Tucatinib Inhibits CYP3A, CYP2C8 and P-gp-mediated Elimination and is Impacted by CYP2C8 Inhibition in Healthy Volunteers

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Background

- Tucatinib (TUC) is a potent, highly selective HER2-directed tyrosine kinase inhibitor approved in the US for treatment of patients with HER2+ metastatic breast cancer.
- **Understanding potential drug-drug interactions (DDIs) is important to inform proper dosing when co-administering drugs.**
  - In vitro metabolism studies suggest that drug metabolizing enzymes CYP2C8 and CYP3A play a role in TUC metabolism.
  - ONT-993 is the predominant metabolite of TUC, formed by CYP2C8 (Fig. 1).
  - TUC exhibits competitive inhibition of CYP2C8, CYP2C9, CYP3A, and P-gp, and metabolism-dependent inactivation of CYP3A in vitro.

ONT-380-012 was a DDI study conducted to evaluate the magnitude of potential enzyme and transporter interactions for TUC (as a victim and perpetrator) and the safety of healthy volunteers when administered TUC doses at therapeutic levels (300 mg BID).

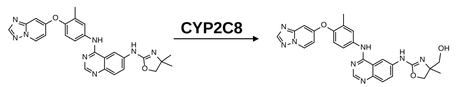


Figure 1: Chemical structures of tucatinib and ONT-993

Clinical Study Methods

- **Perpetrator:** Drug that instigates the interaction, potentially impacting efficacy/safety due to victim drug.
- **Victim:** Drug whose PK is impacted by the interaction, potentially leading to efficacy/safety events

- ONT-380-012 was a Phase 1, open-label, fixed-sequence DDI study of tucatinib conducted in 5 parts.
  - Healthy volunteers (n=116) at two centers were enrolled in the study.
  - Parts A-C evaluated the effects of a strong CYP2C8 inhibitor (gemfibrozil), a strong CYP3A inhibitor (itraconazole, ITZ), and a CYP3A/CYP2C8 inducer (rifampin, RIF) on single-dose tucatinib (300 mg) PK.
  - Parts D and E assessed the effects of steady-state tucatinib (300 mg BID) on single-dose PK of substrate probes for CYP2C8 (repaglinide), CYP2C9 (tolbutamide), CYP3A (midazolam, MDZ), and P-gp (digoxin).

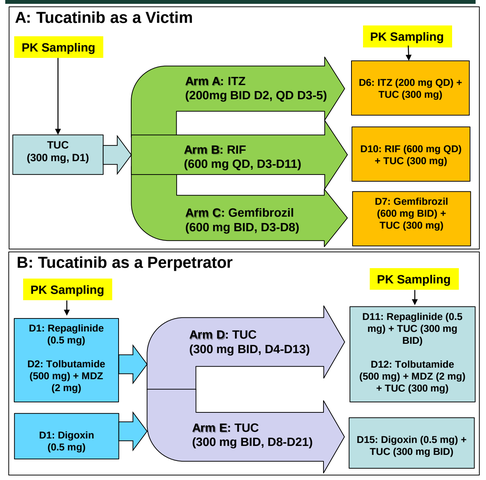
- Plasma samples were collected for PK analysis and drug concentrations were measured using validated LC-MS/MS methods.

- Safety outcome measures included incidence and severity of treatment-emergent adverse events (TEAEs), incidence of laboratory abnormalities based on hematology, clinical chemistry and urinalysis test results, electrocardiogram parameters, vital signs measurements and physical examinations.

Table 1: ONT-380-012 Study Demographics

Demographic Factor		Part A N=28	Part B N=28	Part C N=28	Part D N=17	Part E N=13
Age (years)	Mean (SD)	43 (10)	41 (11)	47 (13)	42 (12)	40 (13)
	Range	24-62	23-57	22-65	24-59	24-60
Sex (%)	Male	22 (79)	24 (86)	23 (82)	14 (82)	10 (77)
	Female	6 (21)	4 (14)	5 (18)	3 (18)	3 (23)
Ethnicity (%)	Hispanic/ Latino	8 (29)	19 (68)	10 (36)	3 (18)	9 (69)
	Not Hispanic/ Latino	20 (71)	9 (32)	18 (64)	14 (82)	4 (31)
Race (%)	White	9 (32)	24 (86)	20 (71)	6 (35)	8 (62)
	Black/African American	17 (61)	4 (14)	8 (29)	10 (59)	5 (39)
	Asian	1 (3.6)	--	--	--	--
	Other	1 (3.6)	--	--	1 (6)	--

Clinical Study Methods, Cont.



Blood samples were taken for the determination of analyte plasma concentrations for PK analysis. Intensive PK sampling was performed for tucatinib (Parts A-E), repaglinide (Part D), midazolam (Part D), tolbutamide (Part D), digoxin (Part E) and selected metabolites. Pre-dose blood samples were collected for trough plasma concentrations of itraconazole, rifampin, and gemfibrozil. Routine clinical and laboratory assessments were included in this DDI safety.

Figure 2: Clinical Study Schema for ONT-380-012, with tucatinib as a (A) victim and (B) perpetrator. All drugs were administered orally.

Impact of CYP3A and CYP2C8 Inhibitors/ Inducers on Tucatinib PK

Tucatinib is a CYP2C8 and CYP3A4 Substrate in Humans

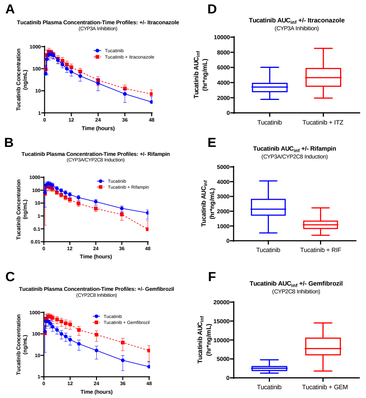


Figure 3: Tucatinib plasma concentration profiles (A-C) and AUC_{inf} values (D-F) in the absence and presence of steady-state itraconazole (A,D), rifampin (B,E) or gemfibrozil (C,F).

Impact of CYP3A and CYP2C8 Inhibitors/ Inducers on Tucatinib PK

- Tucatinib AUC_{inf} and C_{max} increased 3.04-fold and 1.62-fold in the presence of gemfibrozil, a strong CYP2C8 inhibitor.
  - The metabolite-to-parent AUC_{inf} ratio of ONT-993 also decreased from 0.18 to 0.05 in the presence of gemfibrozil, consistent with inhibition of CYP2C8-mediatied metabolite formation.
- Tucatinib AUC_{inf} and C_{max} both increased 1.3-fold in the presence of itraconazole, a strong CYP3A inhibitor.
- Tucatinib AUC_{inf} and C_{max} decreased by 48% and 37%, respectively, in the presence of rifampin, a strong CYP3A and CYP2C8 inducer.
- Together, this data shows tucatinib clearance in humans to be predominantly mediated by CYP2C8 and to a lesser extent by CYP3A.

Table 2: Summary of Tucatinib (300 mg, SD) C_{max} and AUC_{inf} Ratios in the Presence vs. Absence of Strong CYP3A and CYP2C8 Inhibitors and Inducer

Concomitant Drug (Dose)	Geometric Mean Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No Combination	
	C_{max}	AUC_{inf}
CYP3A Inhibition		
Itraconazole (200 mg BID,D2; QD D3-5)	1.32 (1.23, 1.42)	1.34 (1.26, 1.43)
CYP3A/2C8 Induction		
Rifampin (600 mg QD)	0.632 (0.531, 0.753)	0.520 (0.452, 0.597)
CYP2C8 Inhibition		
Gemfibrozil (600 mg BID)	1.62 (1.47, 1.79)	3.04 (2.66, 3.46)

BID = twice daily; QD = once daily C_{max} = maximum concentration; AUC = area under the curve; SD = single dose

Impact of Tucatinib on CYP3A, CYP2C8 and P-gp Substrate PK

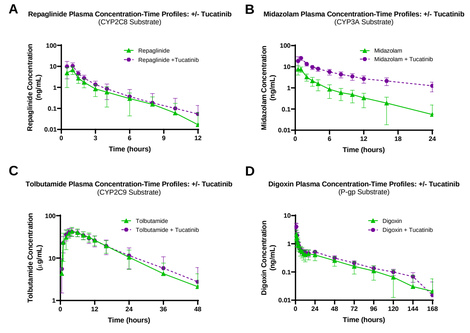


Figure 4: Plasma concentration profiles of (A) repaglinide, (B) midazolam, (C) tolbutamide or (D) digoxin in the absence and presence of steady-state tucatinib.

Impact of Tucatinib on CYP3A, CYP2C8 and P-gp Substrate PK (Cont.)

Tucatinib is a Strong CYP3A Inhibitor in Humans

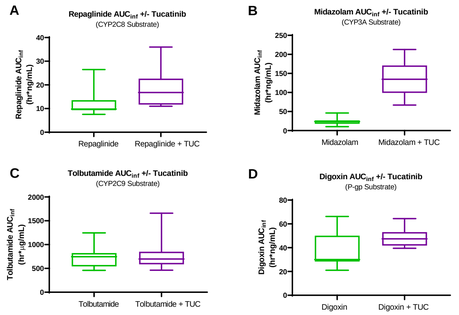


Figure 5: AUC_{inf} values of (A) repaglinide, (B) midazolam, (C) tolbutamide or (D) digoxin in the absence and presence of steady-state tucatinib.

- The exposures of midazolam, repaglinide, and digoxin increased in the presence of tucatinib.
  - Midazolam AUC_{inf} and C_{max} increased 5.7-fold and 3.1-fold, respectively.
  - Repaglinide and digoxin AUC_{inf} increased 1.7-fold and 1.5-fold, respectively.
- There was no change in tolbutamide exposure in the presence of tucatinib.
- Together, these data show tucatinib to be a strong CYP3A inhibitor and a weak CYP2C8 and P-gp inhibitor.

Table 3: Summary of C_{max} and AUC_{inf} Ratios of Sensitive CYP3A, CYP2C8, CYP2C9 and P-gp Substrates in the Presence vs. Absence of Tucatinib (300 mg BID)

Concomitant Drug (Dose)	Geometric Mean Ratio (90% CI) of Exposure Measures of Combination With/Without Tucatinib	
	C_{max}	AUC_{inf}
CYP2C8 Substrate Repaglinide (0.5 mg SD)	1.69 (1.37, 2.10)	1.69 (1.51, 1.90)
CYP3A4 Substrate Midazolam (2 mg SD)	3.01 (2.63, 3.45)	5.74 (5.05, 6.53)
CYP2C9 Substrate Tolbutamide (500 mg SD)	0.961 (0.904, 1.02)	1.05 (1.01, 1.09)
P-gp Substrate Digoxin (0.5 mg SD)	2.35 (1.90, 2.90)	1.46 (1.29, 1.66)

AUC= area under the curve; Cmax = maximum serum concentration; CYP3A= cytochrome P450 3A; CYP2C8 = cytochrome P450 2C8; CYP2C9 = cytochrome P450 2C9; P-gp= P-glycoprotein

Tucatinib Safety Profile in Healthy Volunteers

- All TEAEs were considered mild or moderate (Grade 1 or 2) in severity.
- The most frequently reported TEAEs considered related to TUC, as determined by the investigator, were increased blood creatinine and increased ALT.
- Post-dose serum creatinine elevations were reported but were determined to be due to a drug-drug interaction at the kidney transport level, and did not represent acute kidney injury. Serum creatinine levels returned to baseline upon discontinuing tucatinib.

Table 4: TUC-Related TEAEs of Clinical Interest in ≥2 Patients in the Total Study Population

		Part A N=28	Part B N=28	Part C N=28	Part D N=17	Part E N=13
TEAE / Grade				n (%)		
All TEAEs Related to TUC	G1	1 (3.6)	3 (10.7)	2 (7.1)	2 (11.8)	7 (53.8)
	G2	----	----	1 (3.6)	1 (5.9)	1 (7.7)
Diarrhea	G1/G2	1 (3.6)	----	----	----	1 (7.7)
Blood Creatinine Increased	G1/G2	----	1 (3.6)	----	1 (5.9)	5 (38.5)
ALT Increased	G1/G2	----	----	----	1 (5.9)	4 (30.8)
AST Increased	G1/G2	----	----	----	----	2 (15.4)
Blood Bilirubin Increased	G1/G2	----	1 (3.6)	----	----	----

G = Grade

Conclusions

- Tucatinib at therapeutic doses was well-tolerated in healthy volunteers.
- Together, these data indicate tucatinib is metabolized primarily by CYP2C8 and to a lesser extent via CYP3A.
- Tucatinib was found to be a strong inhibitor of CYP3A, a weak inhibitor of CYP2C8 and P-gp, and had no impact on CYP2C9-mediated metabolism in humans.
- **Clinical implications include:**
  - **Avoiding concomitant use of strong CYP2C8 inhibitors with tucatinib; if concomitant use cannot be avoided, reduce tucatinib dose to 100 mg BID**
  - **Avoiding concomitant use of tucatinib with a strong CYP3A inducer or moderate CYP2C8 inducer.**
  - **Avoiding concomitant use of tucatinib with CYP3A substrates. If concomitant use cannot be avoided, decrease the CYP3A substrate dosage in accordance with approved product labeling.**
  - **Consider reducing the dose of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.**

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

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