PHYSIOLOGICALLY BASED ABSORPTION AND PHARMACOKINETIC MODEL FOR RIVOCERANIB AND ITS MAIN METABOLITE TO ASSESS POTENTIAL CYP3A4-MEDIATED DDI RISK

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Introduction

A PBPK model for anticancer drug rivoceranib (RIV), a tyrosine kinase inhibitor (TKI) that selectively targets vascular endothelial growth factor receptor-2 (VEGFR-2) was developed and validated to assess potential risk of CYP3A4-mediated DDIs.

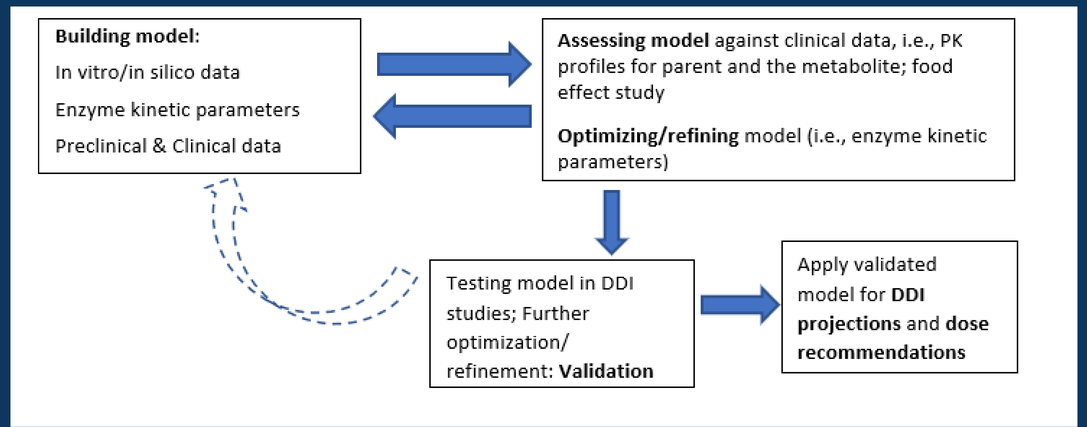
Methods

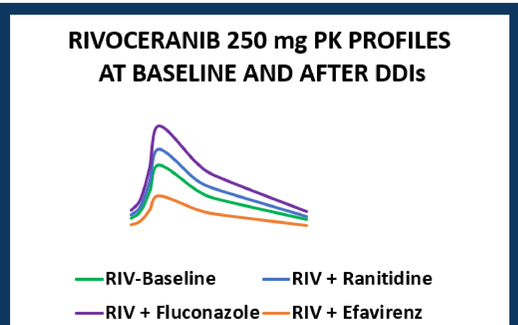
In vivo distribution of RIV was modeled using GastroPlus®. Tissue distribution was estimated using default Kp method [1]. Systemic clearance was parameterized via CYP3A4 and 2D6 saturable kinetics (K_m, V_{max}) [2]. The model was verified against RIV, and its active metabolite M1-1 PK data obtained after oral dosing of RIV (81-750 mg). Clinical DDI studies with rifampicin (rif) and itraconazole (itra) were used to calibrate the CYP3A4 contribution to *in vivo* clearance. Validated model was applied to project RIV's CYP3A4-mediated DDIs with ranitidine (weak inhibitor), fluconazole (moderate inhibitor), and efavirenz (moderate inducer).

Results

The PBPK model accurately described: RIV and M1-1 exposures (Fig 1A); elimination via CYP3A4 and 2D6 (Fig 1B); magnitude of itra-DDIs (Fig 1C and 1D); magnitude of rif-DDIs and food effect (not shown). Predicted/observed AUC_{0-t} and C_{max} across fasted, fed, and DDI studies were within 0.8-1.25-fold range. Estimated RIV metabolism via CYP3A4 was about 70% and <20% via 2D6.

A validated PBPK model is used *in lieu* of clinical studies to assess the risk of CYP3A4-mediated DDIs for an anticancer drug rivoceranib (victim) with weak/moderate CYP3A4 inhibitors (ranitidine/fluconazole), or with a moderate CYP3A4 inducer (efavirenz)





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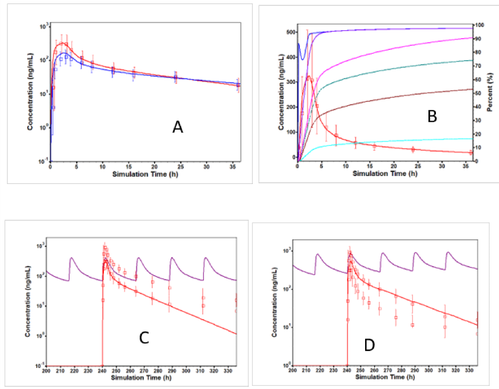
Results, Cont'd: Figure 1

A. Simulated (line) versus observed (mean ± SD, squares) PK profiles of RIV (red) and the main metabolite M1-1 (blue) at baseline following oral administration of 200 mg RIV.
B. Rivoceranib 200 mg oral dose: Percentages dissolved (blue); absorbed (purple); metabolized – total (pink); via CYPR3A4 (green); via CYP3A4 in the liver (brown); via CYP2D6 in the liver (teal)
C. Simulated (red line) versus observed (mean ± SD, squares) PK profile of RIV 200 mg single oral dose at baseline (i.e., without itraconazole – purple line)
D. Simulated (red line) versus observed (mean ± SD, squares) PK profile of RIV 200 mg single oral dose with itraconazole oral 200 mg (purple line)



Discussion and Conclusions

Validated PBPK model was applied to assess DDI potential and inform the DDI label *in lieu* of clinical studies. Model projected increase in C_{max} and AUC_{0-t} by 1.2 and 1.5-fold, 1.5 and 2.3-fold, and 0.6 and 0.4-fold, with ranitidine, fluconazole, and efavirenz, respectively, as summarized in table below.

PBPK model–based DDI risk assessment: Projected impact of CYP3A4 perpetrators on RIV exposure (PK parameter ratio of RIV administered with and without perpetrator)

Perpetrator	AUC_{0-t} Ratio	C_{max} Ratio
Ranitidine 150 mg BID	1.57	1.21
Fluconazole 200 mg QD	2.39	1.53
Efavirenz 600 mg QD	0.445	0.596

1. Lukacova, V., et al., *General Approach to Calculation of Tissue:Plasma Partition Coefficients for Physiologically Based Pharmacokinetic (PBPK) Modeling*, in *AAPS Annual Meeting*. 2008: Atlanta, GA
2. Ding, J., et al., *Metabolism and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor apatinib in humans.* Drug Metab Dispos, 2013. **41**(6): p. 1195-210