

Table S2. Summary of statistical analysis of primary pharmacokinetic parameters of midazolam and warfarin and their major metabolites, before and after co-administration of ceritinib at 750 mg orally QD for 3 weeks

Pharmacokinetic parameter (unit)	n	Adjusted geometric mean	Treatment comparison: Geometric mean ratio (90% CI) ¹
CYP3A			
Midazolam			
AUC_{0-inf} (ng*hr/mL)			
midazolam	20	72.5	5.42
midazolam + ceritinib	20	393	(4.64, 6.34)
C_{max} (ng/mL)			
midazolam	20	23.0	1.82
midazolam + ceritinib	20	42.0	(1.54, 2.16)
1'-hydroxymidazolam			
AUC_{0-inf} (ng*hr/mL)			
midazolam	19	16.2	0.947
midazolam + ceritinib	13	15.4	(0.729, 1.23)
C_{max} (ng/mL)			
midazolam	19	5.43	0.351
midazolam + ceritinib	19	1.90	(0.260, 0.472)
CYP2C9			
S-warfarin			
AUC_{0-inf} (ng*hr/mL)			
warfarin	18	21200	1.54
warfarin + ceritinib	10	32800	(1.36, 1.75)
C_{max} (ng/mL)			
warfarin	20	569	1.05
warfarin + ceritinib	19	598	(0.912, 1.21)
R-warfarin			
AUC_{0-inf} (ng*hr/mL)			
warfarin	10	36300	1.07
warfarin + ceritinib	4	38900	(0.857, 1.33)
C_{max} (ng/mL)			
warfarin	20	560	1.10
warfarin + ceritinib	20	616	(0.969, 1.25)
7-hydroxy-S-warfarin			
AUC_{0-inf} (ng*hr/mL)			
warfarin	12	3090	1.08
warfarin + ceritinib	5	3330	(0.814, 1.43)
C_{max} (ng/mL)			
warfarin	16	39.1	0.890
warfarin + ceritinib	13	34.8	(0.777, 1.02)

Model was a linear mixed effects model of the log-transformed AUC_{0-inf} and C_{max} , and included treatment as a fixed effect and patient as a random effect.

Adjusted geometric mean, geometric mean ratio, and 90% confidence interval (90% CI) of AUC_{0-inf} and C_{max} were all determined from the model and values were back-transformed from log-scale.

AUC_{0-inf} : area under the plasma concentration-time curve $t=0-\infty$; C_{max} : maximum plasma concentration observed; n : number of observations included in the analysis.

¹ Probe substrate + ceritinib / probe substrate alone.