Pharmacokinetics of Tucatinib in Healthy and Hepatically-Impaired Volunteers

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Background

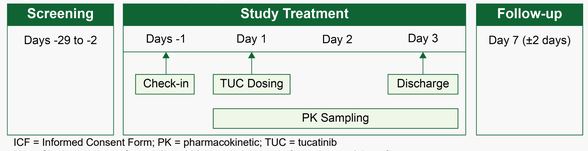
- Tucatinib is a selective human epidermal growth factor receptor 2 (HER2) targeted tyrosine kinase inhibitor approved by the FDA[1] and other regions for the treatment of adult patients with advanced unresectable or metastatic HER2+ breast cancer.
- Tucatinib is cleared via CYP2C8-mediated metabolism (to ONT-993), to a lesser extent by CYP3A, and subsequent biliary excretion.
- Hepatic impairment can cause alterations in drug disposition and pharmacokinetics (PK).[2]
- Given that tucatinib is primarily cleared by hepatic metabolism and biliary excretion, characterizing PK in participants with hepatic impairment was necessary to inform dosing recommendations.

ONT-380-009 (NCT03722823) was a clinical study conducted to evaluate the PK of tucatinib in volunteers with hepatic impairment based on Child-Pugh (CP) score compared to matched healthy participant controls.

Methods

- Volunteers (N=37) at 4 centers were enrolled in the study.
- Participants with mild (CP Class A; n=8), moderate (CP Class B; n=8) or severe (CP Class C; n=6) hepatic impairment were matched to participants with normal hepatic function (n=15) by age, BMI, and sex.
- Tucatinib was administered as a single 300 mg oral dose.
- Plasma samples were collected for PK analysis and tucatinib concentrations measured using validated LC-MS/MS methods.
- The PK and safety profiles between each hepatic impairment group and matched controls were compared.

Figure 1: ONT-380-009 Study Design Schematic



ICF = Informed Consent Form; PK = pharmacokinetic; TUC = tucatinib
Note: Single oral dose of tucatinib at 300 mg administered after at least a 2-hour fast.
Safety assessments completed from signing of ICF to follow-up visit.

Results

Table 1. Summary of Demographic Data

		Normal Hepatic Function (n=15)	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)
Age (years)	Mean (SD)	52 (11.9)	51 (9.8)	55 (10.1)	59 (6.5)
Sex	Male	10 (66.7%)	8 (100%)	4 (50.0%)	5 (83.3%)
	Female	5 (33.3%)	---	4 (50.0%)	1 (16.7%)
Race	American Indian or Alaska Native	---	---	1 (12.5%)	---
	Asian	2 (13.3%)	---	---	---
	Black or African American	1 (6.7%)	2 (25.0%)	---	---
	White	12 (80.0%)	6 (75.0%)	7 (87.5%)	6 (100%)
Ethnicity	Hispanic or Latino	5 (33.3%)	3 (37.5%)	5 (62.5%)	2 (33.3%)
	Not Hispanic or Latino	10 (66.7%)	5 (62.5%)	3 (37.5%)	4 (66.7%)
Weight (kg)	Mean (SD)	84.6 (15.2)	91.2 (16.9)	76.9 (11.8)	93.2 (12.7)
Height (cm)	Mean (SD)	172 (10.7)	175 (6.9)	167 (8.0)	170 (9.1)
BMI (kg/m^2)	Mean (SD)	28.6 (4.8)	29.9 (5.4)	27.7 (4.9)	32.1 (3.0)

Abbreviations: BMI= body mass index; n = number of participants; SD = standard deviation

Pharmacokinetics of Tucatinib and ONT-993 in Healthy Compared to Hepatically-Impaired Volunteers

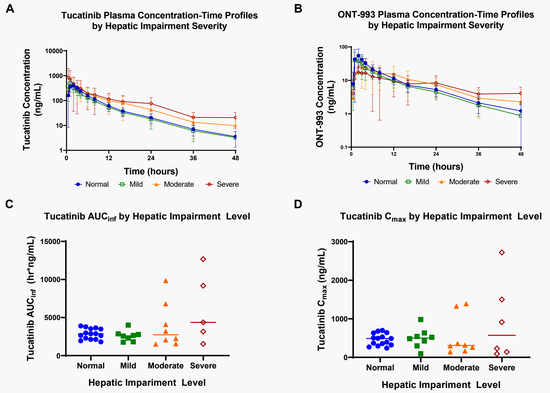


Figure 2: Tucatinib plasma concentration-time profiles (A), AUC_{inf} (C) and C_{max} (D) and ONT-993 plasma concentration-time profiles (B) after a single oral dose of 300 mg tucatinib in participants with normal hepatic function (blue circles) and participants with mild (green squares), moderate (orange triangles), or severe hepatic impairment (open red diamonds).

Tucatinib and ONT-993 plasma concentration-time profiles were similar between participants with mild hepatic impairment and healthy controls.

Participants with moderate or severe hepatic impairment had generally increased tucatinib exposure compared to healthy controls and exhibited large inter-participant variability.

- Tucatinib C_{max} and $AUC_{0-\infty}$ ranged from 67% lower to 3.2-fold higher and 46% lower to 3.6-fold higher in participants with moderate hepatic impairment, respectively, compared to geometric mean (GM) for healthy controls.
- Tucatinib C_{max} and $AUC_{0-\infty}$ ranged from 79% lower to 6.2-fold higher and 45% lower to 4.6-fold higher in participants with severe hepatic impairment, respectively, compared to GM for healthy controls.
- GM ONT-993 to tucatinib metabolite to parent ratio based on $AUC_{0-\infty}$ (MR_{AUC}) was similar for moderate hepatic impairment (not calculated for severe) and metabolite to parent ratio based on C_{max} (MR_{Cmax}) was ~2-fold lower for participants with moderate and severe hepatic impairment compared to healthy controls.

Tucatinib unbound PK was highly variable but similar within all groups.

- GM fraction unbound (f_u) tucatinib ranged from 0.027 to 0.040.

Table 2. Plasma PK parameters of tucatinib following administration of a single oral dose of 300 mg in participants with normal hepatic function and with mild, moderate, or severe hepatic impairment.

PK Parameter	Normal Hepatic Function (n=15)	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)
$AUC_{0\text{-}t}$ (h*ng/mL)	2710 (25.7)	2450 (29.0)	3040 (76.1)	3830 (103)
$AUC_{0-\infty}$ (h*ng/mL)	2760 (25.7)	2510 (26.9)	3140 (77.7)	4770 (102)[b]
C_{max} (ng/mL)	436 (36.3)	423 (78.2)	374 (104)	471 (240)
[a]T_{max} (h)	2.0 (1.0-3.0)	1.0 (1.0-3.0)	2.0 (1.0-4.0)	1.5 (0.5-4.0)
$t_{1/2}$ (h)	8.67 (1.35)	9.64 (3.62)	9.16 (1.48)	12.4 (1.85)[b]
CL/F (L/h)	109 (25.7)	120 (26.9)	95.5 (77.7)	62.9 (102)[b]
MR_{AUC}	0.159 (30.2)	0.146 (49.1)	0.129 (29.3)[c]	NC
MR_{Cmax}	0.125 (36.6)	0.081 (61.1)	0.070 (82.8)	0.028 (46.4)
f_u	0.028 (39.0)	0.031 (38.1)	0.040 (31.3)	0.027 (48.5)

Note: Geometric mean (%CV) data are presented. Abbreviations: $AUC_{0\text{-}t}$ = area under the concentration-time curve from time 0 to the time of last measurable concentration; $AUC_{0-\infty}$ = AUC from time 0 to infinity; C_{max} = maximum observed plasma concentration; Tmax = time of maximum observed plasma concentration; $t_{1/2}$ = apparent plasma terminal elimination half-life; CL/F = apparent total plasma clearance; MR_{AUC} = metabolite to parent ratio of ONT-993 to tucatinib based on $AUC_{0-\infty}$; MR_{Cmax} = metabolite to parent ratio based on Cmax; f_u = unbound fraction in plasma; NC = not calculated. [a]Median (Min-Max) data are provided for Tmax. [b]n=5; [c]n=7

Geomean ratios (GMR) of tucatinib PK parameters show participants with mild hepatic impairment to be similar to healthy controls and <2-fold increase (Table 3) in participants with moderate or severe hepatic impairment compared to healthy controls.

- Changes in tucatinib C_{max} and exposure between moderate or severe hepatic impairment compared to healthy controls exhibited high inter-participant variability (as reflected in the 90% CIs).
- GMR values for tucatinib $AUC_{0-\infty}$ were 1.15-fold and 1.61-fold higher in moderate and severe groups, respectively (compared to healthy controls).

Table 3. Statistical analyses of tucatinib plasma PK following administration of a single oral dose of 300 mg to participants with normal hepatic function and with mild, moderate, or severe hepatic impairment.

PK Parameter	Statistic	Mild vs. Normal (n=8)	Moderate vs. Normal (n=8)	Severe vs. Normal (n=6)
C_{max}	[a]GMR	1.04	0.885	1.17
	[b]90% CI	(0.616, 1.75)	(0.421, 1.86)	(0.366, 3.77)
$AUC_{0\text{-}t}$	[a]GMR	0.980	1.13	1.43[c]
	[b]90% CI	(0.743, 1.29)	(0.652, 1.97)	(0.706, 2.90)
$AUC_{0-\infty}$	[a]GMR	0.990	1.15	1.61
	[b]90% CI	(0.763, 1.28)	(0.653, 2.02)	(0.673, 3.85)

Abbreviations: GMR = geometric mean ratio; CI = confidence interval.
[a]GMR for natural log transformed parameter, natural log transformed back to the linear scale.
[b]90% CI for GMR of natural log transformed parameter, natural log transformed back to the linear scale.
[c]n=5

Safety of tucatinib in participants with mild, moderate, and severe hepatic impairment was similar to matched controls.

- Three treatment-emergent adverse events (TEAEs) were observed in three total participants. Two TEAEs occurred in participants with mild hepatic impairment, and one occurred in a participant with normal hepatic function.
  - Two TEAEs were Grade 1 and one TEAE was Grade 2 in severity.
  - Two TEAEs, Grade 1 nausea and Grade 2 transaminase increased, were considered related to tucatinib.
- Except for one TEAE of transaminase increased, no clinically significant findings in clinical laboratory evaluations, vital signs, ECGs, or physical examinations were reported.
- No deaths or serious adverse events were reported, no participants were withdrawn from the study due to TEAEs, no TEAEs required concomitant medication, and all TEAEs resolved.

Conclusions

- Overall, a single 300 mg oral dose of tucatinib was considered safe and well tolerated in this study for participants with normal hepatic function or with mild, moderate, or severe hepatic impairment.
- Compared to participants with normal hepatic function, those with mild hepatic impairment had similar tucatinib exposures and participants with moderate hepatic impairment had slightly increased tucatinib exposures ($AUC_{0-\infty}$GMR = 1.15).
- Tucatinib exposure was generally increased in participants with severe hepatic impairment; despite large inter-individual variability, the overall $AUC_{0-\infty}$ GMR was 1.6-fold compared to healthy controls.
- The 1.6-fold GMR AUC_{inf} increase in severe hepatic impairment participants supports the recommendation in the tucatinib label[1] to dose reduce from 300 mg twice daily (BID) to 200 mg BID in patients with severe hepatic impairment; no dose adjustment is recommended for patients with mild or moderate hepatic impairment.

References

1. TUKYSA [package insert]. Bothell, WA. Seagen Inc., 2020.
2. Rodighiero V. Clin Pharmacokinet. 1999 Nov;37(5):399-431.

DISCLOSURES: ATE, AL, JM, HS, LA, ER, LW, and CJE are employees and shareholders of Seagen Inc.

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