and AC886 concentration; however, no factors, including sex and age, were identified to have a clinically relevant effect on the concentration-QTc relationship
- Results support clinical recommendation of dose reduction in patients receiving strong CYP3A inhibitors, because strong CYP3A inhibitor use resulted in a 62% increase in the $AUC_{0\text{-}24,ss}$ and a 56% increase in the $C_{max,ss}$ of quizartinib

REFERENCES

1. Daver N, et al. *Leukemia*. 2019;33(2):299-312.
2. Levis M. *Hematology Am Soc Hematol Educ Program*. 2013;2013:220-226.
3. Boissel N, et al. *Leukemia*. 2002;16(9):1699-1704.
4. Ravandi F, et al. *Leuk Res*. 2010;34(6):752-756.
5. Cortes J, et al. *Lancet Oncol*. 2018;19:889-903.
6. Cortes JE, et al. *Blood*. 2018;132:598-607.
7. Cortes JE, et al. *Blood*. 2018:132 [abstract 563].
8. Sandmaier BM, et al. *Am J Hematol*. 2018;93(2):222-231.

ACKNOWLEDGMENTS

The authors would like to thank the patients, volunteers, and their families for participating in the quizartinib studies. Medical writing support was provided by Melanie Vishnu, PhD, of SciMentum, Inc, a Nucleus Global company, and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

To download a copy of this poster
Scan QR code via a barcode reader application

Presented at the 24th Congress of European Hematology Association; June 13-16, 2019; Amsterdam, the Netherlands