#3695

Population Pharmacokinetics of Crenolanib, a Type I FLT3 Inhibitor, in Patients with Relapsed/Refractory Acute Myeloid Leukemia

John Carl Panetta[1], Sharyn Baker[1], Hagop Kantarjian[2], Clinton Stewart[1], Blake Pond[3], Meghan Macaraeg[4], Tolu Makinde[4], Sheetal Vali[4], Yee Ling Lam[4], Naval Daver[2], Abhijit Ramachandran[4], Robert Collins[3], and Jorge E. Cortes[2]

[1]St Jude Children's Research Hospital, Memphis, TN; [2]MD Anderson Cancer Center, Houston, TX; [3]University of Texas Southwestern Medical Center, Dallas, TX; [4]AROG Pharmaceuticals, Dallas, TX

ABSTRACT

Background: Crenolanib besylate is a selective and potent type I tyrosine kinase inhibitor (TKI) of wild-type and mutant FMS-like tyrosine kinase 3 (FLT3). Crenolanib is being studied in patients with relapsed/refractory FLT3+ AML with FLT3-ITD and/or FLT3-D835 mutations. This abstract summarizes the population pharmacokinetics (PK) of crenolanib in patients with relapsed or refractory FLT3+ AML.

Methods: Serum blood samples were collected on Day 1 at pre-dose and at 30 min, 60 min, 120 min, 4 h, 8 h and 24 h after single dose of crenolanib, and steady state levels were obtained on Day 15. All crenolanib serum concentrations were measured by a validated LC-MS/MS. The crenolanib population pharmacokinetics and individual post-hoc estimates were determined by non-linear mixed effects modeling. The inter-individual and inter-occasion (day 1 vs day 15 studies) variability of the parameters was assumed to be log normally distributed. The area under the concentration-time curve from 0 to 24 hours (AUC; nmol hr/L), maximum concentration (C_{max}; nM), and time to maximum concentration (T_{max}; hr) were determined from the concentration-time profile simulated using each individual's post-hoc estimated pharmacokinetic parameters.

Results: Crenolanib was found to be rapidly absorbed with a T_{max} of 2-3 hours after administration. Crenolanib serum concentration data in cancer patients were best described by a one-compartment PK model with first-order oral absorption. The model was parameterized in terms of ka (1/hr), the first-order absorption; T_{lag} (hr), lag time; CL (L/hr), apparent oral clearance; and V (L), apparent volume. The predictive accuracy of the model used to forecast these values showed that most of the predicted values are close to the actual values with approximately equal distribution of points on either side of the diagonal line. Hence, the model can be said to be unbiased and fairly accurate. In an attempt to maximize the trough levels and lower C_{max} of crenolanib to continually inhibit FLT3, patients were administered crenolanib on a TID schedule. Comparable AUC was reached when crenolanib was administered three times daily as opposed to once daily. By day 4 of TID dosing, patients can be expected to reach an approximate steady state. During the fourth day of dosing, the predicted median C_{max} was 478 nM (10^{th} percentile of 169 nM and 90^{th} percentile of 1478 nM) and the predicted median trough value was 290 nM (10^{th} percentile of 89 nM and 90^{th} percentile of 943). 100 mg TID dosing should maintain constant inhibition of FLT3, potentially increasing their rate of response.

Conclusions: Crenolanib is rapidly absorbed with first order pharmacokinetics. Administering crenolanib on a TID schedule allows for a total dose of 300 mg per day of crenolanib, while still maintaining adequate pharmacokinetic properties to lower C_{max} and achieve higher trough levels. Pharmacokinetic profiling of crenolanib over a longer period of time showed that crenolanib does not accumulate with extended use.

Introduction

Features of an Ideal FLT3 Kinase Inhibitor

- Good oral bioavailability
- Little interpatient variability
- Low protein binding
- Predictable metabolism and no active metabolite
- Clearance that does not depend on hepatic function
- Short half-life allowing for combination with cytotoxic chemotherapy
- Little drug accumulation
- No induction of metabolic enzymes that will reduce drug level

Crenolanib - a Potent FLT3 Inhibitor

- **Crenolanib** is a highly potent and specific inhibitor of FMS-like tyrosine kinase 3 (FLT3), Platelet- derived growth factor receptor alpha (PDGFRα) and PDGFRβ (Figures 1 and 2) (1-3).
- This orally-administered, type I tyrosine kinase inhibitor (TKI) is able to intercept both inactive and active kinases (1) and is effective against FLT3 D835 mutants that are commonly resistant to other TKIs (4).

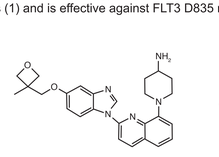


Figure 1. Crenolanib besylate molecular structure.

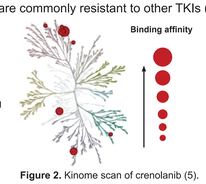


Figure 2. Kinome scan of crenolanib (5).

- About 27 - 37% of **acute myeloid leukemia (AML)** patients have mutation(s) in FLT3 (7).
- Crenolanib is currently being evaluated in phase II clinical trials in patients with FLT3-mutant, relapsed / refractory AML.

Prior Pharmacokinetic Studies of Crenolanib

- *In vitro* data indicate that crenolanib is metabolized via cytochrome P450 (CYP)-3A (AROG data on file).
- The hepatic extraction ratio was estimated to be moderate (0.35-0.53) in human.
- Previous dose finding studies have shown that 300 mg per day is safe for patients with glioma, and TID dosing effectively lowers the C_{max} to minimize toxicity while maintaining a trough level well above the minimum effective concentration (150 nM; 8).
- Food ingestion was found to have no significant effect on crenolanib absorption.
- Crenolanib clinical PK data have been collected in two studies investigating crenolanib in patients with FLT3 mutant AML.

Objectives

- To determine the pharmacokinetics of crenolanib in AML patients
- To compare the pharmacokinetics of crenolanib with body surface area (BSA)-based dosing versus that of fixed dosing

Patients and Trial Design

- Two phase II, single center, non-randomized, open-label, single agent studies (ARO-004 and ARO-005; Table 1) evaluated crenolanib in patients with relapsed or refractory AML and FLT3-ITD and/or activating kinase domain mutation.
- Patients received crenolanib orally daily until disease progression or unacceptable toxicity.
- Twenty-six (26) patients received BSA-based dosing of 200 mg/m^2 per day (divided into three doses), and twenty-nine (29) patients received 100 mg TID (three times per day).
- On the first day of treatment, a single dose of crenolanib (66.7 mg/m^2 or 100 mg) was given to each patient for the purpose of pharmacokinetic study, with the exception of four patients who received three doses.
- Data from a total of 54 patients are presented here.

Study	# of Patients/ PK Samples	Sampling Intensity	Population	Crenolanib Regimen
ARO-004 NCT01522469	14/107	Serial samples on day 1 and 15	Relapsed / refractory AML with FLT3 mutation	N = 10: 100 mg TID N = 4: 200 mg/m^2
ARO-005 NCT01657682	41/352			N = 19: 100 mg TID N = 22: 200mg/m^2

Table 1. Dosing information across single agent crenolanib studies

Pharmacokinetic Evaluations

Sample Collection Serial blood samples were obtained from 55 patients after crenolanib administration during cycle 1 on day 1 and day 15 at the following time points: pre-dose, 30 min (±10), 60 min (±15), 120 min (±15), 4 hours (±1), 8 hours (±2) and 24 hours (± 4).

Assessment of Crenolanib Concentrations All crenolanib serum concentrations were measured by a validated liquid chromatography–mass spectrometry (LC-MS/MS) method.

Pharmacokinetic Modeling The crenolanib population pharmacokinetics and individual post-hoc estimates were determined by non-linear mixed effects modeling via Monolix (version 4.3.0, www.monolix.org) using the Stochastic Approximation Expectation-Maximization (SAEM) approach. The inter-individual and inter-occasion (day 1 vs day 15 studies) variability of the parameters was assumed to be log normally distributed. A proportional residual error model was used with assumed normal distribution of the residuals.

Using a one-compartment model with first-order absorption using non-linear mixed-effects modeling, day 1 pharmacokinetic data were extrapolated to predict the steady-state median, 10^{th} percentile and 90^{th} percentile concentrations, and overall range of crenolanib concentrations.

The pharmacokinetic model is parameterized in terms of ka (1/hr), the first-order absorption; T_{lag} (hr), lag time; CL (L/hr), apparent oral clearance; and V (L), apparent volume. The individual post-hoc parameter values were used as the estimates of each patient's pharmacokinetic parameters. In addition, the area under the concentration-time curve (AUC) from 0 to 24 hours (AUC_{last}; hr*nM), maximum concentration (C_{max}; nM), time to maximum concentration (T_{max}; hr) and half-life ($t_{1/2}$; hr) were determined from the concentration-time profile simulated using each individual's post-hoc estimated pharmacokinetic parameters.

The predictive accuracy of the model was verified by a plot of individual predicted concentrations versus actual concentrations for each measured time point.

Patient Characteristics

Baseline Characteristics	All Patients (N = 54*)
Female, N (%)	30 (56)
Age (years)**,** median (range)	59.5 (21 – 87)
≤ 60	28
61-87	26
Weight (kg)**,** median (range)	69 (48 – 127)
BSA (m^2)**,** median (range)	1.74 (1.43 – 2.54)
Creatinine (mg/dL)**,** median (range)	0.67 (0.34 – 1.93)
Bilirubin (mg/dL)**,** median (range)	0.5 (0.2 – 1.1)
Alanine aminotransferase (U/L)**,** median (range)	35 (8 – 106)
Aspartate aminotransferase (U/L)**,** median (range)	29 (9 – 94)

Table 2. Patient characteristic across two single agent crenolanib studies.
*One patient was enrolled twice under separate indications and disease episodes.This patient contributed to two sets of samples for pharmacokinetic analysis.

Adequate Exposure Achieved

C_{max} Median is 311 nM and T_{max} is ~2 Hours

- On the first day of treatment, a single dose of crenolanib was given to all but four patients.
- The concentration of crenolanib in blood was monitored over time.

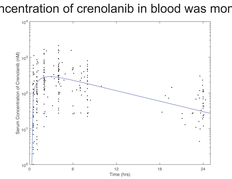


Figure 3. Individual patient's serum crenolanib concentration over time.

Parameters	Day 1, Median (Range) (N = 55)
C_{max}	311 nM (44.94 – 1496.75 nM)
T_{max}	1.96 hours (0.49 – 8.33 hours)
$t_{1/2}$	5.97 hours (2.49 – 13.82 hours)
AUC_{last}	3483 hr*nM (472.31 – 15362.64 hr*nM)

C_{max}: highest observed concentration
T_{max}: time of Cmax
$t_{1/2}$: half-life
AUC_{last}: AUC from 0 to 24 hours was estimated using the trapezoidal rule

Table 3. Key PK parameters of a single dose of crenolanib. Data are the median (range).

PK Model Evaluation

- The actual serum concentration of crenolanib on day 1 is plotted against concentrations of crenolanib predicted by a one-compartment model with first-order oral absorption (Figure 4).
- Most of the predicted values were close to the actual values, and there was approximately equal distribution of points on either side of the diagonal line. As such, the first-order oral absorption model appeared to accurately describe the serum concentration-time data.

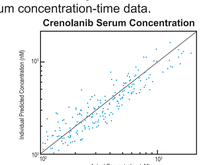


Figure 4. Plot of predicted crenolanib concentration versus actual concentration.

PK Modeling for TID Dosing

TID Dosing Lowered C_{max} and Increased C_{trough}

- Simulations were performed to predict the anticipated peak and trough concentrations (Figure 5 and 6).
- Based on experimental observations, the target concentration range was set to approximately 150 nM to 1000 nM.
- Using a one-compartment model with first-order absorption using non-linear mixed-effects modeling, our day 1 pharmacokinetic data were extrapolated to predict the steady-state median, 10^{th} percentile and 90^{th} percentile concentrations, and overall range of crenolanib concentrations (Figure 5 and 6).
- With 100 mg TID dosing, steady state was expected to be reached on day 4 (Figure 5 and 7).

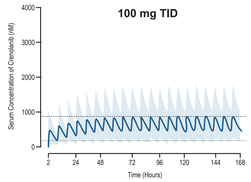


Figure 5. Predicted serum crenolanib concentration with 100 mg TID dosing.

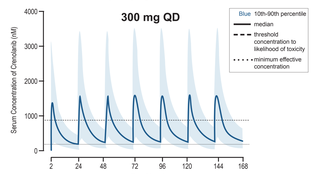


Figure 6. Predicted serum crenolanib concentration with 300 mg QD dosing.

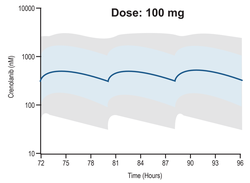


Figure 7. Predicted steady state serum concentration of crenolanib with 100 mg TID dosing.

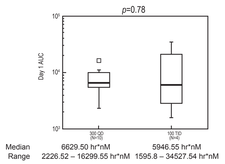
Parameters	Predicted Value
C_{max} median	478 nM
C_{max} 10^{th} percentile	169 nM
C_{max} 90^{th} percentile	1478 nM
C_{trough} median	290 nM
C_{trough} 10^{th} percentile	89 nM
C_{trough} 90^{th} percentile	943 nM

Table 4. Predicted steady state C_{max} and C_{trough} with 100 mg TID dosing.

300 mg QD Versus 100 mg TID Dosing

Similar Drug Exposure with QD and TID Dosing

- Four patients received 100 mg crenolanib three times a day on the first day of treatment.
- Their drug exposure (AUC) was compared to patients from a glioma clinical study (ARO-001), in which 10 patients have taken 300 mg crenolanib once daily.



	300 QD	100 TID
Median	6629.50 hr*nM	5946.55 hr*nM
Range	2226.52 – 16299.55 hr*nM	1595.8 – 34527.54 hr*nM

Figure 8. Crenolanib exposure of 300 mg QD and 100 mg TID dosing scheme.

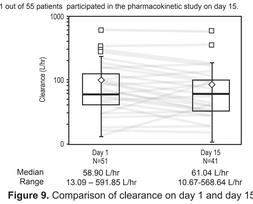
Consistent PK on Day 1 and 15

Crenolanib Trough Level Adequate to Inhibit FLT3

- T_{max} was reasonably consistent on day 1 and day 15, suggesting no time-dependent changes in the rate of crenolanib absorption (Table 5).
- The median C_{trough} value is well within the target concentration range (150 to 1000 nM) (Table 5).
- Crenolanib clearance was similar on day 1 and day 15, implying that crenolanib did not induce its own metabolism (Figure 9).

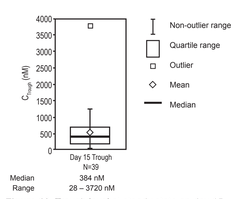
Parameters	Day 1, median (Range) (N=55)	Day 15 pre-dose, median (Range) (N=39*)	Day 15, median (Range) (N=41**)
C_{max}	311 nM (44.94 – 1496.75 nM)	C_{trough} = 384 nM (28 – 3720 nM)	630 nM (95.73 – 2893.70 nM)
T_{max}	1.96 hours (0.49 – 8.33 hours)		1.47 hours (0.49 – 2.94 hours)
$t_{1/2}$	5.97 hours (2.49 – 13.82 hours)		7.06 hours (3.21 – 13.95 hours)
AUC_{last}	3483 hr*nM (472.31 – 15362.64 hr*nM)		7126 hr*nM (833.05 – 43548.40 hr*nM)

Table 5. Comparison of pharmacokinetic parameters between day 1 and day 15. Data are the median (range).
*Two patients, who had a dose-hold just before day 15, were censored.
** Only 41 out of 55 patients participated in the pharmacokinetic study on day 15.



	Day 1 N=51	Day 15 N=41
Median	58.90 L/hr	61.04 L/hr
Range	13.09 – 591.85 L/hr	10.67-568.64 L/hr

Figure 9. Comparison of clearance on day 1 and day 15.



	Day 15 Trough N=39
Median	384 nM
Range	28 – 3720 nM

Figure 10. Trough level at steady state on day 15.

Rapid FLT3 Inhibition

Serum of Patient Efficiently Inhibited FLT3 Phosphorylation

- Serum of a patient treated with 100 mg crenolanib TID was incubated with FLT3-ITD cell line.
- Phosphorylation of FLT3 was inhibited through the 8-hour timepoint, at which the serum concentration of crenolanib was ~150 nM.

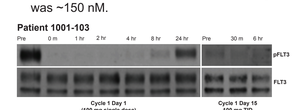


Figure 11. Western blot of inhibition of FLT3 phosphorylation in FLT3-ITD leukemic cells after treatment with serum from patient 1001-103.

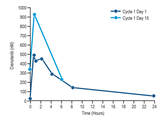


Figure 12. Serum crenolanib concentrations of patient 1001-103 on day 1 and day 15.

Similar Exposure Observed with BSA-based Versus Flat Dosing

- To determine if a BSA-based dosing can reduce interpatient variability of pharmacokinetic parameters, patients were treated with either a BSA-based dosing or flat dosing.
- Twenty-six (26) patients had 200 mg/m^2 TID BSA-based dosing, and twenty-nine (29) patients had 100 mg TID flat dosing.
- On the first day of treatment, patients were given a single dose of 66.7 mg/m^2 or 100 mg.
- Four patients, who received three 100 mg doses on the first day of treatment, were omitted for this single dose PK analysis.

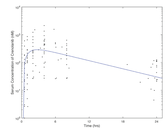


Figure 13. Serum concentration of crenolanib time profiles in individual patients treated with 66.7mg/m^2 BSA-based dose.

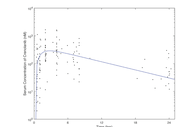
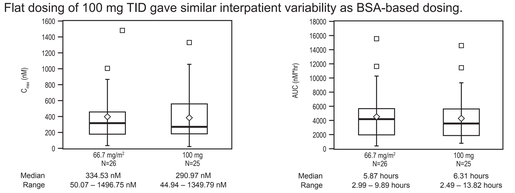


Figure 14. Serum concentration of crenolanib time profiles in individual patients treated with 100 mg flat dose.

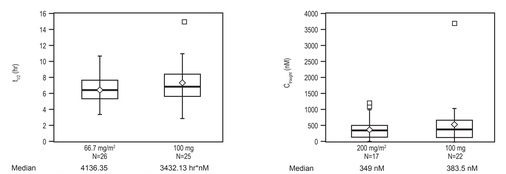
Similar Interpatient Variability Observed with BSA-based Versus Flat Dosing

No Significant Difference with BSA-based Dosing

- Four key pharmacokinetic parameters were compared.
- Flat dosing of 100 mg TID gave similar interpatient variability as BSA-based dosing.



	66.7 mg/m^2 N=26	100 mg N=25
Median	334.53 nM	290.97 nM
Range	50.07 – 1496.75 nM	44.94 – 1349.79 nM
Median	5.87 hours	6.31 hours
Range	2.99 – 9.89 hours	2.49 – 13.82 hours



	66.7 mg/m^2 N=26	100 mg N=25
Median	4136.35	3432.13 hr*nM
Range	472.31- 15362.64 hr*nM	796.8 – 14482.84 hr*nM
Median	200 mg/m^2 N=17	100 mg N=22
Range	349 nM	383.5 nM
	28 - 1197 nM	74 – 3720 nM

Figure 15. Comparison of C_{max}, AUC, $t_{1/2}$ and C_{trough} of patients treated with 66.7 mg/m^2 and 100 mg.

Conclusions

- Good exposure of crenolanib was achieved in most patients.
- Pharmacokinetic modeling showed that TID dosing optimized C_{max} and C_{trough} to minimize peak concentrations while maintaining minimal effective concentrations of crenolanib over the entire dosing period.
- Steady state pharmacokinetics are consistent with that of day 1 (no time-dependent changes in crenolanib disposition were observed).
- No significant difference was observed between flat (100 mg TID) and BSA-based (66.7 mg/m^2) dosing.
- 100 mg TID of crenolanib is selected as the dosing scheme for phase III randomized trials.

References

1.Smith *et. al.* (2014) *PNAS.* 111: 5319-5324.
2.Wang *et. al.* (2014) *OncoTargets and Therapy.* 7: 1761-1768.
3.Heinrich, *et. al.* (2012) *Clinical Cancer Research.* doi: 10.1158.
4.Smith *et. al.* (2015) *Leukemia.* doi:10.1038.
5.Kinome assay by Discover RX.
6.Fathi (2013) *Blood.*122: 3547 – 3548.
7.Patel *et. al.* (2012) *NEJM.* 366: 1079-1089.
8.Galanis *et. al.* (2014) *Blood* 123: 94-100.

American Society of Hematology Annual Meeting, December 5-8, 2015