Tucatinib Does Not Alter Oxaliplatin PK or Associated Renal Function: An OCT2 and MATE Transport Inhibition Study

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Background

- Tucatinib is a potent HER2-directed TKI that has received:
  - Approval for adult patients with HER2+ metastatic breast cancer who have received one or more prior anti-HER2 therapies in the metastatic setting, and
  - Accelerated approval for adult patients with RAS WT HER2+ metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine- oxaliplatin- and irinotecan-based chemotherapy (US only)[1]
- Tucatinib inhibits MATE-mediated transport of metformin and creatinine in vitro and in vivo.[2]
- Oxaliplatin-containing regimens are frequently utilized to treat GI cancers.
- Oxaliplatin is eliminated predominately via urinary excretion.
  - GFR and active tubular secretion via OCT2 (uptake) and MATE1/2-K (efflux) contribute to oxaliplatin excretion though the contribution of active transport to oxaliplatin clearance is not fully elucidated.
- TKIs are frequently found to interact with OCT2/MATE transporters;[3] however, a gap in knowledge remains between their clinical potential to impact oxaliplatin PK and in turn, impact renal function.
- SGNTUC-024 (NCT04430738) is a Phase 1b/2 clinical study in patients with HER2+ GI cancers.
  - Cohorts 1A and 1B evaluated the impact of tucatinib on oxaliplatin PK and renal function.

Methods

- An in vitro inhibition study was conducted to determine the impact of tucatinib (0.005-25 µM) on OCT2/MATE-mediated transport of oxaliplatin (20 µM). Incubations (20 min) were performed in OCT2, MATE1, or MATE2-K-expressing MDCK-II cells.
- In the clinical study SGNTUC-024, patients in the dose escalation cohorts (1A/B) received tucatinib 150 mg (Cohort 1A) or 300 mg (Cohort 1B) BID starting on C1D8 of a 2-week cycle in combination with FOLFOX (**Figure 1**). Cohorts 1A/B enrolled patients with HER2+ colorectal, gastric, bile duct, esophageal and GEJ cancers.

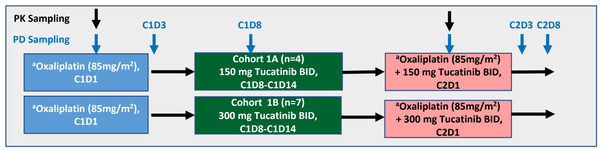

Figure 1: SGNTUC-024 dose administration, PK, and PD timepoints for Cohorts 1A and 1B
[a]Oxaliplatin dosed as part of FOLFOX regimen

- Intensive PK was collected in plasma and urine for oxaliplatin alone (C1D1) or with steady-state tucatinib (C2D1). PK and PD data are shown from PK-evaluable patients.
- Total plasma Pt (analyzed as a surrogate for oxaliplatin and catabolites), PUF Pt (unbound), and urine Pt were quantitatively analyzed via ICP-MS.
- SCysC was measured as a PD renal function marker. eGFR using SCysC was calculated using equations 1 and 2,[2] where SCysC is in mg/L and age is in years:

Eq. 1 $If\ SCysC \leq 0.8\frac{mg}{L}: 133x\left(\frac{SCysC}{0.8}\right)^{-0.499} x0.996^{Age} x\ 0.932\ if\ Female$

Eq.2 $If\ SCysC > 0.8\frac{mg}{L}: 133x\left(\frac{SCysC}{0.8}\right)^{-1.328} x0.996^{Age} x\ 0.932\ if\ Female$

Results

Tucatinib inhibits in vitro MATE1 and MATE2-K mediated transport of oxaliplatin

- FDA DDI guidance suggests that an investigational drug has potential to inhibit OCT2, MATE1 and MATE2-K transporters in vivo if $I_{max,u}/IC_{50}$ is ≥0.1.[4]
- Although tucatinib inhibited in vitro oxaliplatin transport by OCT2, the $I_{max,u}/IC_{50}$ of <0.1 values suggest minimal impact in vivo.
- Tucatinib $I_{max,u}/IC_{50}$values for MATE1 and MATE2-K were >0.1 at both 150 and 300 mg BID tucatinib $C_{max,u}$ values, suggesting potential in vivo inhibition.

Table 1. IC_{50} values for tucatinib inhibition of transport by renal transporters in MDCK-II cells using oxaliplatin as a probe substrate

Transporter	IC_{50} (µM)	$I_{max,u}/IC_{50}$	
		150 mg BID TUC	300 mg BID TUC
OCT2	0.49	0.02	0.05
MATE1	0.064	0.19	0.38
MATE2-K	0.038	0.31	0.64

$I_{max,u}$ = inhibitor maximum unbound concentration
$I_{max,u}$ from SGNTUC-024 tucatinib GM C_{max} values (using MW tucatinib of 480.52 and 2.9% unbound[1]) of 0.012 µM (150 mg BID cohort) and 0.024 µM (300 mg BID cohort)

Oxaliplatin (Platinum) plasma PK is not altered in the presence of tucatinib

- PK-evaluable patients included n=4 in Cohort 1A (150 mg BID tucatinib) and n=7 in Cohort 1B (300 mg BID tucatinib)
- Total plasma (bound) and plasma ultrafiltrate (unbound) platinum concentrations were similar with and without tucatinib (both cohorts).

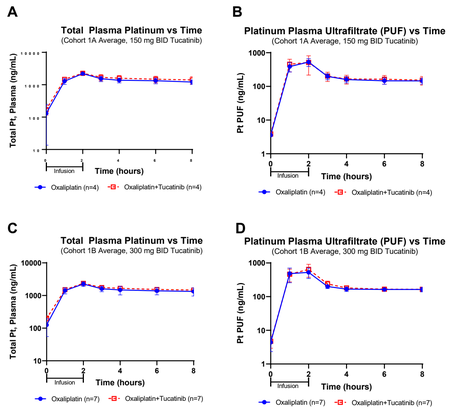

Figure 2: Platinum concentration-time profiles in total plasma (bound: **A**,**C**) or in PUF (unbound: **B**,**D**) in patients administered oxaliplatin without (blue circles) or with (red squares) either 150 mg BID tucatinib (**A**,**B**) or 300 mg BID tucatinib (**C**,**D**).

Oxaliplatin (Platinum) urine excretion is not altered in the presence of tucatinib (PK)

- Urinary platinum excretion 0-24h post-oxaliplatin (fraction of total oxaliplatin dose) was similar with and without tucatinib (both cohorts).

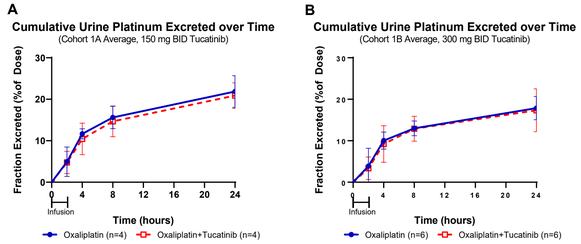

Figure 3: Platinum cumulative excretion in urine shown as percent of total oxaliplatin dose excreted over time in patients administered oxaliplatin without (blue circles) or with (red squares) either 150 mg BID TUC (A) or 300 mg BID tucatinib (B).

Table 2. Oxaliplatin PK parameters in plasma, PUF and urine in the absence (C1D1) and presence (C2D1) of 150 or 300 mg BID tucatinib

	150 mg BID Tucatinib (n=4)			300 mg BID Tucatinib (n=7[a])		
	C1D1	C2D1	GMR (90% CI)	C1D1	C2D1	GMR (90% CI)
Total Plasma Pt						
$AUC_{0\text{-}8h}$ (ng*hr/mL)	10430 (13)	11650 (20)	1.1 (0.98,1.3)	11210 (23)	12070 (10)	1.1 (0.96,1.2)
C_{max} (ng/mL)	2200 (6)	2250 (16)	1.0 (0.88,1.2)	2240 (15)	2350 (11)	1.1 (0.97,1.3)
PUF						
$AUC_{0\text{-}8h}$ (ng*hr/mL)	1700 (21)	1740 (44)	1.0 (0.78,1.4)	1880 (30)	1970 (26)	1.0 (0.98,1.1)
C_{max} (ng/mL)	520 (25)	490 (64)	0.94 (0.60,1.5)	500 (52)	590 (54)	1.2 (1.1, 1.3)
[a]Urine						
$f_{e,24h}$ (%)	22 (17)	21 (15)	0.96 (0.89, 1.0)	18 (16)	17 (35)	0.94 (0.73,1.2)
$CL_{0\text{-}8h}$ (mL/min)	277 (33)	249 (78)	0.90 (0.57, 1.4)	189 (37)	177 (40)	0.94 (0.81,1.1)

Abbreviations: $AUC_{0\text{-}8h}$ = area under the plasma/PUF curve from time 0 to 8h post oxaliplatin dose; C_{max} = maximum platinum concentration in plasma; $f_{e,24h}$ = fraction platinum excreted in the urine between 0 and 24h post oxaliplatin dose; $CL_{0\text{-}8h}$ = renal clearance from 0 to 8h post oxaliplatin dose (as plasma collected up to 8h post-dose); GMR = geometric mean ratio; CI = confidence interval. C1D1 and C2D1 PK values are reported as geometric mean (%CV)
[a]n=6 for PK in urine available from 300 mg BID tucatinib cohort.

Tucatinib PK following administration of 150 and 300 mg BID as expected

- Tucatinib steady-state PK after 7 days of 150 or 300 mg BID was in range of previously published values in healthy volunteers[5]

Table 3. Tucatinib geometric mean (CV%) plasma steady-state PK parameters (C2D1) following 150 or 300 mg BID tucatinib

PK Parameter	150 mg BID Tucatinib (n=4)	300 mg BID Tucatinib (n=7[a])
$AUC_{0\text{-}8h}$ (ng*h/mL)	1130 (110)	1970 (34)
C_{max} (ng/mL)	198 (110)	403 (43)

[a]One patient took 250 mg tucatinib BID, included in stats as tucatinib plasma concentrations within range of other patients taking 300 mg BID tucatinib.

Cystatin C and eGFR values were similar in the absence and presence of tucatinib (PD)

- Reversible slight increases in CysC (normalized to baseline) on day 3 of each cycle, irrespective of tucatinib, were observed.

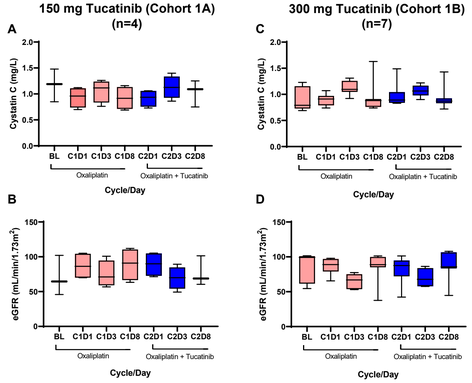

Figure 4: Serum Cystatin C (**A**,**C**) and eGFR calculated using Cystatin C (**B**,**D**) values in patients administered oxaliplatin without (Cycle 1) or with (Cycle 2) either 150 mg BID tucatinib (**A**,**B**) or 300 mg BID tucatinib (**C**,**D**).

Conclusions

- **This comprehensive investigation demonstrates that co-administration of tucatinib does not alter oxaliplatin plasma PK or renal clearance.**
- **Renal function (per Cystatin C assessment) was not impacted by combining tucatinib with oxaliplatin.**

Abbreviations
BID: twice a day; **C_{max}:** maximum platinum concentration in plasma; **DDI:** drug-drug interaction; **eGFR:** estimated glomerular filtration rate; **FDA:** Federal Drug Administration; **GEJ:** gastroesophageal junction; **GI:** gastrointestinal; **GMR**: geometric mean ratio; **HER2+:** human epidermal growth factor receptor positive; **$I_{max,u}$:** inhibitor maximum unbound concentration; **IC_{50}:** half maximum inhibitory concentration; **ICP-MS:** inductively coupled plasma mass spectrometry; **PD:** pharmacodynamic; **PK:** pharmacokinetic; **Pt:** platinum; **PUF:** plasma ultrafiltrate; **[S]CysC,:**[serum] Cystatin C; **TKI:** tyrosine kinase inhibitor; **TUC:** tucatinib; **WT:** wild-type

Disclosures
AT-E, **AL**, **VK**, **MU**, **JGM**, **LIA**, **CMH**, **JAW** and **CJE** are employees and shareholders of Seagen Inc.

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