Tucatinib Inhibits Creatinine and Metformin Renal Tubule Secretion but has No Effect on Renal Function (GFR)

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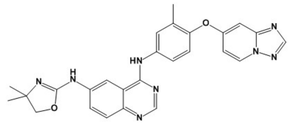
Background

Rationale and Hypothesis

- Tucatinib is a potent, highly selective HER2-directed tyrosine kinase inhibitor approved in the US for patients with HER2+ metastatic breast cancer and being developed for advanced colorectal cancer.
- In a pivotal study[1] in metastatic breast cancer (HER2CLIMB), serum creatinine (SCr) levels increased in 33% of patients after administration of 300 mg BID tucatinib and were reversible after discontinuing tucatinib.
- Inhibition of kidney transporters (OCT2 and MATE1/2-K) by tyrosine kinase inhibitors have been shown to cause serum creatinine elevations (e.g., abemaciclib[2]).

WE HYPOTHESIZED THAT TUCATINIB INHIBITS KIDNEY TRANSPORTERS, RESULTING IN ELEVATED SCr IN THE ABSENCE OF ACUTE KIDNEY INJURY

Figure 1: Chemical structure of tucatinib

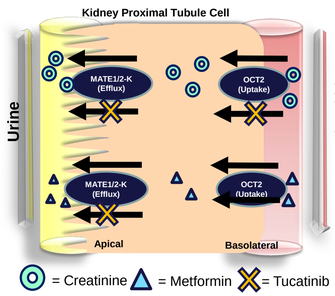


Methods

In vitro assessments and a separate clinical study in humans (SGNTUC-020) were performed to determine if tucatinib inhibited OCT2 and MATE1/2-K-mediated transport of creatinine and metformin.

- Serum creatinine (SCr): a biomarker for glomerular filtration rate (GFR) routinely measured in clinical studies and clinical practice to monitor for potential renal injury and known endogenous substrate of OCT2 and MATE1/2-K transporters.
- Metformin: a sensitive OCT2 and MATE1/2-K substrate used as an exogenous probe for kidney transporter inhibition.

Figure 2. Kidney proximal tubule cell transport of creatinine and metformin by OCT2 uptake and MATE1/2-K efflux transporters with in vitro inhibition pathways by tucatinib.



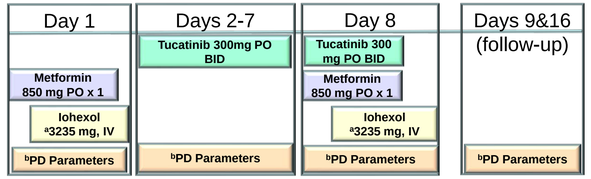
In Vitro Determination of Tucatinib-Mediated Inhibition of OCT2, MATE1 and MATE2-K Transporters

- Estimation of tucatinib inhibition of OCT2, MATE1 and MATE2-K-mediated transport was performed in transfected MDCK-II cells using creatinine and metformin as probe substrates.
- The resulting in vitro IC_{50} values were imputed into a physiologically-based pharmacokinetic (PBPK) model to simulate the in vivo impact of tucatinib on metformin PK.

Clinical Drug-Drug Interaction Study Design

Investigational Products and Endogenous Measurements of Interest:

- Tucatinib = inhibitor of MATE transport (hypothesis)
- Metformin = probe substrate of OCT2 and MATE transporters
- Iohexol = probe for actual GFR (aGFR)
  - Freely filtered through the kidneys without impact from secretion or reuptake
- Cystatin C = endogenous biomarker for used as an alternative to serum creatinine in calculating estimated GFR (eGFR)
- Serum Creatinine = endogenous biomarker, substrate of OCT and MATE



[a]Iohexol administered using 5 mL of a 300 mg/mL iodine solution (total of 1500 mg iodine, 3235 mg iohexol) 10 hours after metformin administration.
[b]Pharmacodynamic (PD) parameters included serum levels of creatinine and cystatin C, 24-hour urine creatinine and microalbumin. Estimated GFR (eGFR) was calculated using cystatin C.
Blood samples were taken for the determination of SCr and cystatin C (control endogenous biomarker for GFR) levels at screening and on Days 1, 8 and 9. 24-hour urine sampling was performed on Days 1 and 8 post-metformin to calculate creatinine clearance.

Figure 3: Schema of Tucatinib Renal Transporter DDI Study.

Tucatinib In Vitro Transport Inhibition

Tucatinib Inhibits OCT2, MATE1 and MATE2-K Transporters In Vitro

- Tucatinib inhibited the uptake transport of creatinine by OCT2 and efflux transport by MATE1 with IC_{50} values of 0.107 and 0.086 µM, respectively.
- Tucatinib inhibited MATE1 (IC_{50} = 0.340 µM) and MATE2-K (IC_{50} = 0.135 µM) but not OCT2-mediated (IC_{50} = 14.7 µM) transport of metformin.
- Together, these data show that transporter inhibition by tucatinib is substrate-dependent.
- Potential in vivo interactions exist for OCT and MATE when $I_{max,u}/IC_{50} \geq 0.1$
- The resulting PBPK model simulated a 1.19-fold (1.18, 1.21) and 1.47-fold (1.43, 1.50) increase of metformin C_{max} and AUC_{inf}, respectively, in the presence of tucatinib.

Table 1: IC_{50} and Inhibitory Potential Values ($I_{max,u}/IC_{50}$) of Tucatinib on Renal Proximal Tubule Transporters OCT2, MATE1, and MATE2-K, Determined Using Metformin or Creatinine as Probe Substrates

	Metformin		Creatinine	
Transporter	IC_{50} (µM)	$I_{max,u}/IC_{50}$	IC_{50} (µM)	$I_{max,u}/IC_{50}$
OCT2	14.7	0.0027	0.107	0.38
MATE1	0.340	0.12	0.0855	0.47
MATE2-K	0.135	0.30	ND	ND

IC_{50}, half maximal inhibitory concentration; $I_{max,u}$, the maximal unbound plasma concentration of the interacting drug at steady state, determined as 0.0403 µM (C_{max} of 1.39 µM and unbound fraction in plasma of 0.029, unpublished data); MATE, multidrug and toxin extrusion protein; OCT2, organic cation transporter 2; ND, not determined (insufficient MATE2-K mediated uptake of creatinine was observed compared with the control cells so the IC_{50} value was not determined). $I_{max,u}/IC_{50}$ potential for in vivo interactions from FDA Guidance (2020).

Impact of Tucatinib on Metformin Pharmacokinetics

Metformin Exposure (AUC_{inf}) Increased and Renal Clearance (CLr) Decreased in the Presence of Tucatinib.

- Metformin exposure (AUC_{inf}) increased approximately 1.4-fold in the presence of tucatinib (in line with PBPK model).
- Metformin plasma clearance (CL/F) geometric mean (CV%) decreased from 105 (27) to 77.4 (35) in the presence of tucatinib.
- Tucatinib had no apparent effect on metformin C_{max}, indicating the predominant impact was on metformin elimination.
- Metformin renal clearance (CL_{renal}) decreased from 29.99 L/h to 17.64 L/h in the presence of tucatinib.
- Given the wide therapeutic range of metformin, this DDI is unlikely to be clinically meaningful and will not require dose modification of metformin or tucatinib.
- **Together, these data demonstrate tucatinib to be a weak inhibitor of MATE1/2-K kidney transporters.**

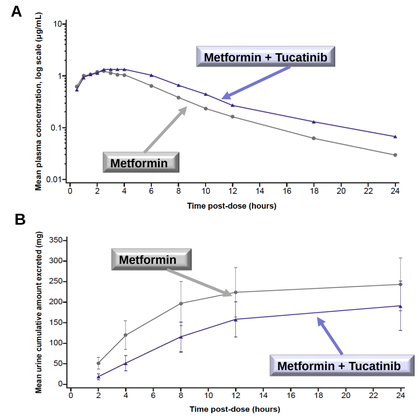


Figure 4: Metformin pharmacokinetics when administered alone (gray circles) or with tucatinib (purple triangles) (A) in plasma and (B) in urine.

Table 2: Metformin pharmacokinetics in plasma and urine in humans

Pharmacokinetic parameter	Metformin (n=17)	Metformin+TUC (n=17)	Metformin (n=17)	Metformin+TUC (n=17)	Estimate	90% CI
	Arithmetic mean (CV%)		*Geometric LSM*		*Geometric LSM ratio*	
Plasma						
AUC_{0-last} (h*µg/mL)	8.415 (26.2)	11.582 (29.9)	8.147	11.054	1.357	1.220, 1.509
AUC_{0-inf} (h*µg/mL)	8.608 (26.4)	12.129 (30.5)	8.333	11.558	1.387	1.251, 1.539
C_{max} (µg/mL)	1.334 (18.0)	1.470 (27.9)	1.314	1.418	1.079	0.951, 1.225
T_{max} (h)[a]	2.5 (1.5, 4.0)	3.0 (1.0, 4.1)	–	–	–	–
$t_{1/2}$ (h)	4.546 (11.7)	5.569 (12.2)	–	–	–	–
CL/F (L/h)	105.4 (26.7)	77.4 (34.9)	–	–	–	–
Urine			–	–	–	–
A_{e0-24} (mg)	242.62 (26.5)	190.79 (31.7)	–	–	–	–
F_{e0-24} (%)	28.54 (26.5)	22.44 (31.7)	–	–	–	–
CL_{renal} (L/h)	29.99 (27.0)	17.64 (36.0)	–	–	–	–

A_{e0-24}, mean amount of metformin excreted unchanged in urine; AUC_{0-inf}, area under the plasma concentration–time curve from time zero to infinity; AUC_{0-last}, area under the plasma concentration–time curve from time zero to the last available measurement; CI, confidence interval; CL/F, apparent oral clearance; CL_{renal}, renal clearance; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; F_{e0-24}, mean cumulative fraction of metformin excreted unchanged in urine; LSM, least squares mean; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}. [a]Median (range) is presented

Impact of Tucatinib on Iohexol PK and PD Parameters

Iohexol Plasma Clearance Did Not Change in the Presence of Tucatinib

- Iohexol concentration-time profiles and aGFR GM (CV%) values calculated from iohexol PK were unchanged in the absence and presence of tucatinib (94.99 (17.4) and 94.56 (16.9) mL/min/1.73m^2, respectively).

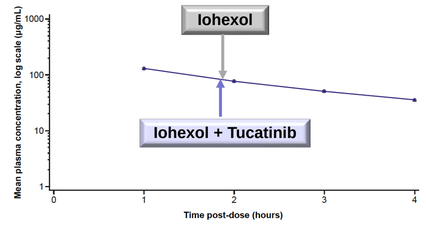


Figure 5: Iohexol pharmacokinetics when administered alone (gray circles) or with tucatinib (purple triangles).

PD Parameters Behaved as Expected in the Presence of Tucatinib

- SCr increased and creatinine clearance decreased in the presence of tucatinib, in line with what was expected based on the in vitro data.
- Cystatin C and urine albumin values were consistently within normal clinical range throughout the study, indicating that there was no negative impact on kidney function.
- eGFR using cystatin C was in agreement with iohexol aGFR

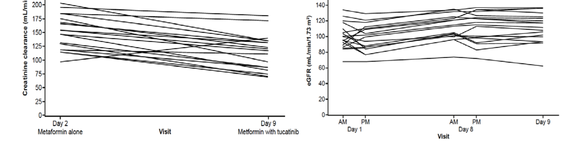


Figure 6: Individual values for (A) creatinine clearance, (B) eGFR calculated from cystatin-C over time.

Conclusions

- Tucatinib inhibition of OCT2 and MATE1/2-K in vitro is substrate dependent.
- Extent of metformin inhibition (1.4-fold increase) showed tucatinib to be a weak inhibitor of MATE1/2-K renal extrusion transporters.
- While increases in SCr were observed, there was no impact on aGFR or eGFR.
- **Together, these data demonstrate that the observed SCr increase in clinical studies with TUC is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1 and not due to an effect on kidney function.**

References: [1]Murthy et.al., N Engl J Med 2020; 382:597-609; 2Chappell et.al., Clin Pharmacol Ther. 2019; May 105(5): 1187-1195

DISCLOSURES: ATE, AL, JM, ELR, LA, LW, CJE are employees of Seattle Genetics, Inc.

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