Therapeutic Drug Monitoring (TDM) of Tyrosine Kinase Inhibitors (TKIs): [redacted] focus on drug-drug interaction (DDI)

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Conflicts of Interest

none

Introduction (Plan)

- Almost all TKIs are substrates of cytochromes P450 3A4 (CYP3A4)
- Drug-Drug-Interaction (DDI) is one of the rationale for their TDM
- DDI with clinical impact: those due to either an inhibitor (e.g., antifungal azoles) or inducer (e.g., rifamipicin) of their metabolism (CYP3A4 isoenzyme)
- However, this DDI does not impact the same pharmacokinetic (PK) parameter for all TKIs
- Moreover, the extent of this DDI is very different from one TKI to another
- Clinical implications of these differences

TDM of imatinib in Chronic Myeloid Leukemia and GIST

Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia

Blood 2007

Stephane Picard,[1,2,3] Karine Titier,[1,2,3] Gabriel Etienne,[4] Emmanuelle Teilhet,[1,2,3] Dominique Ducint,[1,2,3] Marie-Agnes Bernard,[1] Regis Lassalle,[1] Gerald Marit,[2,5,6] Josy Reiffers,[4] Bernard Begaud,[1,2,3] Nicholas Moore,[1,2,3] Mathieu Molimard,[1,2,3] and Francois-Xavier Mahon[2,5,6]

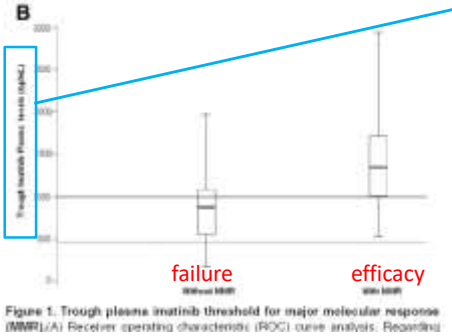
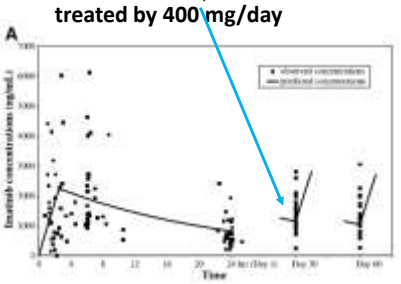


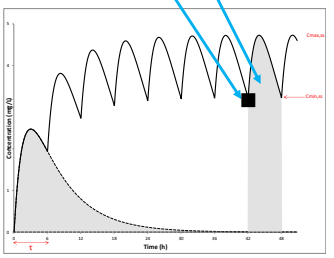
Figure 1. Trough plasma imatinib threshold for major molecular response (MMR).(A) Receiver operating characteristic (ROC) curve analysis. Recording

$C_{min,ss}$ and $AUC_{\tau,ss}$ (plasma drug exposure) are highly correlated

Trough C = $C_{min,ss}$ for patients all treated by 400 mg/day



Clin Cancer Res 2006;12(20) October 15, 2006



TDM of cabozantinib in metastatic renal cell carcinoma

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Volume 6 ■ Issue 6 ■ 2021

L. Cerbone[1†], D. Combarel[2,3†], A. Geraud[3,4], E. Auclin[5], S. Foulon[6], C. Alves Costa Silva[1], E. Colomba[1], L. Carril[1], L. Derosa[1], R. Flippot[1], O. Mir[1], N. Khoudour[7], B. Blanchet[7,8], B. Escudier[1], A. Paci[2,3] & L. Albiges[1,3*]

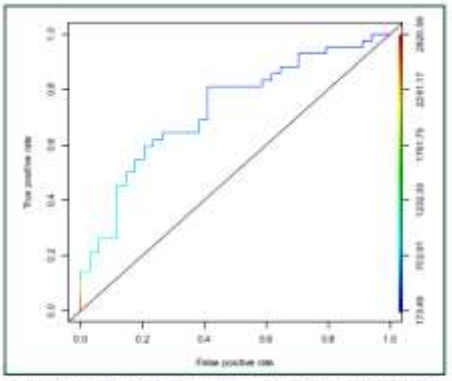


Figure 2. Receiver operating characteristic curve (ROC) for prediction of progression to cabozantinib in mRCC patients, based on the assessment of cabozantinib C_{trough}.
A threshold of 536.8 ng/ml for C_{trough} had a 64.3% sensitivity and a 73.5% specificity to detect disease progression.

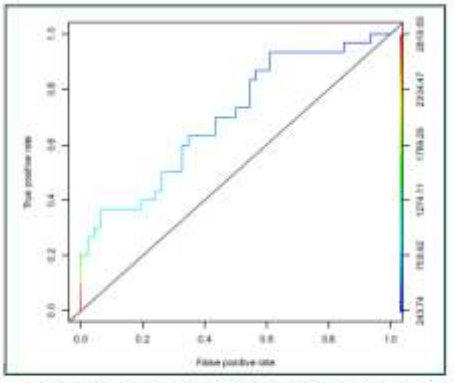


Figure 3. Receiver operating characteristic curve (ROC) for prediction of relevant toxicity to cabozantinib in mRCC patients.
A threshold of 617.7 ng/ml for C_{trough} had a 63.3% sensitivity and a 65.3% specificity to detect relevant toxicity (i.e. G3-4 toxicities and G2 toxicities ... drug discontinuation).

$C_{min,ss}$: >536 (efficacy) and <617 µg/L (toxicity)

CYP3A4 inhibitors and inducers have an impact on TKIs concentrations: DDI clinical trials (EMA guidelines) are mandatory

Guideline on the investigation

A) Interaction studies with inhibit

If cytochrome P450 enzymes are ident ... n
pathways of the drug (or in major form
metabolites), evaluation of the pharma
concomitant administration of a strong ... ded to
verify and quantify the involvement of ... if

Table 3 Examples of strong inhibitors of specific enzyme activities in vivo

ENZYME	INHIBITOR
CYP1A2	enoxacine
CYP2B6	ticlopidine
CYP2C8	gemfibrozil
CYP2C9	fluconazole*
CYP2C19	omeprazole*
CYP2D6	quinidine, paroxetine, fluoxetine
CYP3A	itraconazole, ketoconazole, ritonavir, clarithromycin

C) Interaction studies with inducers

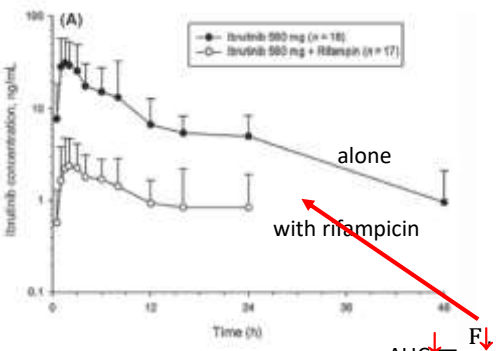
The effect of enzyme inducers on the pharmacokinetics of the investigational drug also needs consideration. If the drug is eliminated through metabolism mainly catalysed by one or more inducible enzymes, or if elimination is catalysed by CYP3A only to a limited extent, an interaction study with a potent inducer is recommended. This also applies to situations where it may not be excluded that

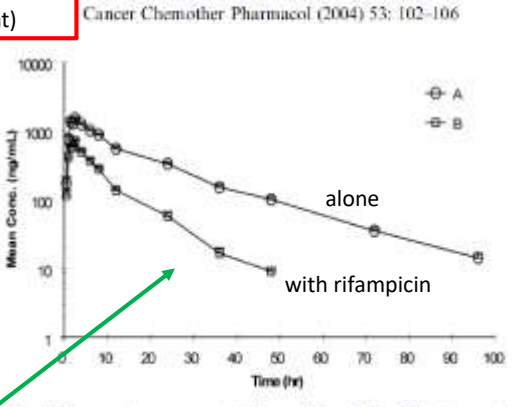
In studies of the effects of potent inducers on an investigational drug, rifampicin is often chosen

TKIs as victim of inducers: e.g. Ibrutinib vs. Imatinib

Log scale !

Decrease of AUC by:
≈7-fold (ibrut) vs. ≈4-fold (imat)





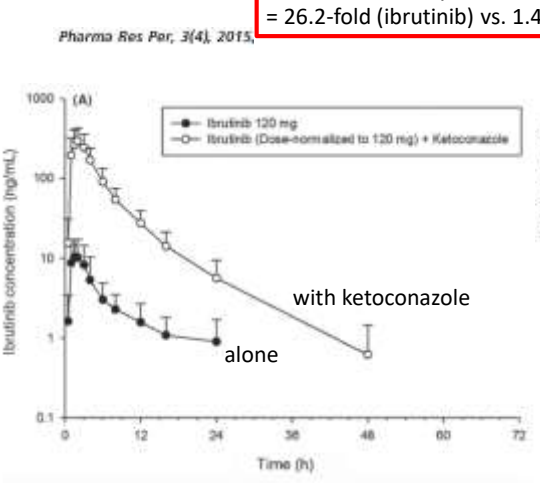
$$AUC \downarrow = \frac{F \downarrow Dose}{CL \uparrow}$$

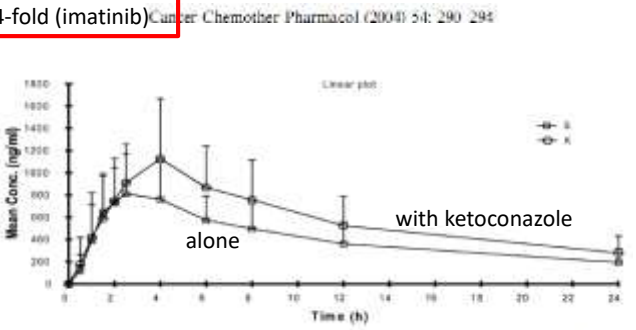
$$T1/2 \leftrightarrow = \frac{0.7 \cdot Vd}{CL \uparrow}$$

F: oral bioavailability
CL: elimination clearance
T1/2: elimination half-life

TKIs as victim of inhibitors: e.g. Ibrutinib vs. Imatinib

Increase of AUC by:
= 26.2-fold (ibrutinib) vs. 1.4-fold (imatinib)





Link between extent of DDI and oral bioavailability: lower F is associated with higher DDI

Lower F

drug	Oral F	AUCinD/ AUC	AUCinH/ AUC
ibrutinib	0.04	0.15	26.20
ceritinib	0.25	0.30	2.90
acalabrutinib	0.25	0.21	4.96
nilotinib	0.30	0.18	3.11
bosutinib	0.34	0.08	8.15
alectinib	0.37	0.26	1.75
crizotinib	0.43	0.18	3.16
entrectinib	0.50	0.23	6.04
axitinib	0.58	0.21	2.06
mean	**0.34**	**0.20**	**6.48**

Higher F

drug	Oral F	AUCinD/ AUC	AUCinH/ AUC
erlotinib	0.59	0.31	1.69
gefinitib	0.59	0.17	1.58
vemurafenib	0.64	0.53	1.31
ponatinib	0.65	0.37	1.66
osimertinib	0.70	0.20	1.26
lorlatinib	0.81	0.15	1.42
afatinib	0.92	0.67	1.47
ruxolitinib	0.95	0.30	1.91
imatinib	0.98	0.26	1.38
mean	**0.76**	**0.33**	**1.52**

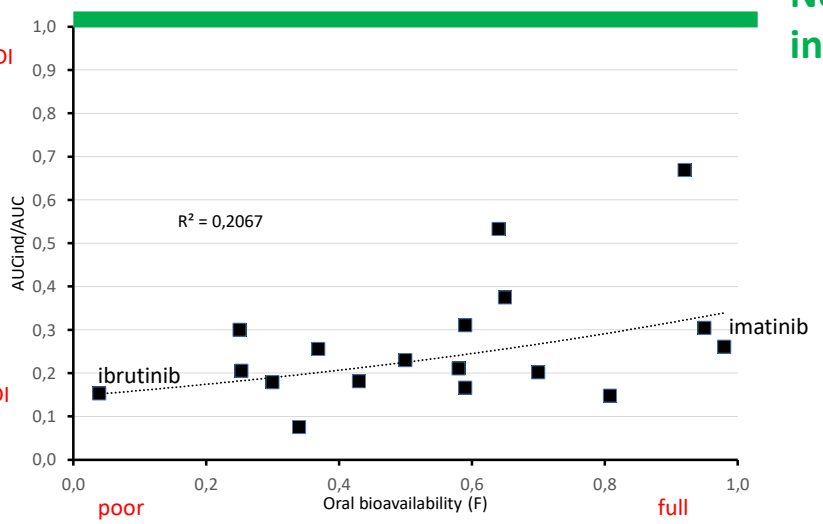
more impact of DDI than for

AUC with inducer/AUC alone vs. F

Low extent of DDI

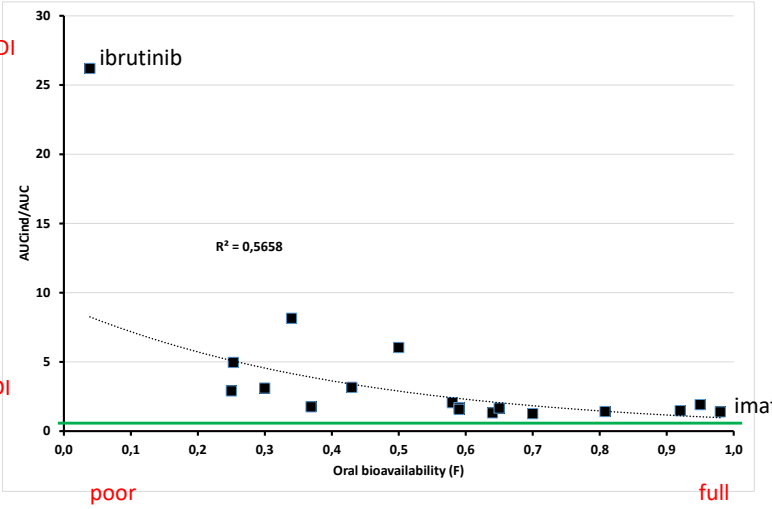
High extent of DDI

No interaction



AUC with inhibitor/AUC alone vs. F

High extent of DDI

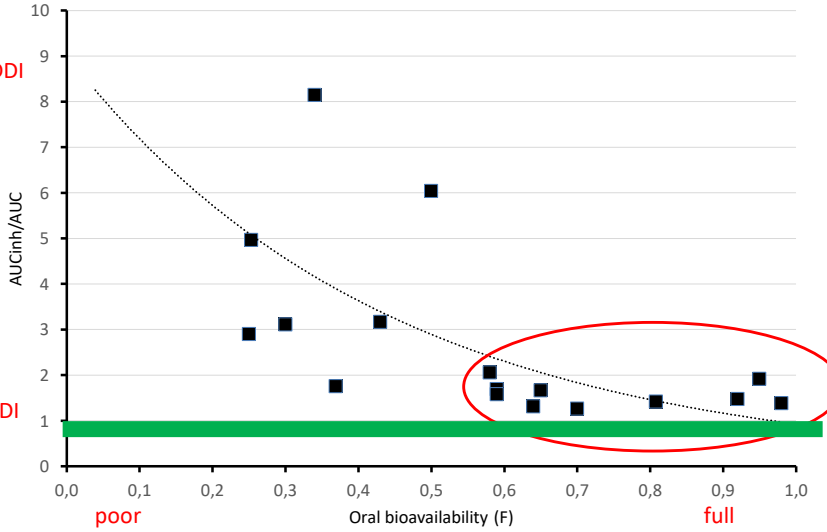


Low extent of DDI

No interaction

AUC with inhibitor/AUC alone vs. F

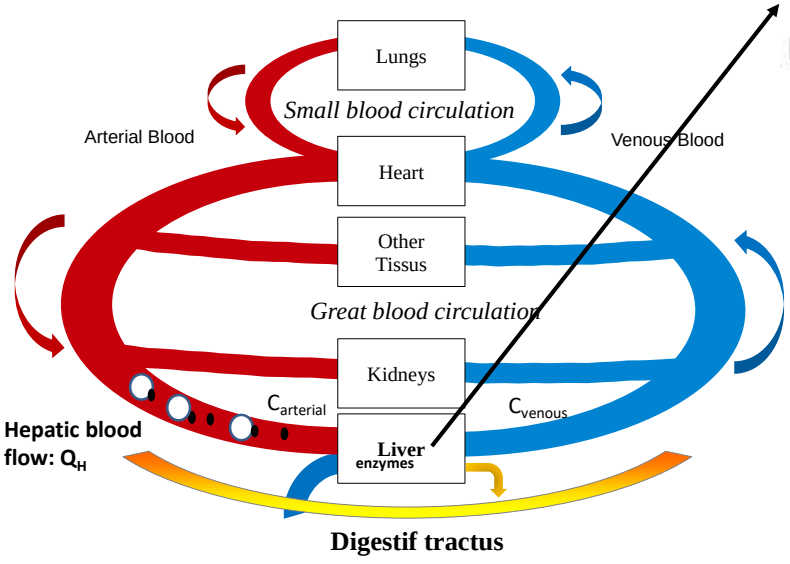
High extent of DDI



Low extent of DDI

No interaction

DDI due to CYP3A4 induction or inhibition:
Why the changed PK parameter (CL or F) depends on F value ?



Hepatic extraction ratio:

$$E_H = \frac{C_{arterial} - C_{venous}}{C_{arterial}}$$

value from low (<30%) (e.g., imatin.) to high (>70%) (e.g., ibrutinib)

$CL = E_H \cdot Q_H$
Oral $F \leq 1 - E_H$

E_H depends of the affinity of the drug (TKI) for the enzyme (CYP3A4)

30 June to 2 July 2022 European Conference of Oncology Pharmacy

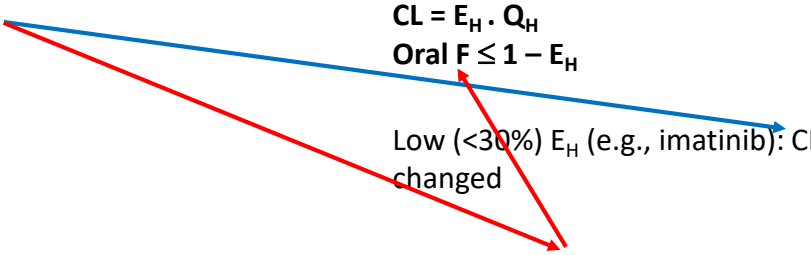
Change of E_H due to an inducer (increase of the enzyme expression) or inhibitor (decrease of activity or affinity)

Hepatic extraction ratio:

$$E_H = \frac{C_{arterial} - C_{venous}}{C_{arterial}}$$

value from low (<30%) (e.g., imatin.) to high (>70%) (e.g., ibrutinib)

$CL = E_H \cdot Q_H$
Oral $F \leq 1 - E_H$



Low (<30%) E_H (e.g., imatinib): CL is changed

High (>70%) E_H (e.g., ibrutinib): CL is ≈ unchanged (≈ hepatic blood flow)

But, considering only the hepatic first-pass effect does not explain the link:
a higher extent of DDI is associated with poor oral bioavailability

e.g., if rifampicine increases the expression of CYP3A4 by 4-fold:

for TKIs with high F (low E_H): CL increases by 4-fold (and F is ≈ unchanged)

for TKIs with low F (high E_H): F decreases by 4-fold (and CL is ≈ unchanged)

$$AUC = \frac{F \cdot Dose}{CL}$$

Should be associated with a decrease of AUC by 4-fold for both drugs

Link between F and the extent of the DDI: two hypotheses

Hypothesis 1: *"other enzymes are involved or not"*

- TKIs with high E_H (and then low F) has a strongest affinity for CYP3A4 than those with low E_H (high F) ⇒ those with low E_H are metabolised **by other enzymes not (or less) affected** by inducers/inhibitors

  e.g., ibrutinib (mainly CYP3A4) vs. erlotinib (both CYP3A4 and CYP1A2)

drug	Oral F	AUCinD/ AUC	AUCinH/ AUC
ibrutinib	0.04	0.15	26.20

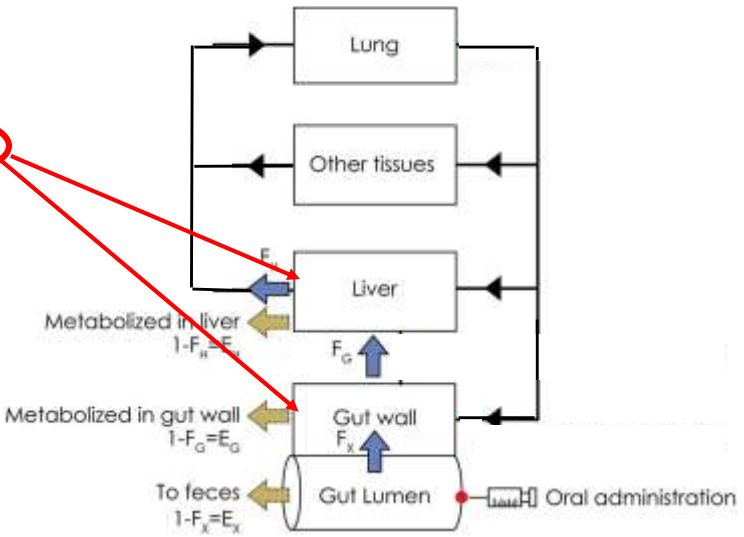
drug	Oral F	AUCinD/ AUC	AUCinH/ AUC
erlotinib	0.59	0.31	1.69

… but, imatinib (mainly CYP3A4)

drug	Oral F	AUCinD/ AUC	AUCinH/ AUC
imatinib	0.98	0.26	1.38

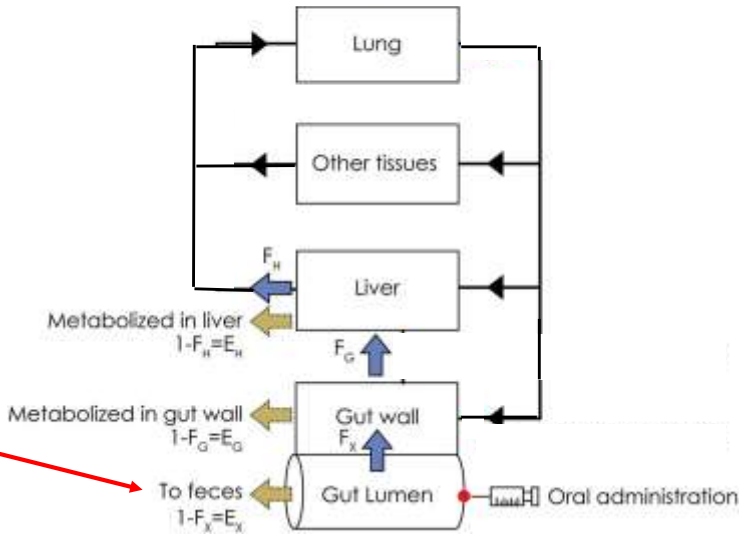
2nd hypothesis : *« there is also an intestinal first-pass effect or not »*

- TKIs with high E_H have (also) a significant **intestinal first-pass metabolism** (E_G) since CYP3A4 is also expressed in the enterocyte
- Their enteric extraction ratio (E_G) is also affected by inducers/inhibitors
- This additional site of DDI is associated with a higher extent of DDI (e.g., ibrutinib)



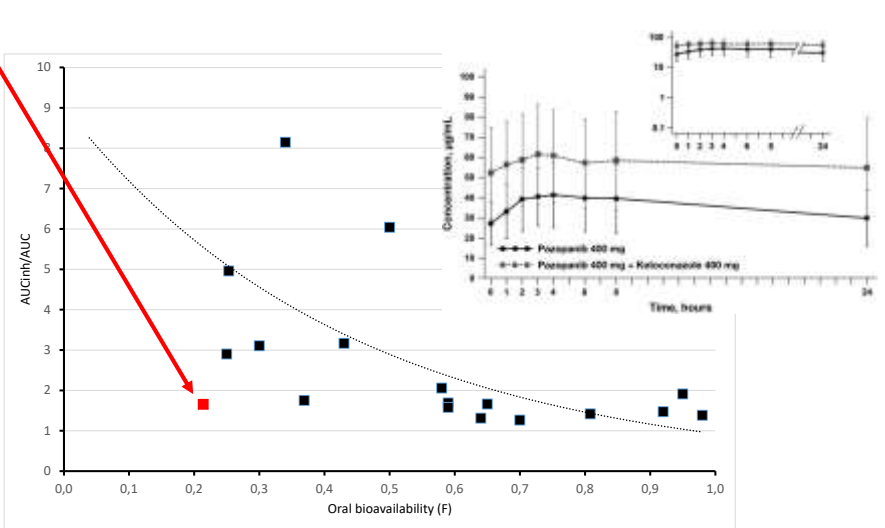
2nd hypothesis

Other TKIs with a significant loss in digestive tractus (e.g., pazopanib): low F due to poor solubility



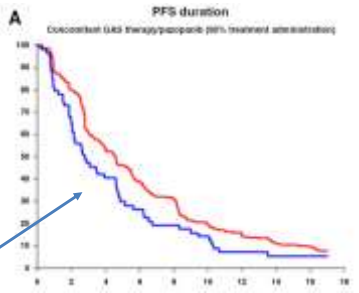
Pazopanib: low oral bioavailability (F) due to poor solubility in digestive tractus

Clinical trial: DDI with CYP3A4 inhibitor (ketoconazole)



Pazopanib: low oral bioavailability (F) due to poor solubility in digestive tractus

- Food effect: higher F with meal vs. fasted condition
- DDI with gastric acid-suppressive agents (e.g., Proton Pump Inhibitors)

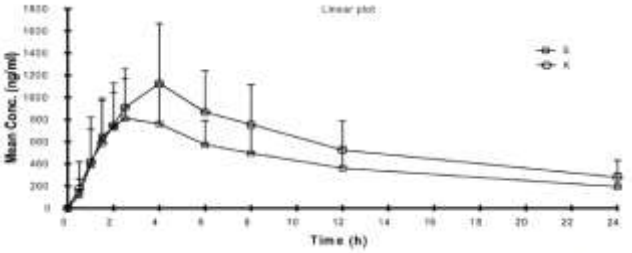


With gastric acid-suppressive agent

Clinical implications (conclusion 1/2)

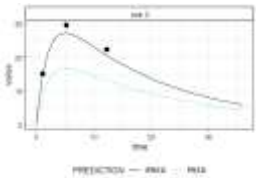
- Understanding the mechanism of DDI allows pharmacists to anticipate the extent of the interaction, and the final recommendation (contra-indication vs. change of dose)
- Interindividual variability of the extent of DDI justifying Therapeutic Drug Monitoring (TDM) of TKIs: e.g.,

Increase of AUC by ≈1.4-fold (imatinib) in average



Clinical implications f/u (conclusion 2/2)

- TDM by on Bayesian analysis: $C_{min,ss}$ or limiting sampling strategy to estimate whole exposure ($AUC_{\tau,ss}$)



CPT Pharmacometrics Syst Pharmacol. 2021;10:1208–1220.

An open-source R package for maximum a posteriori Bayesian estimation of pharmacokinetic parameters: mapbayr

Félicien Le Louedec et al

choice of the "structural" PK model:

CL affected by DDI perpetrator vs. F affected by DDI perpetrator ; is it an issue ?

- Another DDI issue: **DDI and binding of TKI to plasma protein** (albumin, α1-glycoprotein acid): no clinical implications (unchanged unbound C, C_u) but should be taken into account with TDM (increased unbound fraction, f_u) : low total concentration (C), but optimal C_u