Population pharmacokinetics of ripretinib in patients with advanced malignancies

Suzanne George[1], Filip Janku[2], Ping Chi[3], Margaret von Mehren[4], Neeta Somaiah[5], Hans Gelderblom[6], Robin L. Jones[7], Martine Allard[8], Adekemi Taylor[8], Xiaoyan Li[9], Julie Meade[9], Vienna Reichert[9], Rodrigo Ruiz-Soto[9], Jing Wang[9], Michael Heinrich[10]

[1]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Human Oncology and Pathogenesis Program/Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA; [5]Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands; [7]Sarcoma Unit, Royal Marsden and Institute of Cancer Research, London, UK; [8]Certara, Princeton, NJ, USA; [9]Deciphera Pharmaceuticals, LLC, Waltham, MA, USA; [10]Hematology/Medical Oncology, OHSU Knight Cancer Institute, Portland, OR, USA

CT123

INTRODUCTION

- Ripretinib is a kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib[1]
- The dose of 150 mg once daily (QD) is approved in the US, Canada, Australia, and Hong Kong[1–3]
- DP-5439 is an active metabolite of ripretinib with in vitro activity and in vivo exposure similar to that of ripretinib[4]
- In a phase 1 study (NCT02571036), the maximum tolerated dose was not reached with doses up to 200 mg twice daily (BID). In the phase 1 and phase 3 (INVICTUS, NCT03353753) clinical studies, ripretinib dose escalation to 150 mg BID was offered to patients after radiologic progression of disease at 150 mg QD. This regimen has been well tolerated with a similar safety profile as seen at 150 mg QD[5–7]
- Steady-state pharmacokinetic (PK) exposures following ripretinib 150 mg BID were approximately 2-fold higher compared with that of ripretinib 150 mg QD
- In this analysis, we characterize the population PK (popPK) of ripretinib and identify covariates influencing ripretinib exposure

METHODS

- The popPK models for ripretinib and DP-5439 were developed using 5284 and 5160 quantifiable concentrations, respectively, from 350 patients pooled from the phase 1 (NCT02571036) and INVICTUS studies (**Table 1**)
- The model was developed using the first-order conditional estimation with interaction method in NONMEM® (version 7.3; ICON, Hanover, MD, US) and evaluated based on standard goodness-of-fit metrics
- A covariate analysis was conducted to assess the sources of variability in ripretinib PK using a full model approach with backward elimination (significance level = 0.005)
- Evaluated covariates included age, body weight, sex, race, tumor type, prior gastrectomy (full, partial, or unknown type), and mild hepatic impairment and renal function (body surface area-normalized creatinine clearance)

Table 1. Clinical studies included in the analysis

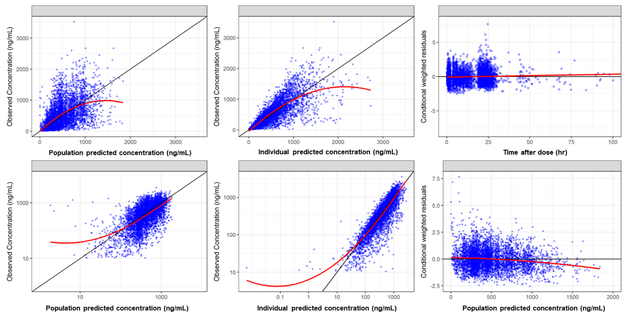
Study No.	Study design, N[a]	Drug dose and regimen	Plasma PK sampling
NCT02571036	A multicenter, phase 1, open-label study of ripretinib to assess safety, tolerability, efficacy, and PK in patients with advanced malignancies Escalation Phase 68 patients enrolled Expansion Phase 169 patients	28-day cycles Escalation Phase 20, 30, 50, 100, 150, and 200 mg BID; 100, 150, and 250 mg QD Intrapatient dose escalation was permitted Expansion Phase 150 mg QD Patients could be dose escalated to 150 mg BID	Escalation Phase Cycle 1, Days −7 (food effect), 1, 15: Predose; 0.5, 1, 2, 4, 6, 8, 10−12, and 24 h (Days −7 and 1 only) postdose Cycle 1, Days 8 and 22; Day 1 of later cycles: predose Intrapatient dose escalation (next visit after dose escalation): predose; 1 and 6 h postdose Expansion Phase Cycle 1 Days 1 and 15: predose (Day 15 only); 1 and 6 h postdose Cycle 1 Day 8 and Day 1 of later cycles: predose Additional subset (both phases; N ≈ 12) After steady-state attainment: predose; 24, 36, 48, 72, 96, 120, 144, and 168 h postdose
NCT03353753 (INVICTUS)	A phase 3, randomized, double-blind, placebo-controlled study; 129 patients enrolled (85 randomized to ripretinib and 44 randomized to placebo) N = 129	150 mg QD or matching placebo (2:1)	Cycle 1 Day 1: predose and 6 h postdose Cycle 1 Day 15: predose; 2 and 6 h postdose Day 1 of Cycles 2, 3, and every other cycle thereafter (Cycles 5, 7, etc); at intrapatient dose escalation, disease progression, and EOT visit: predose Same PK sampling as above after crossover from placebo to ripretinib

[a]Number of patients as of the 01 March 2019 data cutoff for Study NCT02571036 and 31 May 2019 data cutoff for Study NCT03353753; INVICTUS.
BID = twice daily; EOT = end of treatment; N = number of patients; PK = pharmacokinetics; QD = once daily.

RESULTS

- Ripretinib oral PK was well described by a 2-compartment model with zero-order drug release at the absorption site followed by first-order absorption, with a modest, linear dose-dependent decrease in relative bioavailability and linear elimination
- The PK of DP-5439 was described by a 1-compartment model with linear elimination

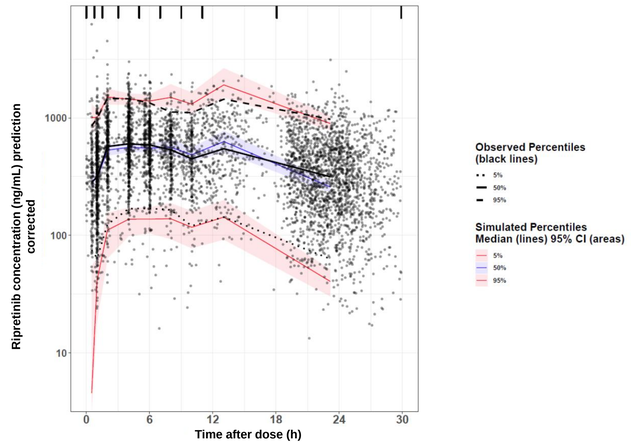
Figure 1. Goodness-of-fit plots for the final ripretinib population PK model



Blue open circles represent individual data points. Black lines represent the line of unity for observation versus prediction plots and y = 0 for the conditional weighted residual plots. Red lines represent LOESS smooth regression lines.
LOESS = locally estimated scatterplot smoothing; PK, pharmacokinetic.

- The goodness-of-fit plots demonstrate that the model was generally able to describe the data well (**Figure** 1)

Figure 2. Prediction-corrected visual predictive checks for the final ripretinib population PK model



Closed circles represent observed concentrations. Solid lines represent the median of the observed data. Dashed lines represent the 5th and 95th percentiles of the observations. The blue shaded region represents the 95% CIs of the medians of the simulations. The pink shaded regions represent the 95% CIs of the 5th and 95th percentiles of the simulations.
CI = confidence interval; PK = pharmacokinetic.

- The prediction-corrected visual predictive checks indicated a good predictive performance of the model (**Figure 2**)

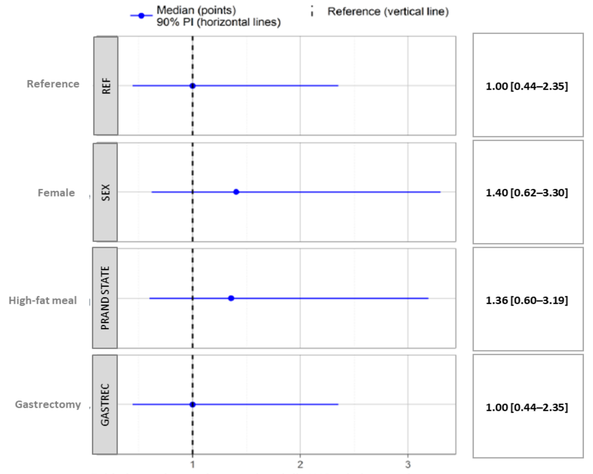
Table 2. Final population PK estimates for ripretinib

Parameter	Fixed effects		BSV CV%		Shrinkage
	Estimate	RSE%	Estimate	RSE%	
CL/F (L/h)	12.7	4.0%	53.6%	3.9%	7.0%
Vc/F (L)	20.4	8.7%	58.2%	17.5%	57.1%
Q/F (L/h)	7.30	3.0%	0 FIXED	N/A	N/A
Vp/F (L)	675	7.2%	1465%	7.3%	26.4%
Ka (1/h)	0.0832	2.7%	43.2 %	5.9%	22.3%
D1 (h)	1.459	6.6%	71.4%	6.6%	38.2%
Frel vs dose slope (1/mg)	−0.00293	8.8%	N/A	N/A	
D1 ~ high-fat meal fold-change	3.47 FIXED	0 FIXED	N/A	N/A	
Frel ~ high-fat meal fold-change, <100 mg	1.131 FIXED	N/A	N/A	N/A	
Frel ~ high-fat meal fold-change, 100 mg or 150 mg	1.356 FIXED	N/A	N/A	N/A	
Frel ~ high-fat meal fold-change, >150 mg	1.683 FIXED	N/A	N/A	N/A	
CL/F ~ female fractional change	−0.287	14.4%			
Ka ~ prior gastrectomy fractional change	0.230	40.3%			
Proportional residual error (CV%)	41.0%	0.85%			
Additive residual error standard deviation (ng/mL)	29.6	1.9%			

BSV = between-subject variability; CL/F = apparent clearance; CV% = percent coefficient of variation; D1 = duration of zero-order release; Frel = relative bioavailability; Ka = first-order absorption rate constant; N/A = not applicable; PK = pharmacokinetic; Q/F = apparent inter-compartmental clearance; RSE = relative standard error; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution.

- There were no clinically meaningful differences in the PK of ripretinib based on age, race, body weight, or tumor type. The covariate analysis did not identify these variables as covariates on ripretinib clearance and volume of distribution (data not shown)
  - A 28.7% decrease in apparent clearance was estimated in females relative to males

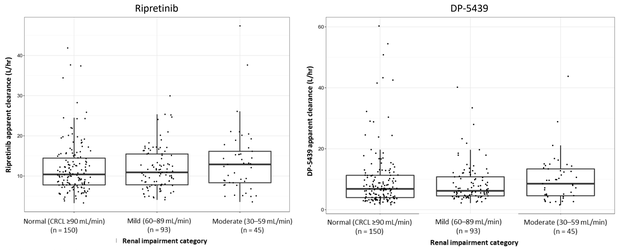
Figure 3. Forest plot of covariate effects on steady-state ripretinib AUC (ratios)



For all covariate scenarios, all other covariates were maintained at values for the reference patient (male patient without prior gastrectomy taking 150 mg QD ripretinib in the fasted state). The median simulated ripretinib AUC for the reference patient was 11.6 µg*h/mL. Numbers in the right-hand panel represent median (90% PI).
AUC = area under the plasma concentration-time curve; GASTREC = gastrectomy; PI = prediction interval; PRAND = prandial; QD = once daily; REF = reference.

- Ripretinib area under the plasma concentration-time curve (AUC) was predicted to be 40% higher in females compared to males (**Figure 3**)
- A high-fat meal administered with 150 mg QD was predicted to result in a 36% increase in ripretinib AUC relative to the fasted state
- Although there was a 23% increase in the first-order absorption rate, there was no effect of prior gastrectomy on the exposure of ripretinib

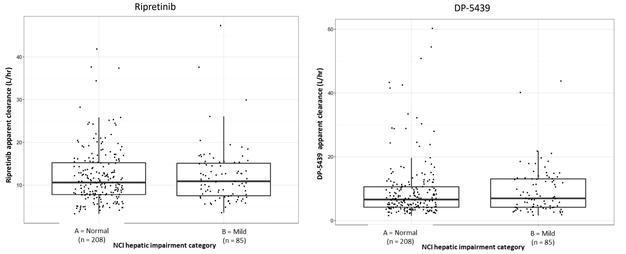
Figure 4. Plasma ripretinib and DP-5439 apparent clearance vs renal function category in patients who received a starting dose of 150 mg once daily



CRCL = creatinine clearance.

- Ripretinib apparent clearance (CL/F) and apparent clearance of metabolite DP-5439 (CLm/F) at the 150 mg QD dose for patients with mild and moderate renal impairment were comparable to values in patients with normal renal function (**Figure 4**)

Figure 5. Plasma ripretinib and DP-5439 apparent clearance vs hepatic function category in patients who received a starting dose of 150 mg once daily



NCI = National Cancer Institute.

- Ripretinib CL/F and DP-5439 CLm/F at the 150 mg QD dose for patients with mild hepatic impairment based on the National Cancer Institute hepatic dysfunction classification[8] were comparable to values observed in patients with normal hepatic function (**Figure 5**)
- DP-5439 was predicted to decline in parallel with ripretinib in the terminal phase, indicating the decline of DP-5439 plasma concentrations is formation-rate limited

CONCLUSIONS

- Ripretinib oral PK was well described by a 2-compartment model and had a modest, linear dose-dependent decrease in relative bioavailability and linear elimination
- There were no clinically meaningful differences in the PK of ripretinib based on age, race, body weight, or tumor type
- No effect of prior gastrectomy on the exposure of ripretinib was observed
- Based on the safety profile of ripretinib observed in patients with advanced malignancies, dose escalation of ripretinib to 150 mg BID after progression on 150 mg QD showed a similar safety and tolerability profile.[6] Steady-state pharmacokinetic (PK) exposure following ripretinib 150 mg BID were approximately 2-fold higher compared with that of ripretinib 150 mg QD
- The magnitude of increased ripretinib exposures in females or with high-fat meals does not suggest a need for dose adjustment in those conditions
- No dose adjustment is recommended for patients with mild to moderate renal impairment or patients with mild hepatic impairment

Presented at the AACR Virtual Annual Meeting 2021, April 10–15

References

1) Qinlock. Prescribing information. Waltham, MA: Deciphera Pharmaceuticals, LLC; 2020. Last revised: 05/2020. Available at: https://qinlockhcp.com/Content/files/qinlock-prescribing-information.pdf; 2) Health Canada, DIN 02500833. https://pdf.hres.ca/dpd_pm/00056679.PDF; 3) Australian Government Department of Health, ARTG 327899. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-02677-1; 4) Smith BD, et al. *Cancer Cell* 2019;35:738–51; 5) Janku F, et al. *J Clin Oncol* 2020;38:3294–303; 6) Janku F, et al. *Ann Oncol* 2020;31(Suppl 4):S974–5; 7) Blay JY, et al. *Lancet Oncol* 2020;21:923–34; 8) NCI. Protocol for Organ Dysfunction Studies. 2019. https://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Organ_Dysfunction_Protocol_Template.docx., Accessed March 10, 2021.

Acknowledgments

We would like to thank the patients, their families and caregivers, the investigators, and the investigational site staff of the phase 1 and INVICTUS studies. The studies were sponsored by Deciphera Pharmaceuticals, LLC (Waltham, MA, USA). Writing and editorial support was provided by AlphaBioCom, LLC (King of Prussia, PA, USA), and was funded by Deciphera Pharmaceuticals, LLC.