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Updated Population Pharmacokinetic Model of Cabozantinib Integrating Various Cancer Types Including Hepatocellular Carcinoma

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Abstract

An integrated population pharmacokinetic (PPK) model was used to evaluate the effects of liver dysfunction on the pharmacokinetics (PK) of cabozantinib in patients with hepatocellular carcinoma and to determine whether clinical dosage adjustment may be necessary in this population. An integrated PPK model previously developed in healthy volunteers and patients with various cancer types was updated with cabozantinib concentration data from hepatocellular carcinoma patients in phase 2 and 3 studies (total 2023; hepatocellular carcinoma 489 patients). Covariate effects of cancer type including hepatocellular carcinoma population and liver dysfunction per the National Cancer Institute Organ Dysfunction Working Group criteria were evaluated (normal 1425; mild liver dysfunction 558; moderate/severe liver dysfunction 15/1 patients). With hepatocellular carcinoma patients, PK parameter estimates and covariate effects were similar to the previous PPK model (2 compartments with first- and zero-order absorption and first-order elimination). Only medullary thyroid cancer had appreciable PK differences from healthy volunteers. PK parameter estimates were similar with and without addition of liver dysfunction covariates. Patients with mild liver dysfunction were predicted to have minimal differences in apparent clearance of cabozantinib relative to patients with normal liver function. Therefore, no initial cabozantinib dosage adjustment is recommended for cancer patients with mild liver dysfunction. The small sample size for patients with moderate and severe liver dysfunction limited dosing recommendations in these subpopulations. The results from this PPK analysis were different from those of the single-dose hepatic impairment study in healthy volunteers and more reflective of exposure in cancer patients following daily cabozantinib dosing.

Keywords

cabozantinib, hepatocellular carcinoma, liver dysfunction, population pharmacokinetics

Cabozantinib is an inhibitor of receptor tyrosine kinases, including hepatocyte growth factor receptor, vascular endothelial growth factor receptor 2 (VEGFR2), AXL (GAS6 receptor), and RET (glial cell-derived neurotrophic factor receptor), known to promote tumor growth, metastasis, and angiogenesis.[1] In addition to these targets, cabozantinib inhibits a number of other receptor tyrosine kinases implicated in tumor pathobiology including VEGFR1, VEGFR3, MER, TYRO3, KIT, FLT3, ROS1, TRKB, and TIE2.

Cabozantinib is being developed for the treatment of a variety of advanced solid tumors. Available formulations include capsules and tablets, which are not interchangeable.[2] Cabozantinib (capsules, 140 mg) is approved in the United States for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC.[3,4] Cabozantinib (tablets, 60 mg) is indicated in the United States, Europe, and other regions for advanced renal cell carcinoma (RCC) (different patient populations depending on region).[5,6]

Recently, cabozantinib (tablets, 60 mg) has been approved in the United States and Europe for hepatocellular carcinoma patients who have been previously treated with sorafenib.[5,6] The hepatocellular carcinoma approval was based on the randomized placebo-controlled phase 3 study (CELESTIAL) in subjects with advanced hepatocellular carcinoma who had received previous therapy with sorafenib. Subjects in CELESTIAL were required to have progressed during or following previous systemic therapy, and up to 2 previous lines of systemic therapy were allowed.[7] This pivotal trial showed a significant improvement in overall survival for cabozantinib with median overall

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survival of 10.2 months for cabozantinib as compared to 8.0 months for placebo (hazard ratio for death, 0.76; 95%CI, 0.63 to 0.92; $P = .005$).

Cabozantinib is a substrate of cytochrome P450 (CYP) 3A4 in vitro.[8] In healthy volunteers (HV), cabozantinib plasma exposure by area under the plasma concentration-time curve (AUC) was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin.[9]

A population pharmacokinetic (PPK) model of cabozantinib was previously developed in HV and patients with various malignancies including MTC, RCC, castration-resistant prostate cancer (CRPC), and glioblastoma multiforme.[10] Age, weight, sex, race, and cancer type were predicted to have low impact on cabozantinib apparent clearance (CL/F), except for MTC; patients with MTC show approximately 90% higher CL/F relative to HV. Cabozantinib was also studied in HV with varying degrees of liver dysfunction based on the Child-Pugh (CP) criteria. Cabozantinib exposure (AUC) after a single dose increased by 81% and 63% in CP-A (mild) and CP-B (moderate) liver impairment, respectively, compared with matched HV with no liver dysfunction.[11] The pharmacokinetics (PK) of cabozantinib in cancer patients with liver dysfunction had not been studied. To investigate cabozantinib PK in cancer patients with liver dysfunction, the previously developed PPK model was updated to include data from hepatocellular carcinoma patients with CP-A liver dysfunction from the CELESTIAL trial (99% had CP-A classification) and from a phase 2 randomized discontinuation trial (RDT). To further understand the effect of liver dysfunction on the PK of cabozantinib in cancer subjects across studies and cancer types, the liver function status was classified by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, which stratifies liver function based on total bilirubin (TB) and aspartate aminotransferase (AST) levels. The PPK analysis investigated whether dose adjustment is necessary for patients with hepatocellular carcinoma and other cancer types with liver dysfunction.

Methods

Clinical Trials Pooled Data

All protocols were approved by institutional review boards of participating institutions, and written informed consent was obtained from all HV and patients prior to enrollment. The cabozantinib PPK model was developed using data pooled from 10 clinical studies. The clinical trials included a phase 1 study in cancer patients with advanced malignances,[12] 2 phase 1 studies in HV,[2] phase 2 studies in patients with glioblastoma[13] and CRPC[14,15] or hepatocellular carcinoma,[16] and phase 3 studies in patients with MTC,[17] CRPC,[18] RCC,[19] or hepatocellular carcinoma.[7] Details regarding the design and PK sampling scheme for each study are provided in Supplementary Table S1. The 2 studies pertinent to hepatocellular carcinoma patients used in the updated PPK model are described in Table 1, which includes the phase 2 RDT[16] and phase 3 CELESTIAL[7] study.

Bioanalytical Assay

Cabozantinib concentrations in plasma matrix were quantified using a validated liquid chromatographic-tandem mass spectrometry assay with 0.5 ng/mL as the lower limit of quantification.[8]

Analysis of Data Files

The analytical data preparation was previously described by Lacy et al[10] with new liver dysfunction covariates defined by the NCI-ODWG criteria.[20] From Supplementary Table S2, the classification stratifies liver dysfunction into 4 groups according to TB and AST levels: normal (TB and AST $\leq$ upper limit of normal [ULN]), mild (TB $\leq$ ULN and AST $>$ ULN or TB $>$ 1-3 $\times$ ULN with any AST), moderate (TB $>$ 1.5-3 $\times$ ULN with any AST level), or severe (TB $>$ 3 $\times$ ULN with any AST level). A summary of demographics and covariates for hepatocellular carcinoma patients and of all studies is presented in Table 2 with details of all 10 trials in Supplementary Table S3.

Population PK Model

The analysis was performed by nonlinear mixed-effects modeling using the NONMEM software system, version 7.3 (ICON Development Solutions, Ellicott City, Maryland). Estimation methods that include stochastic approximation expectation-maximization and importance sampling were used for parameter estimation.[21] Pre- and postprocessing of data from each modeling step were performed using SAS (SAS Institute, Cary, North Carolina), S-plus (TIBCO, Palo Alto, California), and/or R (R Foundation, Vienna, Austria). Graphical analysis of the data or output from the models was performed using S-plus or R.

Prior Integrated PPK Model

An integrated PPK model was previously developed to characterize the cabozantinib concentration-time profile in HV and subjects with various cancer types.[10] The exponential relationship was applied to the model's interindividual variability for the PK parameters. The relationship between continuous covariates and typical value of PK parameters was modeled using the power function with centering by median values. Categorical covariates were recoded to indicator variables and represent multiplicative change from the typical PK

Table 1. Study Description and PK Sampling Summary for HCC Studies

Phase Study	Design	Nominal Doses	PK Sampling
Phase 2 (RDT) Study XL184-203	RDT of cabozantinib in patients with advanced solid tumors, including HCC	100-mg FBE capsule once daily	Predose at the end of "even" weeks after WK12 lead-in period (eg, 18, 24, ...) or early termination or adverse event
Phase 3 (CELESTIAL) Study XL184-309	Randomized, double-blind, controlled study of cabozantinib vs placebo in patients with HCC who have received prior sorafenib	60-mg FBE tablet once daily	~8 hours or more after the previous dose of study treatment on the WK3D1, WK5D1, and WK9D1 visits

D indicates day; FBE, free base equivalent; HCC, hepatocellular carcinoma; PK, pharmacokinetic; RDT, randomized discontinuation trial; WK, week.

parameter. The residual variability was modeled using the log-transformed additive-error model. The 90%CIs were calculated from standard errors outputted from successful NONMEM covariance step.

All studies listed in Supplementary Table S1 were used to develop this model except CELESTIAL (Study XL184-309) and hepatocellular carcinoma subjects from RDT (Study XL184-203) (Table 1). The integrated PPK model was a 2-compartment model with first-order elimination and combined zero-order and first-order absorption. The first-order absorption process included a lag time and a dose-dependent effect on the absorption rate (K_a) that was characterized using a power model. In addition, a formulation effect was included on K_a and relative bioavailability based on earlier findings from a capsule and tablet bioequivalence study.[2]

K_a and relative oral bioavailability for the capsule formulation were 58% and 14% lower than the reference tablet formulation, respectively.[10] Prespecified covariates including formulation, age, sex, race, body weight, and cancer types were included in the integrated PPK model. The magnitude of these covariate effects was generally small except for the MTC population, which was predicted to have an approximately 93% increase in apparent clearance resulting in over 40% lower steady-state maximum plasma drug concentration ($C_{max,ss}$) and 50% lower steady-state minimum plasma drug concentration ($C_{min,ss}$) relative to HV.[10]

Updating the Prior Integrated PPK Model

The previously described integrated cabozantinib PPK model and the concentration-time data from hepatocellular carcinoma subjects in CELESTIAL and RDT trials were used to perform an external visual predictive check (VPC)[22] in order to assess the predictive performance of the integrated PPK model for the hepatocellular carcinoma population. Following the external visual predictive check, the integrated PPK model was refit to the updated data set including subjects with hepatocellular carcinoma. In addition to liver dysfunction, the impact of previously evaluated demographic covariates and cancer type was reevaluated in the updated data set. Finally, a VPC was performed on the final updated model following the reassessment of covariate effects. All covariates in the prior model were kept and evaluated in the updated model.

Covariate Effects

The impact of covariates was assessed on steady-state CL/F for specified covariate values (ie, test conditions) relative to a reference set of covariate values. The reference condition was defined as a healthy white male subject with a body weight of 80 kg, 60 years of age, receiving a 60-mg free base equivalent cabozantinib tablet dose once daily with steady-state PK profile simulated on day 57. The test condition differs from the reference by changing a specific covariate value. All other covariate values were identical to the reference. For continuous covariates such as age and weight, 5th and 95th percentiles in the updated integrated analysis data set (age 37 and 79 years; weight 54 and 109 kg) were used to represent extreme covariate values.

Results

Data

The updated integrated PPK analysis included 9510 quantifiable cabozantinib concentrations from 2023 subjects, including 489 hepatocellular carcinoma patients.

Nearly all patients (99%) had a CP-A classification. The median age was 64 years (range 18 to 87 years), and median body weight was 78 kg (range 30.4 to 190.7 kg). Cancer patients were generally older (20 to 87 years) than healthy subjects (18 to 55 years). Subjects were predominately male (84%) and white (77%). Per NCI-ODWG criteria, most subjects had normal liver function (70%) or mild liver dysfunction (28%). Approximately one third of the data were obtained with the capsule formulation and two thirds with the tablet formulation.

Table 2. Demographics by HCC Studies and All Studies

	XL184-203 RDT-HCC Cohort	XL184-309 CELESTIAL	All Studies
Number of subjects, n (%)	37 (2)	452 (22)	2023
Age (y)			
Mean (SD)	59.2 (11.5)	63 (10.9)	61.7 (12.7)
Median	60	64	64
Range	32-82	22-86	18-87
Sex, n (%)			
Male	28 (76)	365 (81)	1706 (84)
Female	9 (24)	87 (19)	317 (16)
Body weight,[a] kg			
Mean (SD)	76 (20.3)	70.8 (15.0)	79.5 (17.5)
Median	73.9	68.9	78
Range	52.0-126.3	35.0-130.0	30.4-190.7
Race, n (%)			
White	20 (54)	253 (56)	1556 (77)
Black	3 (8)	8 (2)	53 (3)
Asian	13 (35)	152 (33)	211 (10)
Other	0	8 (2)	47 (2)
Unknown	1 (3)	31 (7)	156 (8)
Population, n (%)			
Healthy volunteers	0	0	140 (7)
Castration-resistant prostate cancer	0	0	823 (41)
Renal cell carcinoma	0	0	282 (14)
Metastatic medullary thyroid cancer	0	0	210 (10)
Glioblastoma multiforme	0	0	39 (2)
Hepatocellular carcinoma	37 (100)	452 (100)	489 (24)
Other malignancies	0	0	40 (2)
Formulation, n (%)			
Capsule	37 (100)	0	648 (32)
Tablet	0	452 (100)	1375 (68)
Liver Dysfunction,[b] n (%)			
Normal	12 (32)	128 (28)	1425 (70)
Mild	24 (65)	308 (68)	558 (28)
Moderate	1 (3)	11 (2)	15 (1)
Severe	0	1 (<1)	1 (<1)
Missing	0	4 (1)	24 (1)

HCC indicates hepatocellular carcinoma; RDT, randomized discontinuation trial.

[a]Body weight is missing for 7 patients, including 1 patient from CELESTIAL.

[b]Liver dysfunction per National Cancer Institute Organ Dysfunction Working Group criteria.

Updated Integrated Population PK Model

Cabozantinib concentrations in patients with hepatocellular carcinoma were predicted using the previously described integrated PPK model. The predictive performance of the model was evaluated assuming the reference condition for hepatocellular carcinoma relative to RCC patients, for whom the model was first developed. The external VPC in Figure 1 showed that the observed concentrations were generally contained within the prediction intervals, suggesting that cabozantinib PK for hepatocellular carcinoma is similar to that for RCC patients. From this exploratory analysis, initial values were used from the previous integrated model in developing the updated model.

A 2-compartment model with first-order elimination and dual absorption (first- and zero-order) processes adequately described the observed cabozantinib PK data. Initially, the hepatocellular carcinoma population effect on CL/F and apparent central distribution volume (Vc/F) was evaluated in addition to the previously defined covariates in the earlier integrated PPK model. Subsequently, the effect of liver dysfunction per NCI-ODWG criteria on CL/F and Vc/F was assessed using the categorical covariates of mild and combined moderate/severe liver dysfunction per NCI-ODWG criteria due to limited data for these latter 2 groups. The additional 4 parameters to the model to describe liver dysfunction on CL/F and Vc/F dropped the objective function by ~10 units, and the difference in parameter estimates was <15% with and without liver dysfunction covariates. This subsequent model suggests limited improvement in the model fit after accounting for minor population effects due to liver dysfunction. The initial model including the hepatocellular carcinoma

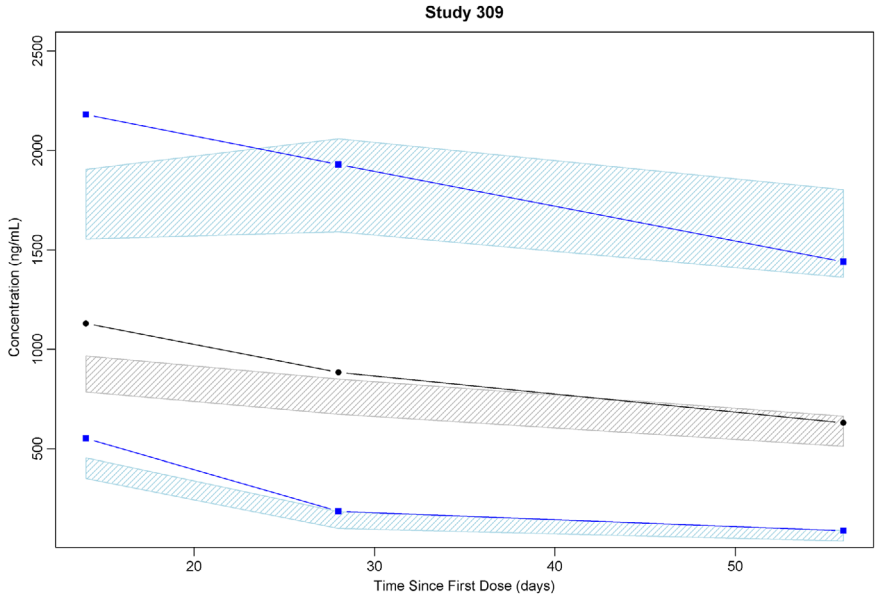

Figure 1. External visual predictive check plots for HCC patients in study XL184-309. Lower, middle, and upper shaded areas correspond to 90% prediction intervals for 10th (blue solid squares), 50th (black solid circles), and 90th percentiles (blue solid squares), respectively. Blue solid squares and black solid circles represent observed data. HCC indicates hepatocellular carcinoma.

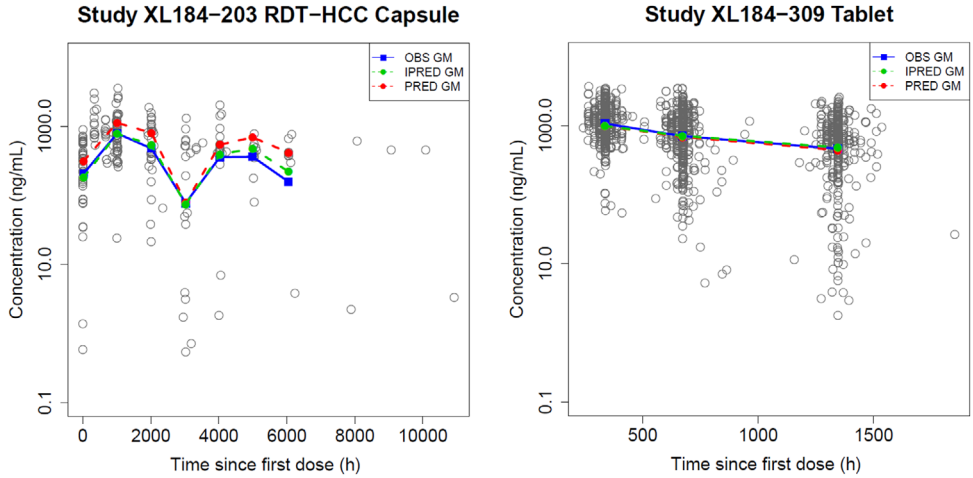

Figure 2. Goodness-of-fit plots for updated PK model by HCC study. Gray open circles correspond to individual PK observations; blue solid squares, green dashed lines, and red dashed lines represent geometric means (GM) of observations (OBS), individual predictions (IPRED), and typical individual predictions (PRED), respectively. HCC indicates hepatocellular carcinoma; PK, pharmacokinetic; RDT, randomized discontinuation trial.

population was considered the final updated integrated PPK model. Goodness-of-fit plots (all studies and hepatocellular carcinoma specific studies) and VPC plots for the updated integrated PPK model for cabozantinib are shown in Supplementary Figure S1, Figure 2, and Figure 3, respectively. Inspection of these figures suggests good agreement between the geometric mean of the observed data and model predictions.

Transformed parameter estimates and corresponding 90%CIs are shown in Table 3 for the updated integrated model including hepatocellular carcinoma patients and for the same model including the assessment of liver dysfunction effects on cabozantinib PK. With the addition of hepatocellular carcinoma patients, PK parameter estimates and covariate effects were similar to the previous integrated PPK model.[10] For a white male subject, CL/F at steady state was estimated as 2.48 L/h and Vc/F as 212 L. Distributions of individual predicted CL/F and Vc/F across population are shown in Figure 4 (A,B). Interindividual variability (expressed as percentage coefficient of variation) was approximately 46% for CL/F and 67% for Vc/F.

PK parameter estimates were similar with and without the addition of covariates related to liver function. Patients with mild or moderate/severe liver dysfunction were predicted to have minimal differences (12% or less)

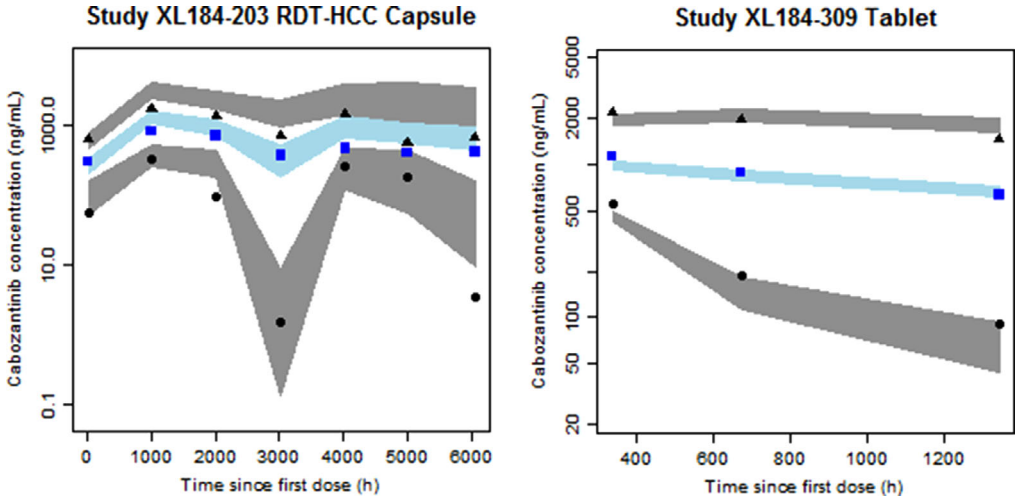

Figure 3. HCC study 90% prediction intervals and observed geometric means of cabozantinib concentration-versus-time profiles. Lower, middle, and upper shaded areas correspond to 90% prediction intervals for 10th percentile (black solid circles), geometric means (blue solid squares), and 90th percentile (black solid triangles), respectively. HCC indicates hepatocellular carcinoma.

in CL/F and Vc/F relative to subjects with normal liver function. Compared to healthy subjects, hepatocellular carcinoma patients showed a statistically significant difference in CL/F (similar to RCC patients) and a nonsignificant effect on Vc/F. The magnitude of the hepatocellular carcinoma population effect on CL/F was small (12% lower CL/F comparable to 13% lower in RCC) and not likely to be clinically meaningful.

The covariate effects on CL/F are illustrated as forest plots in Supplementary Figure S2. Similar to the previous analysis,[10] age, body weight, and race did not have an impact on cabozantinib CL/F. The MTC cancer type had the largest effect on cabozantinib PK parameters and exposure metrics among the covariates examined. Relative to healthy subjects, MTC patients are predicted to have a 90% larger CL/F and approximately 40% lower $C_{max,ss}$ and 50% lower $C_{min,ss}$ and steady-state area under the plasma drug concentration-time curve over the 24-hour dosing interval ($AUC_{0\text{-}24h,ss}$). The CL/F estimate was 24% lower in women, resulting in 27% higher $C_{max,ss}$ and 35% higher $C_{min,ss}$ and $AUC_{0\text{-}24h,ss}$. The impact of covariate sex on PK, although statistically significant for CL/F, was not considered to be clinically significant given the high interindividual variability exhibited by cabozantinib and the marginal effect for the female covariate shown in the forest plot.

Figure 5 (A-D) displays boxplots for individual predicted CL/F and $AUC_{0\text{-}24h,ss}$ for 60-mg dose administration by liver function classification including all subjects in the analysis and for hepatocellular carcinoma subjects in the CELESTIAL trial only. There were no apparent differences across groups, suggesting that cabozantinib clearance, and thus exposure, may not be affected by varying degrees of liver dysfunction.

Discussion

Pooling of data from 10 clinical trials allowed an integrated PPK analysis of cabozantinib in healthy subjects and cancer patients with different malignancies to be updated to include patients with hepatocellular carcinoma. The updated model adequately characterized the PK data by a 2-compartment model with dual first- and zero-order absorption processes and first-order elimination. The prespecified covariate effects of hepatocellular carcinoma cancer type and liver dysfunction per NCI-ODWG criteria on primary PK parameters CL/F and Vc/F showed minimal effects. The lack of effect of mild liver dysfunction on cabozantinib PK suggests that dose adjustment will not be required in this population. However, with limited data for moderate or severe liver impairment in the analysis, further investigation is needed to understand the PK in these patients.

There is no single marker that measures liver function to reliably classify liver disease with good predictive value for dose adjustment due to several etiologies involved in liver dysfunction.[23] The Food and Drug Administration[24] and European Medicines Agency[25] have issued similar guidance for studies on the effect of liver impairment, and both recommend the CP classification as the preferred criterion for addressing liver dysfunction. The CP score is a composite of 2 clinical assessments (ascites and encephalopathy) and 3 biochemical markers (total bilirubin, albumin, and international normalized ratio) for placement in 3 ordinal levels of liver impairment (mild, moderate, and severe). The classification is generally used in patients diagnosed with chronic liver disease who have progressed to cirrhosis. The studies conducted in HV with cirrhosis may not be clinically predictive of the PK effects in cancer patients with liver metastases.[26]

Table 3. Parameter Estimates for Updated Cabozantinib Integrated Population Pharmacokinetic Model

	Including HCC Population Transformed Estimate (90%CI)[a]	Including HCC Population and Liver Dysfunction Covariates Transformed Estimate (90%CI)
PK parameters		
K_a (h^{-1})	1.24 (0.849, 1.8)	1.23 (0.833, 1.82)
Duration for zero-order absorption process (h)	2.48 (2.2, 2.8)	2.53 (2.25, 2.84)
CL/F (L/h)	2.48 (2.27, 2.71)	2.47 (2.26, 2.7)
Vc/F (L)	212 (180, 250)	214 (181, 251)
Q/F (L/h)	30.0 (27.3, 33)	30.2 (27.6, 33.1)
Vp/F (L)	177 (165, 189)	179 (167, 191)
ALAG1 (h)	0.821 (0.795, 0.848)	0.82 (0.795, 0.846)
Fraction of dose in first absorption depot F1[b]	0.83 (0.80, 0.87)	0.83 (0.80, 0.87)
Dose-dependent K_a	0.734 (0.331, 1.14)	0.564 (0.138, 0.989)
Covariates		
Capsule on K_a[c]	0.402 (0.223, 0.725)	0.528 (0.28, 0.994)
Capsule on overall relative oral availability[c]	0.847 (0.83, 0.865)	0.841 (0.824, 0.859)
Age on CL/F	–0.157 (–0.264, –0.0509)	–0.16 (–0.266, –0.0539)
Female on CL/F[c]	0.76 (0.714, 0.81)	0.762 (0.715, 0.811)
Black on CL/F[c]	1.18 (1.04, 1.33)	1.18 (1.04, 1.33)
Asian on CL/F[c]	0.935 (0.869, 1.01)	0.934 (0.868, 1)
Other race on CL/F[c]	1.03 (0.903, 1.17)	1.02 (0.9, 1.16)
Weight on CL/F	–0.0393 (–0.147, 0.0679)	–0.0209 (–0.128, 0.0863)
RCC on CL/F[c]	0.87 (0.785, 0.965)	0.862 (0.778, 0.956)
CRPC on CL/F[c]	0.989 (0.893, 1.09)	0.968 (0.874, 1.07)
MTC on CL/F[c]	1.9 (1.72, 2.11)	1.88 (1.69, 2.08)
GB on CL/F[c]	1.2 (0.997, 1.43)	1.2 (1, 1.44)
Other malignancies on CL/F[c]	1.19 (1.01, 1.4)	1.14 (0.971, 1.35)
Age on Vc/F	0.0644 (–0.148, 0.277)	0.077 (–0.136, 0.29)
Female on Vc/F[c]	1.1 (0.973, 1.24)	1.08 (0.952, 1.22)
Black on Vc/F[c]	1.05 (0.773, 1.41)	1.07 (0.789, 1.44)
Asian on Vc/F[c]	0.696 (0.558, 0.867)	0.739 (0.595, 0.918)
Other Race on Vc/F[c]	0.882 (0.615, 1.26)	0.965 (0.681, 1.37)
Weight on Vc/F	1.19 (0.934, 1.46)	1.2 (0.934, 1.46)
RCC on Vc/F[c]	0.656 (0.41, 1.05)	0.711 (0.454, 1.11)
CRPC on Vc/F[c]	0.743 (0.602, 0.917)	0.721 (0.583, 0.891)
MTC on Vc/F[c]	0.936 (0.79, 1.11)	0.912 (0.769, 1.08)
GB on Vc/F[c]	0.479 (0.333, 0.689)	0.448 (0.304, 0.659)
Other malignancies on Vc/F[c]	0.762 (0.593, 0.979)	0.749 (0.583, 0.962)
HCC covariates		
HCC on CL/F[c]	0.878 (0.794, 0.971)	0.82 (0.738, 0.912)
HCC on Vc/F[c]	0.847 (0.694, 1.03)	0.81 (0.652, 1.01)
Liver dysfunction (NCI-ODWG) covariates		
Mild liver dysfunction on CL/F[c]		1.12 (1.06, 1.18)
Mild liver dysfunction on Vc/F[c]		1.04 (0.904, 1.2)
Moderate and severe liver dysfunction on CL/F[c]		0.978 (0.781, 1.22)
Moderate and severe liver dysfunction on Vc/F[c]		1.06 (0.658, 1.71)
Variance		
σ^2	0.127 (0.123, 0.131)	0.127 (0.123, 0.131)
ω^2 Ka	2.02 (1.59, 2.45)	2.21 (1.67, 2.75)
ω^2 CL/F	0.213 (0.198, 0.227)	0.210 (0.195, 0.224)
ω^2 CL/F:Vc/F	0.211 (0.178, 0.245)	0.199 (0.166, 0.232)
ω^2 Vc/F	0.443 (0.370, 0.516)	0.430 (0.361, 0.5)
ω^2 F1	2.55 (1.99, 3.1)	2.73 (2.11, 3.36)

ALAG1 indicates absorption lag time for the first absorption depot; CL/F, apparent clearance; CRPC, castration-resistant prostate cancer; GB, glioblastoma multiforme; HCC, hepatocellular carcinoma; K_a, absorption rate constant from the first absorption depot; MTC, metastatic medullary thyroid cancer; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; Q/F, apparent flow parameter between compartments; RCC, renal cell carcinoma; Vc/F, apparent distribution volume of the central compartment; Vp/F, apparent distribution volume of the peripheral compartment; σ^2, variance of population predicted concentration modeled using the log-transformed additive error model; ω^2, variance of population parameter modeled using exponential model.

Transformed estimate is a PK parameter obtained by exponentiating the original estimate.

[a]Final updated integrated model.

[b]Anti-logit transformation was used to obtain F1.

[c]For categorical covariates (eg, capsule), transformed estimates correspond to multiplicative change from the typical PK parameter.

In a liver impairment phase 1 study in HV, subjects with CP-A (mild) and CP-B (moderate) liver dysfunction had a 60% to 80% increase in cabozantinib exposure compared to matching subjects with normal liver function.[11] Findings from this single-dose study in healthy subjects with liver dysfunction may not accurately reflect steady-state exposures in cancer patients (including the hepatocellular carcinoma population) who are taking cabozantinib for a longer duration. In this updated PPK analysis, TB and AST values, which are readily available from all the studies, were used to classify liver dysfunction patients based on the NCI classification. In this analysis, patients with mild liver dysfunction showed similar cabozantinib clearance to patients with normal hepatic function.

Many oncology trials have used the NCI-ODWG to classify severity of liver dysfunction in clinical trials.[20,27–30] From these trials, the use of NCI classification has been implemented for dose labeling recommendation for hepatic impairment for oncology therapeutics nivolumab, vorinostat, crizotinib, imatinib, ixazomib, panobinostat, and vismodegib. A study examining liver impairment effects per NCI-ODWG criteria on the PK of vismodegib in patients with

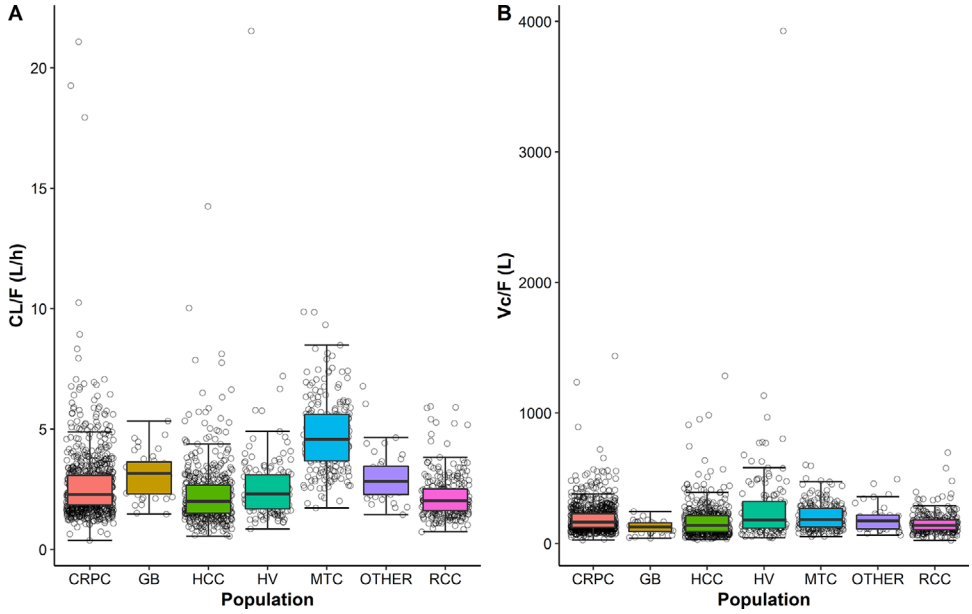

Figure 4. Cabozantinib individual predicted apparent clearance (CL/F [A]) and distribution volume of central compartment (Vc/F [B]) by population. Boxplot showing first quartile, median, third quartile, upper error bar (third quartile plus 1.5 times interquartile range), lower error bar (first quartile minus 1.5 times interquartile range), and circles (individual values). CRPC indicates castration-resistant prostate cancer; GB, glioblastoma multiforme; HCC, hepatocellular carcinoma; HV, healthy volunteers; MTC, metastatic medullary thyroid cancer; OTHER, other malignancies; RCC, renal cell carcinoma.

advanced solid malignancies (including two thirds of patients with hepatocellular carcinoma) concluded that no dose adjustment is warranted in liver dysfunction patients due to the minimal impact of liver dysfunction groups on vismodegib PK when compared with patients with normal liver function.[31]

Recognizing the potential limitations of the CP criteria to assess liver dysfunction in cancer patients, the investigators in a phase 1 liver impairment PK study of imatinib evaluated liver dysfunction using the NCI-ODWG criteria for enrolled subjects.[20] There was a correlation when comparing to NCI-ODWG to CPC in this study. For the CP-A group, approximately 94% of the patients fell within the NCI-ODWG normal or mild group ranges, whereas for CP-B or CP-C, 65% and 100%, respectively, fell within the NCI-ODWG moderate or severe group ranges. Ramanathan et al concluded that imatinib exposure did not differ between patients with normal liver function and those with mild liver dysfunction but recognized that dosing in moderate and severe liver dysfunction remained undetermined.

The PK parameters estimated for hepatocellular carcinoma patients in the CELESTIAL study (99% with CP-A status) were similar to non–hepatically impaired RCC patients receiving cabozantinib. Furthermore, covariate effects related to liver dysfunction were also considered in this updated integrated PPK analysis. The NCI-ODWG classifications were used to identify subjects with normal liver function or mild, moderate, or severe liver dysfunction across the spectrum of the 10 pooled studies in the PPK analysis. Covariates related to liver function did not display significant impact on cabozantinib PK. Patients with mild or moderate/severe liver dysfunction per NCI-ODWG were predicted to have minimal differences in CL/F and Vc/F relative to subjects with normal liver function. Hepatocellular carcinoma patients in the CELESTIAL study also showed similar predicted steady-state CL/F and AUC across liver dysfunction groups. Although cabozantinib exposure in HV increased after a single dose in subjects with CP-A and CP-B class in the phase 1 liver impairment study,[11] hepatocellular carcinoma subjects (CP-A) in the CELESTIAL study appeared to have similar steady-state exposure as compared to other tumor types, including RCC subjects. Moreover, the updated integrated PPK analysis indicated cabozantinib exposure to be similar among cancer patients with normal, mild, and moderate liver dysfunction based on NCI-ODWG classification; however, limited data were available for hepatocellular carcinoma patients with moderate (n = 12) or severe (n = 1) liver dysfunction to provide accurate conclusions regarding cabozantinib exposure in these subpopulations. The results reflect the updated cabozantinib FDA prescribing information for no initial dose adjustment from the approved 60-mg dose for hepatocellular carcinoma and RCC patients with hepatic impairment CP-A; an initial dose reduction to 40 mg is recommended

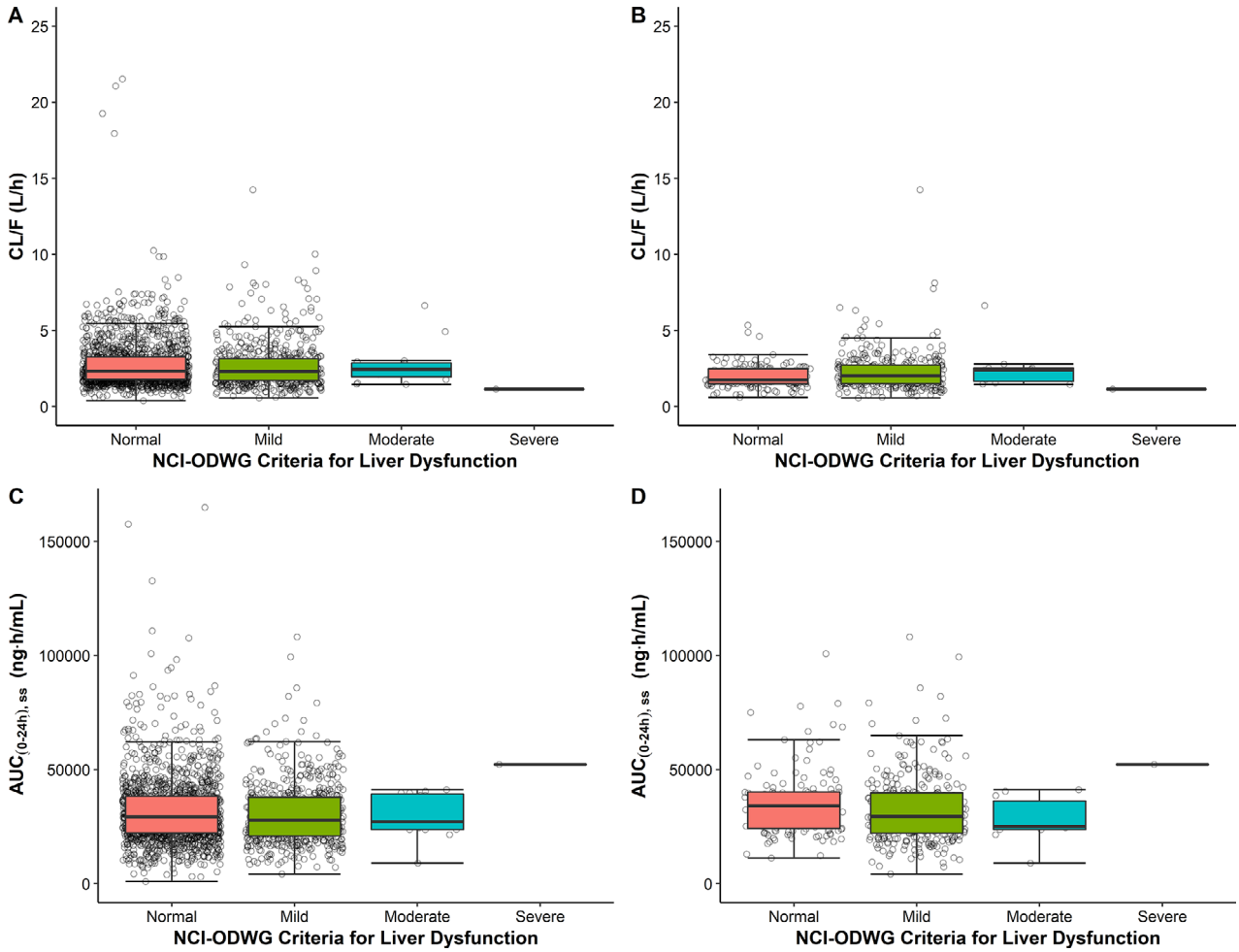

Figure 5. Cabozantinib individual predicted apparent clearance (CL/F) for all subjects (A) and subjects in CELESTIAL study (B) by NCI-ODWG criteria for liver dysfunction. Cabozantinib individual predicted area under the plasma concentration-time curve at steady state over 24-hour dosing interval [$AUC_{(0\text{-}24h),\,ss}$] for simulated 60 mg for all subjects (C) and subjects in the CELESTIAL study (D) by NCI-ODWG criteria for liver dysfunction. For explanation of boxplot refer to Figure 4. NCI-ODWG indicates National Cancer Institute Organ Dysfunction Working Group.

for patients with CP-B status, whereas patients with CP-C class are recommended to avoid cabozantinib treatment.[5]

The uncorrelated effects of liver dysfunction on cabozantinib PK for a single-dose in noncancer subjects versus repeat daily dosing in cancer patients are consistent with findings observed for gefitinib.[32] The AUCs of gefitinib after a single dose of 250 mg in subjects with liver dysfunction due to cirrhosis were increased by 40%, 263%, and 166% for CP-A (mild), CP-B (moderate), and CP-C (severe) liver dysfunction, respectively, as compared with HV with normal liver function. However, for patients with liver metastases in a second study, the gefitinib exposure at steady state on day 28 in subjects with normal liver function was similar to that in patients with moderate liver dysfunction but lower than that in patients with severe liver dysfunction. Different PK outcomes may result from testing patient populations with liver dysfunction with different underlying etiologies (cirrhosis or metastases) and classification.

Conclusions

The updated integrated PPK model showed similar PK in hepatocellular carcinoma patients as observed across various cancer types, with the exception for MTC. Due to minimal PK and predicted exposure differences between normal and mild liver dysfunction, no initial dosage adjustment is recommended for cancer patients with mild liver dysfunction. Limited data available for patients with moderate and severe liver dysfunction preclude providing any dosing recommendations for these subpopulations.

Disclosures

An abstract form of the results was presented at the American Society of Clinical Oncology Gastrointestinal Cancer

Symposium in January 2019. Steven Lacy, Linh Nguyen, and Benjamin Duy Tran are stockholders and current employees of Exelixis, Inc.

Data Sharing

Data supporting the findings of this study cannot be shared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.