HTN Meeting, Les Diablerets (September 3, 2019)

Sorafenib metabolism, transport, and enterohepatic recycling

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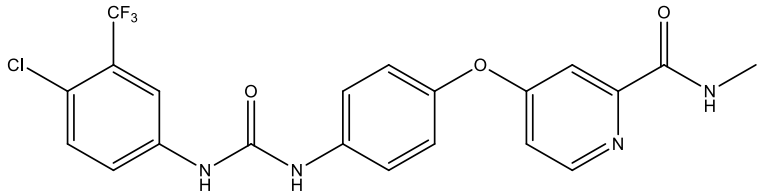
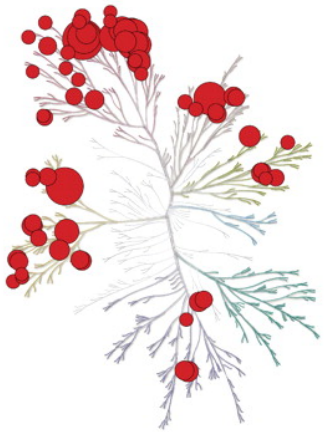
Sorafenib – a multikinase inhibitor

- Biaryl urea initially developed as a Raf-1 kinase inhibitor

- FDA approved for renal cell and hepatocellular carcinomas and thyroid cancer



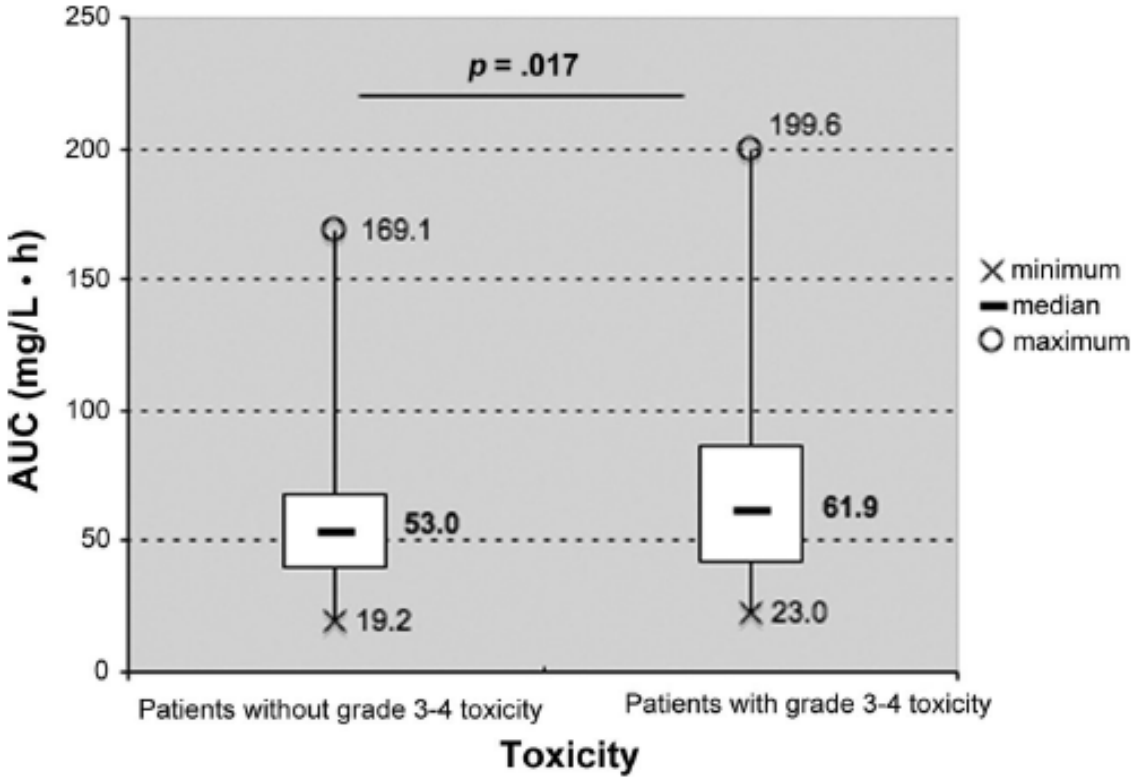
BAY 43-9006 (Sorafenib)



Kinase	Kd (nM)
BCR-ABL	680
c-KIT	31
PDGFR (-α, -β)	62, 37
FLT-3 (-WT, -ITD)	13, 79
VEGFR (-1, -2)	31, 59
RET	13
FGFR (-1, -2)	2800, 2700
RAF-1	230
Additional kinases	At <10μM

Wilhelm *et al*. *Nature Reviews Drug Discovery* 2006
Karaman MW *et al*. *Nat Biotechnol* 2008 (317 protein kinase screen)

Association of sorafenib AUC and toxicity in adults

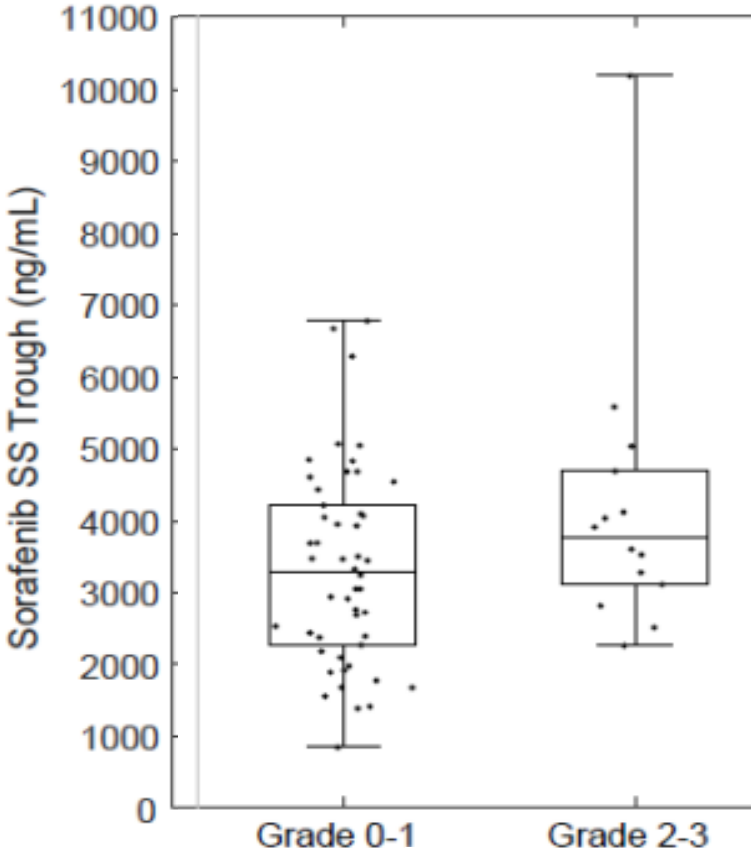


• 84 adult patients received sorafenib 200 or 400mg twice daily.

• Dose-normalized sorafenib AUC0–12 preceding grade 3–4 toxicities (HFSR, diarrhea, hypertension) was significantly higher than that observed in the remaining population (61.9 mg/L*h vs. 53 mg mg/L*h).

Boudou-Rouquette P et al. *Oncologist* 2012

Association of sorafenib Css,trough and skin toxicity in children and AYA



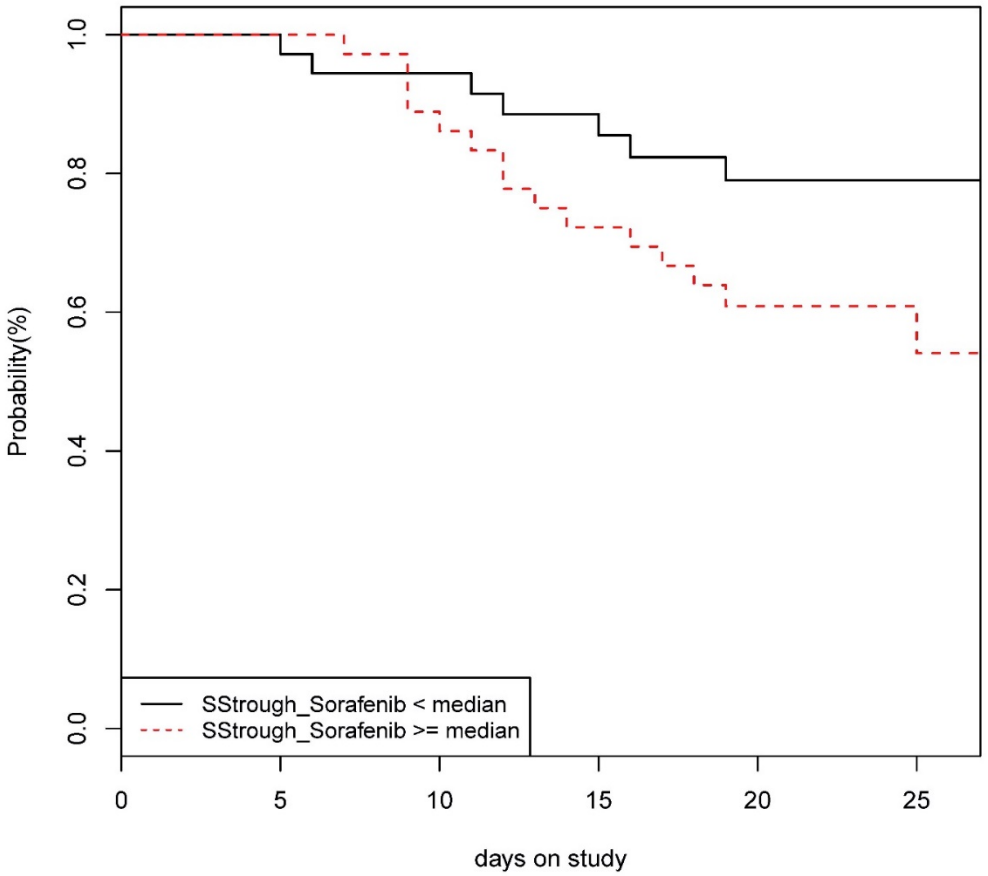
- 82 patients (median age, 10 years; range, 6 months to 25 years) received sorafenib 90 - 200 mg/m^2 twice daily.

- A 1000-ng/mL increase in the sorafenib Css,trough was associated with a 1.45-fold increase in the HFSR rate (95% CI = 1.18, 1.78; **P = 0.0004**)

- The upper quartile concentration associates with an HFSR rate that is 2.16 times that of the lower quartile (95% CI = 1.41, 3.32)

Inaba H, et al. Clin Cancer Res 2019

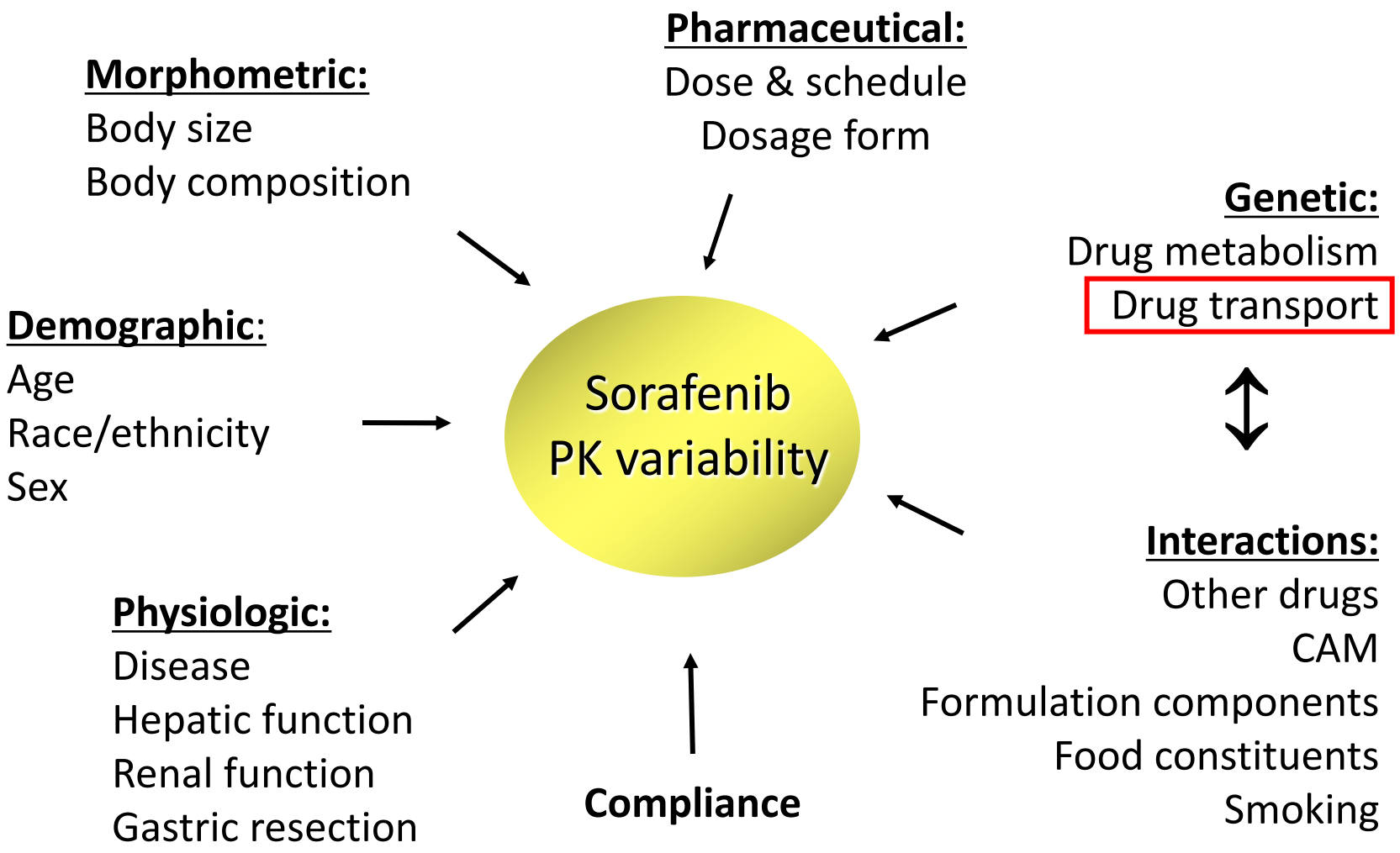
Association of sorafenib Css,trough and skin toxicity in children and AYA



- Probability of absence of grade 2–3 hand-foot skin reaction (HFSR) was associated with lower (< median) sorafenib Css,trough

Inaba H, et al. Clin Cancer Res 2019

Sources of PK variability

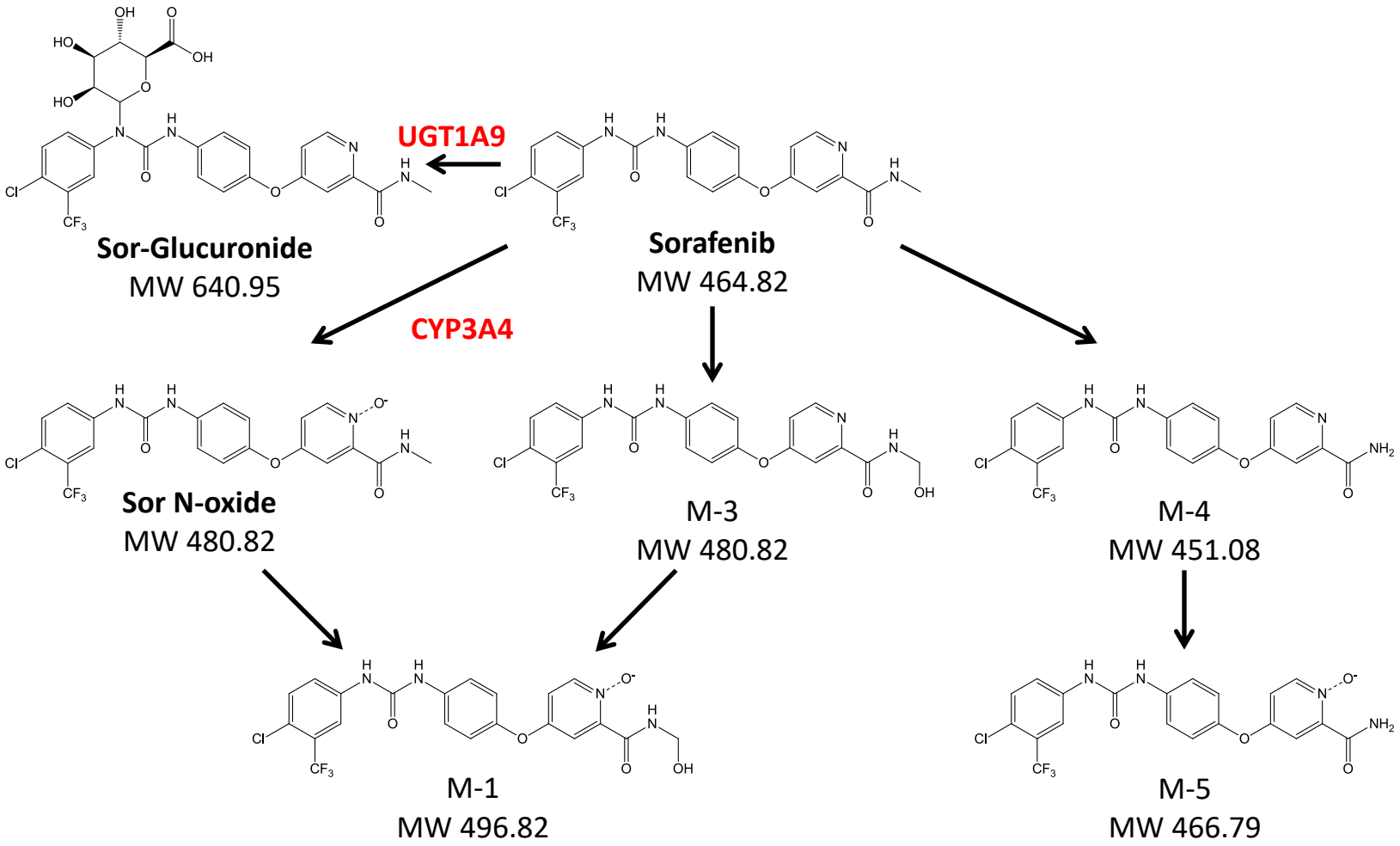


Sorafenib elimination

- Mass balance study in healthy adults: 19% of dose excreted in urine (almost exclusively as glucuronide conjugates); 77% of dose excreted in feces (50% as unchanged drug)

Lathia et al. *Cancer Chemother Pharmacol* 2006
Nexavar package insert (berlex.bayerhealthcare.com)

Sorafenib metabolic pathways



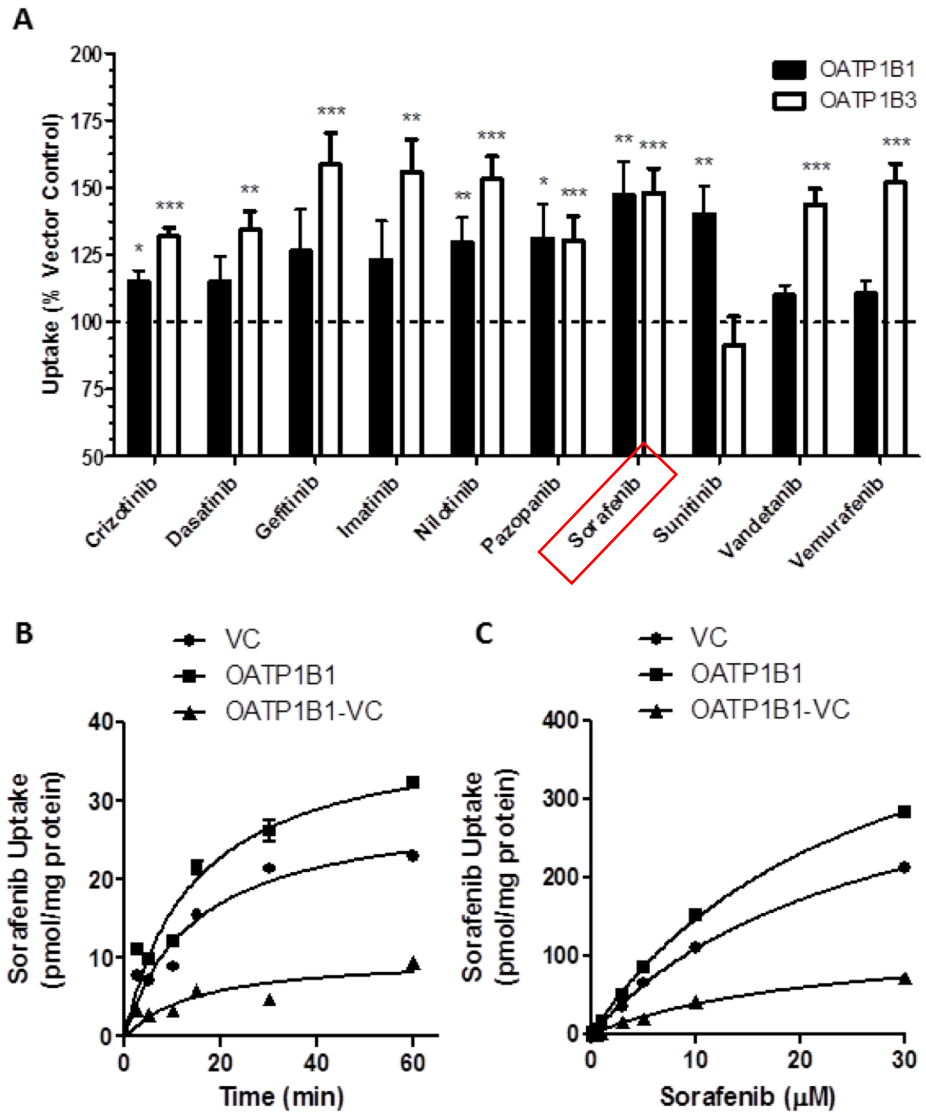
Zimmerman et al. *Clin Cancer Res* 2011
Adapted from Lathia et al. *Cancer Chemother Pharmacol* 2006

Sorafenib elimination

- Thought to undergo enterohepatic recirculation following bacterial β-glucuronidase-mediated deconjugation of sorafenib glucuronidation in intestinal luman
- Interference of sorafenib-glucuronide de-conjugation by treatment with neomycin decreased sorafenib systemic exposure to sorafenib by > 50%

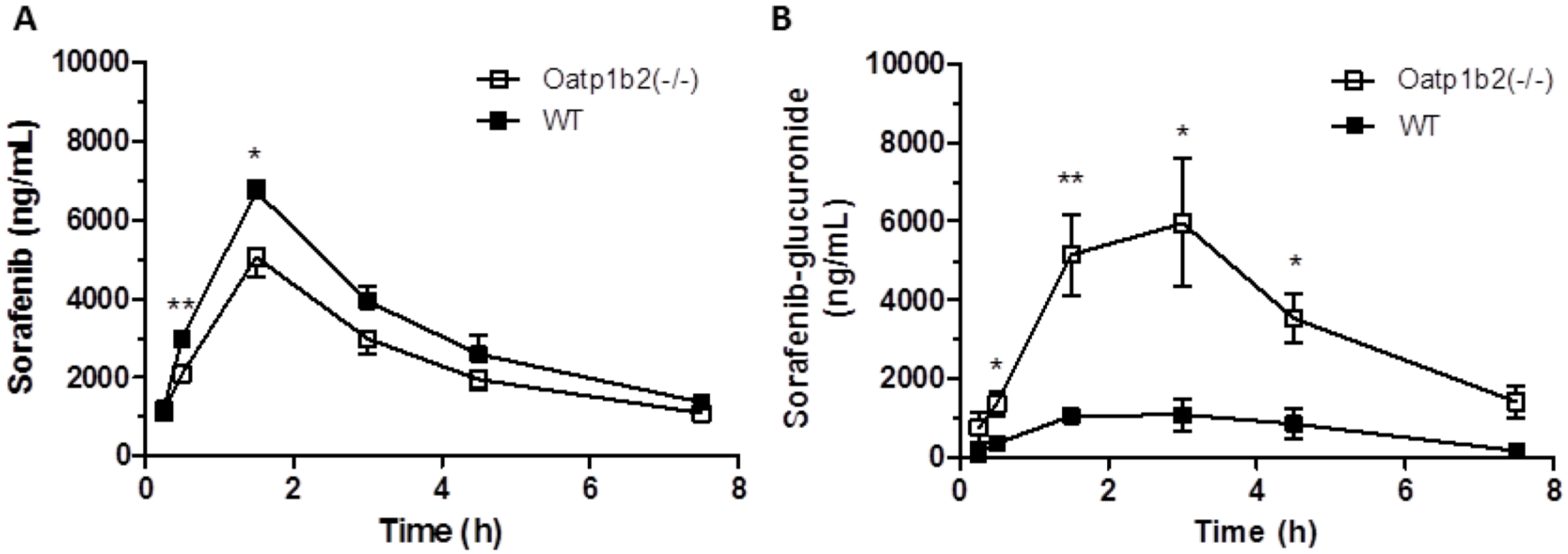
Jain et al. *Br J Clin Pharmacol* 2011
Hilger et al. *Int J Clin Pharmacol* Ther 2009
Nexavar package insert (berlex.bayerhealthcare.com)

TKI transport *in vitro* by OATP1B1/OATP1B3



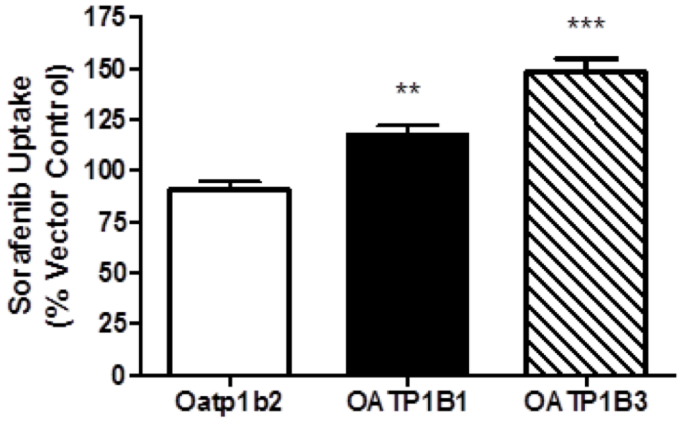
Zimmerman et al. *Clin Cancer Res 2013*

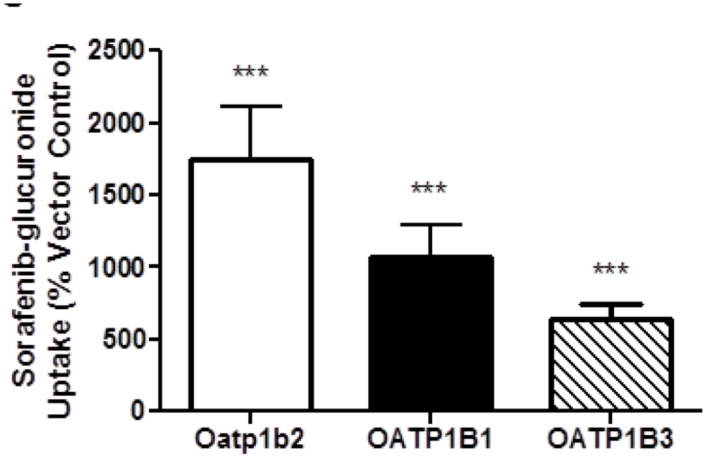
Altered pharmacokinetics of sorafenib and sorafenib-glucuronide in Oatp1b2(-/-) mice



Zimmerman et al. *Clin Cancer Res 2013*

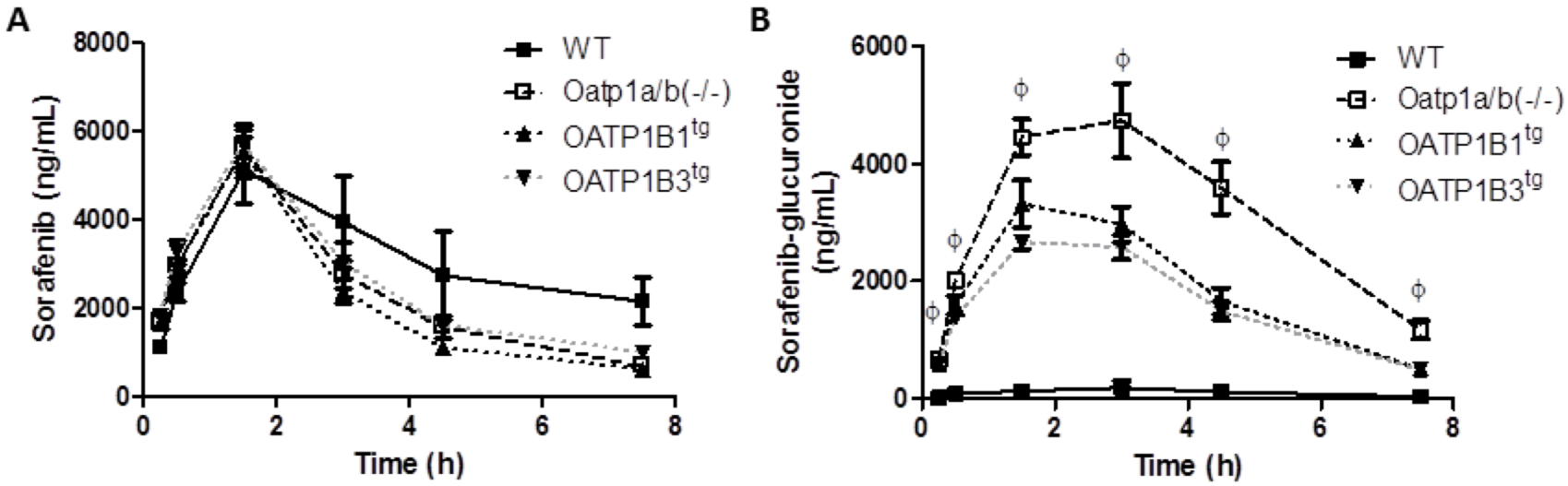
Sorafenib-glucuronide but not sorafenib is transported by Oatp1b2 *in vitro*





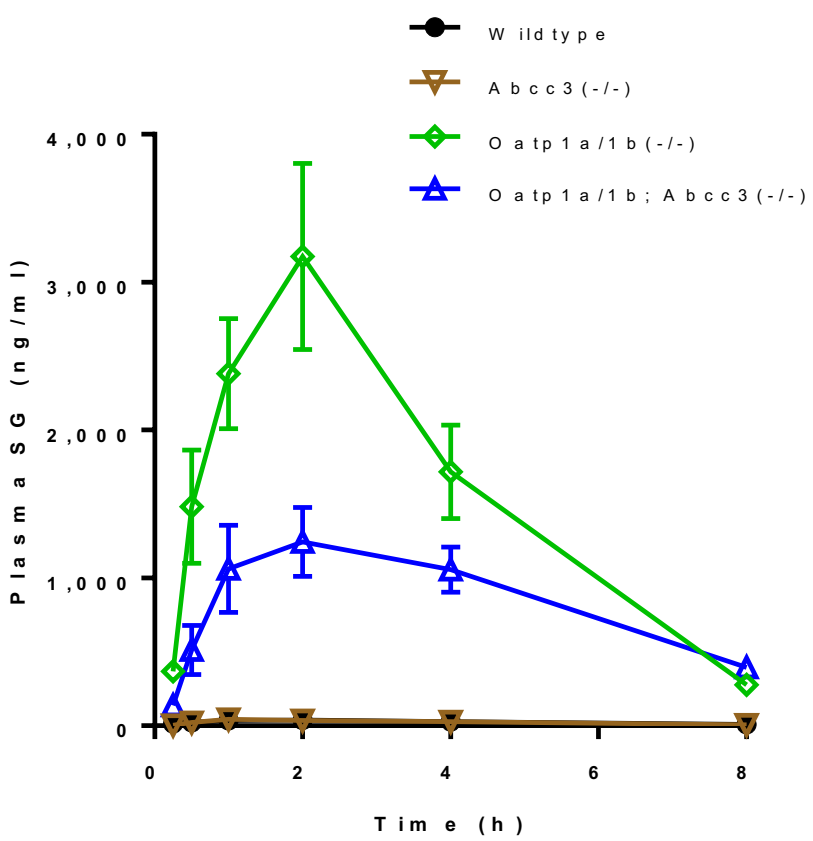
Zimmerman et al. *Clin Cancer Res 2013*

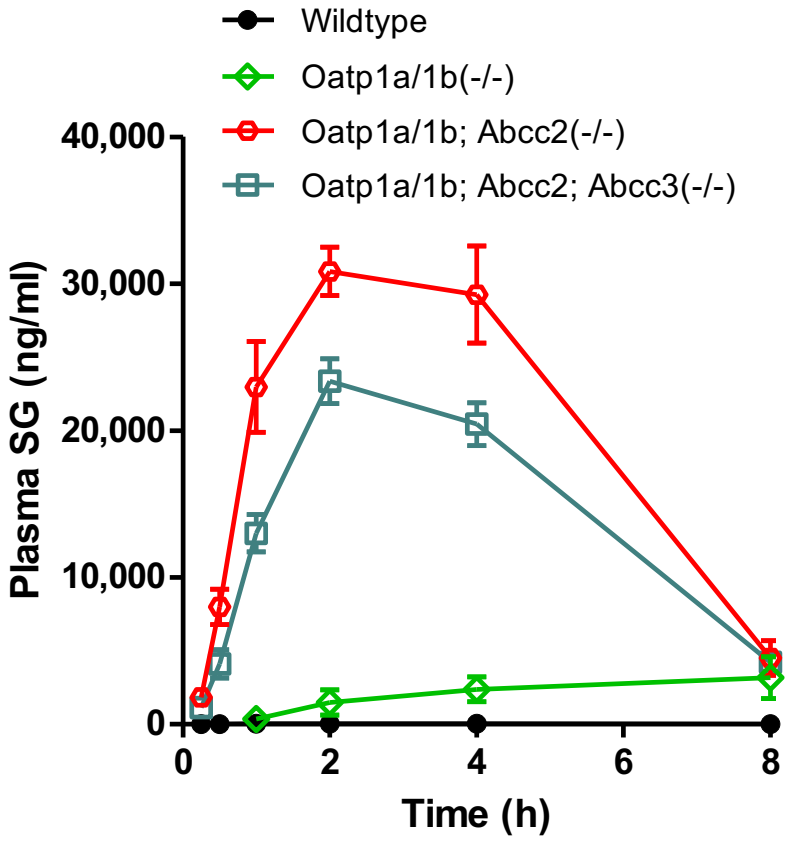
Altered pharmacokinetics of sorafenib and sorafenib-glucuronide in Oatp1a/1b(-/-) and humanized OATP1B1/3 mice



Zimmerman et al. *Clin Cancer Res 2013*

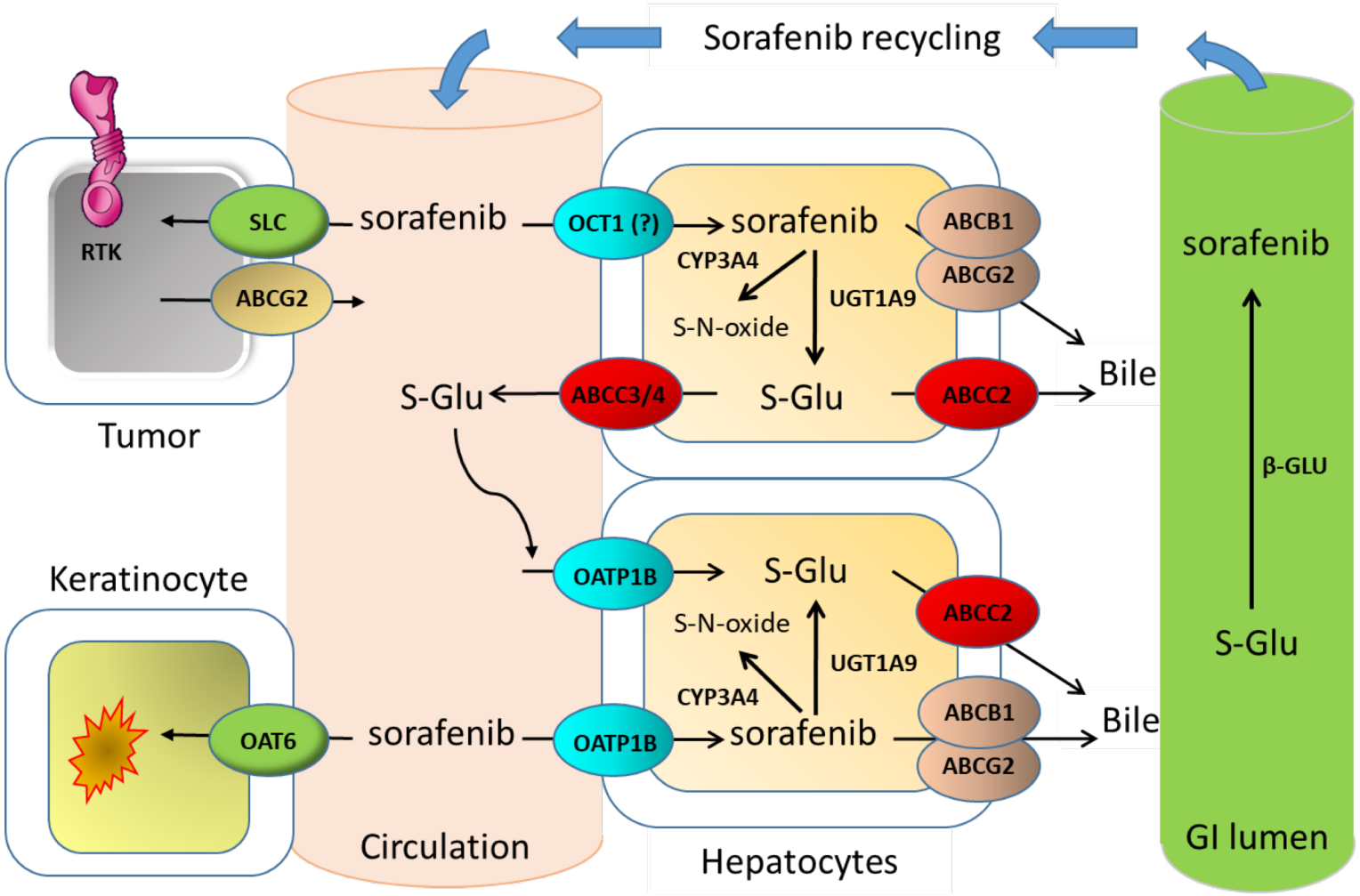
Contribution of ABCC3 and ABCC2 to sorafenib-glucuronide (SG) plasma disposition





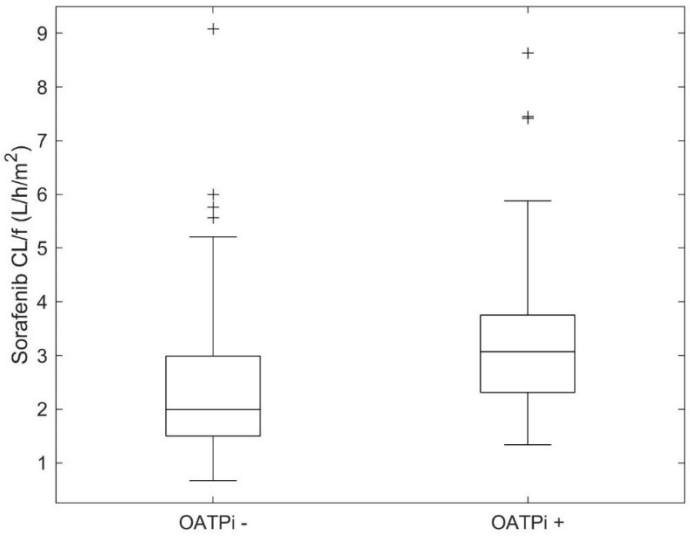
Vasilyeva et al, *Cancer Res* 2015

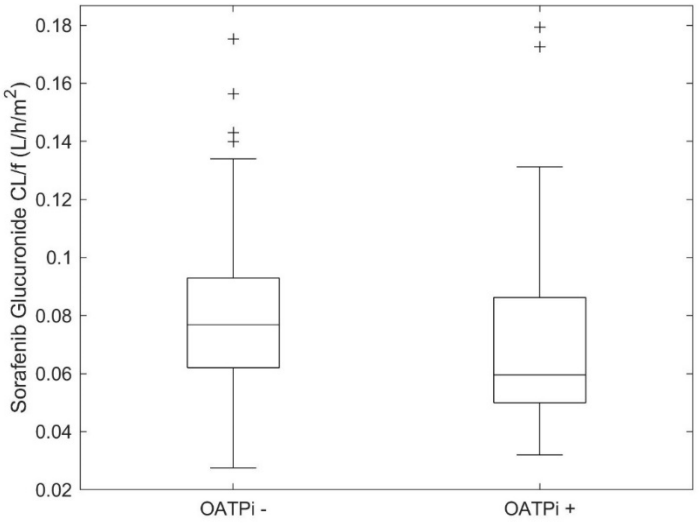
Contribution of sorafenib-glucuronide (S-Glu) transport to enterohepatic recirculation of sorafenib



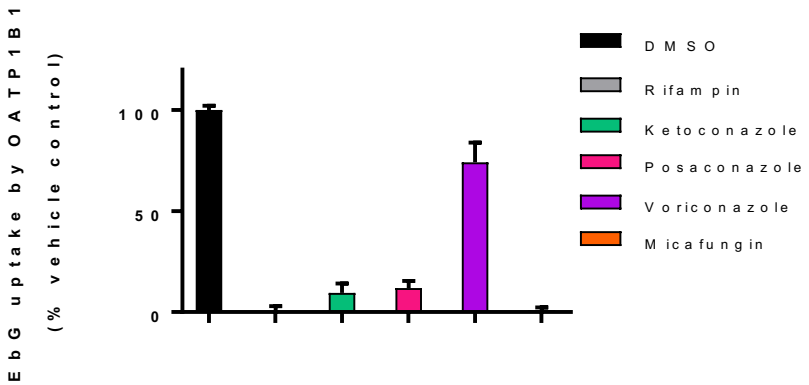
Hu et al. *Clin Cancer Res* 2009; Vasilyeva et al. *Cancer Res* 2015; Zimmerman et al. *Cancer Res* 2016; Edginton et al, *CCP* 2016; Chen et al, *CPT* 2019

Implication of S-Glu hepatocyte hopping for DDIs (1)





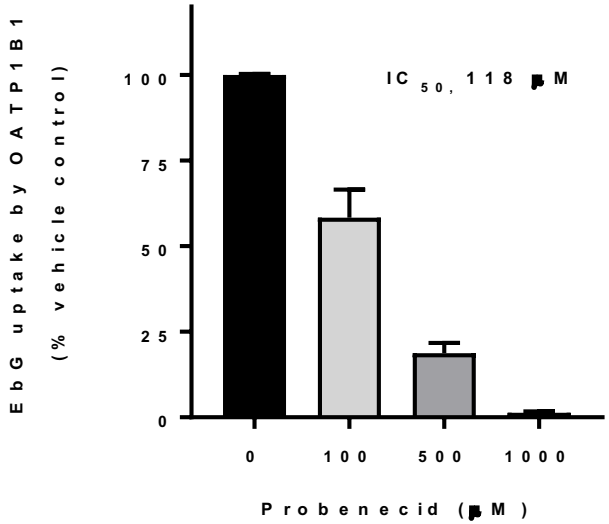
- In children and AYA, micafungin (an OATP1B1 inhibitor) increased sorafenib CL/F 50% (lower exposure) and decreased sorafenib-glucuronide CL/F 22% (higher exposure) (P=0.003)
- Suggests OATP1B1 inhibitors can reduce the enterohepatic recirculation of sorafenib



Inaba H, et al. Clin Cancer Res 2019

Implication of S-Glu hepatocyte hopping for DDIs (2)

- In adult patients, probenecid (an OATP1B1 inhibitor) decreased exposure to sorafenib 36%, while exposure to sorafenib-glucuronide increased by 27% (P = 0.01), suggesting that OATP1B1 inhibitors can reduce the enterohepatic recirculation of sorafenib.



Hussaarts et al, ESMO 2019; accepted

Conclusion

Understanding inter-patient PK variability requires detailed knowledge of the pathways involved in drug absorption and disposition

- Provides insights into potential sources of PK variability for individual drugs
- A pre-requisite for strategies to manage PK variability

Sorafenib is extensively glucuronidated, and the metabolite formed (SG) undergoes OATP1B-dependent hepatocyte hopping and contributes to enterohepatic recirculation

- Provides insights into DDIs of sorafenib with OATP1B-inhibitors in both adults and children with cancer

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