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ORIGINAL PAPER

Cabozantinib exposure–response analyses of efficacy and safety in patients with advanced hepatocellular carcinoma

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Abstract

Cabozantinib, a multi-kinase inhibitor, is approved in the United States and European Union for treatment of patients with hepatocellular carcinoma following prior sorafenib treatment. In the Phase III CELESTIAL trial, hepatocellular carcinoma patients receiving cabozantinib showed longer overall survival (OS) and progression-free survival (PFS) than those receiving placebo. The approved cabozantinib (Cabometyx®) dose is 60 mg once daily with allowable dose modifications to manage adverse events (AE). Time-to-event Cox proportional hazard exposure–response (ER) models were developed to characterize the relationship between predicted cabozantinib exposure and the likelihood of various efficacy and safety endpoints. The ER models were used to predict hazard ratios (HR) for efficacy and safety endpoints for starting doses of 60, 40, or 20 mg daily. Statistically significant relationships between cabozantinib exposure and efficacy and safety endpoints were observed. For efficacy endpoints, predicted HR were lower for OS and PFS at 40 and 60 mg relative to the 20 mg dose: HR for death (OS) are 0.84 (40 mg) and 0.70 (60 mg); HR for disease progression/death (PFS) are 0.73 (40 mg) and 0.62 (60 mg). For safety endpoints, predicted HR were lower for palmar-plantar erythrodysaesthesia (PPE), diarrhea, and hypertension at 20 or 40 mg relative to the 60 mg dose: HR for PPE are 0.31 (20 mg) and 0.66 (40 mg); HR for diarrhea are 0.61 (20 mg) and 0.86 (40 mg); HR for hypertension are 0.46 (20 mg) and 0.76 (40 mg). The rate of dose modifications was predicted to increase in patients with lower cabozantinib apparent clearance. OS and PFS showed the greatest benefit at the 60 mg dose. However, higher cabozantinib exposure was predicted to increase the likelihood of AE and subsequent dose reductions appeared to decrease these risks.

Keywords Cabozantinib · PK/PD · Exposure–response modeling · Time-to-event analysis · Hepatocellular carcinoma

Introduction

Liver cancer was the fourth leading cause of cancer death in 2015 and led to 810,000 deaths globally that year [1]. Hepatocellular carcinoma is the most common type of primary liver cancer with several genomic defects implicated in its heterogenous pathways for hepatocarcinogenesis [2]. Cabozantinib is an inhibitor of multiple receptor tyrosine kinases with potent activity against MET, VEGFR2, RET, AXL, and KIT [3], in which targeting MET is thought to overcome sorafenib resistance in hepatocellular carcinoma [4].

Recently, the cabozantinib tablet formulation (Cabometyx®) was approved in the United States and the European Union at a 60 mg free-base-equivalent (FBE) daily dose for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib [5, 6]. The hepatocellular carcinoma indication was based on results from the randomized placebo-controlled Phase III trial (CELESTIAL) in advanced hepatocellular carcinoma patients (99% had Child–Pugh A classification) [7]. The CELESTIAL trial showed significant improvement in overall survival (OS) for cabozantinib with median OS of 10.2 months for cabozantinib as compared to 8.0 months for placebo (hazard ratio [HR] for death, 0.76; 95% confidence interval, 0.63 to 0.92; p value = 0.005).

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In CELESTIAL, adverse events (AE) were managed with dose modifications (dose reduction or hold) and supportive care [7]. A total of 62% of subjects in the cabozantinib arm and 13% of subjects in the placebo arm had a dose reduction due to an AE [7]. The median time to first dose reduction due to AE was 38 days in the cabozantinib arm [7]. Exposure–response (ER) models were developed to understand the relationship between cabozantinib exposure and the likelihood of various endpoints, including OS, progression-free survival (PFS), AE, and dose modification. The ER models were used to predict the HR for efficacy and safety endpoints for starting cabozantinib doses of 60, 40 or 20 mg daily and to support the rationale for dose modification in hepatocellular carcinoma patients.

Methods

Study design

All protocols were approved by institutional review boards of participating institutions and written informed consent was obtained from patients prior to enrollment. The ER models were developed using data from the CELESTIAL Phase III, randomized, double-blind, controlled study of cabozantinib versus placebo in hepatocellular carcinoma patients who have received prior sorafenib treatment [7]. A total of 707 patients were randomly assigned in a 2:1 ratio to receive a cabozantinib dose of 60 mg tablet FBE daily or matching placebo. Treatment hold and dose reduction in 20 mg increments based on specific tolerability issues were permitted. Randomization was stratified based on etiology of disease (hepatitis B virus with or without hepatitis C virus, hepatitis C virus without hepatitis B, or other), geographic region (Asia versus other regions), and the presence of extrahepatic spread of disease and/or macrovascular invasion (yes or no).

Bioanalytical PK assay

Blood samples for PK assessment were collected at approximately 8 or more hours after the prior evening's dose on days 15, 29, and 57. 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].

Software

The time-to-event analyses were performed using the Cox proportional hazards regression (PHREG) procedure within SAS v 9.3 (SAS Institute, Cary, NC). Post-processing of model output was performed using SAS, S-Plus v 8.2 (TIBCO, Palo Alto, CA), or R v 3.1.0 (R Foundation, Vienna, Austria) software. Graphical analysis of the data or output from the models was performed using S-Plus or R.

Population pharmacokinetics

The ER modeling was a sequential two-step pharmacokinetic/pharmacodynamic (PK/PD) fitting process. Initially, a cabozantinib population pharmacokinetic (PPK) model was developed using data pooled from 10 clinical studies totaling 2023 subjects, including 489 hepatocellular carcinoma patients (99% with Child–Pugh class A mild liver impairment). Methods for PPK model development used in this ER modeling was described in a previous manuscript [9]. From the PPK model, the predicted PK parameters and exposures using actual dosing history from hepatocellular carcinoma patients in the CELESTIAL trial were used in the second step to develop ER models for selected endpoints.

Exposure response analysis for time-to-event endpoints

Efficacy and safety endpoints

Efficacy endpoints include OS ($\geq$ 12 weeks survival) and PFS (defined as the time from randomization to radiographic progression by the independent radiology committee according to Response Evaluation Criteria in Solid Tumors version 1.1 or death from any cause, whichever occurred first). The severity of AE was assessed by the investigator according to the National Cancer Institute Common Terminology Criteria for AE version 4.0. The safety endpoints evaluated included dose modifications, fatigue (grade $\geq$ 3), palmar-plantar erythrodysesthesia syndrome (PPE, grade $\geq$ 1), nausea or vomiting (N/V, grade $\geq$ 3), diarrhea (grade $\geq$ 3), hypertension (HTN, systolic blood pressure $>$ 160 mmHg or diastolic blood pressure $>$ 100 mmHg), alanine/aspartate aminotransferase (ALT/AST) elevation (Grade $\geq$ 3), and total bilirubin elevation (Grade $\geq$ 3).

Dataset construction

At least one measurable PK concentration was required for the ER analysis dataset for response endpoints to link with individual predicted cabozantinib exposure. For the OS endpoint, intent-to-treat (ITT) hepatocellular carcinoma patients from CELESTIAL must receive cabozantinib for at least 12 weeks. Patient population in PFS included ITT hepatocellular carcinoma patients with an evaluable valid baseline and at least one post-baseline tumor assessment.

For safety endpoints, hepatocellular carcinoma patients were required to receive at least one dose of the study medication.

Censorship for OS was the last known date to be alive or study cutoff date. For PFS, censoring rules included: date of last tumor assessment from post-randomization for subjects without event at time of data cutoff and date of most recent tumor assessment prior to missing two or more scheduled tumor assessments followed by an event. Censoring time for AE was the date of the last dose plus 30 days, date of death, or study cutoff date (if date of last dose or death date is missing), whichever was earlier. For dose modification, censoring occurred at study drug discontinuation date or the study cutoff date. Censorship was the date of the last dose if discontinuation reasons were not due to the AE, while the event was assigned on the date after the date of last dose if discontinuation reasons were related to AE. Supplementary Table S1 summarizes the details for dataset construction including analysis population and censorship per clinical endpoint.

Exposure metrics

Specific exposure metrics were evaluated for each efficacy and safety endpoint and were selected to be consistent with a previous ER analysis in renal cell carcinoma (RCC) patients [10]. The exposure metric for the OS analysis was the average cabozantinib concentration (C_{avg}) calculated over the 28 days prior to the Week 12 landmark (C_{avg}OS). For PFS, the exposure measures were the C_{avg} calculated over the 3 weeks prior to time of response measure (C_{avg}3W) and the C_{avg} calculated from time zero to time of event or censoring (C_{avg}AT). Considering that apparent clearance (CL/F) is log normally distributed, a log transformed CL/F (logCLF) was evaluated as the exposure metric for dose modifications in addition to the untransformed CL/F. Exposure measures for all safety endpoints included C_{avg} calculated over the 2 weeks prior to time of response measure (C_{avg}2W) and the C_{avg}AT. These two-exposure metrics were selected to address potential cumulative effects of cabozantinib on the incidence of an event. For HTN AE, the C_{avg} was calculated over 24 h prior to time of response measure (C_{avg}1D) in place of C_{avg}2W. The cumulative area under the cabozantinib concentration time curve from time zero to event or censoring (AUC_{AT}) was also evaluated for PFS and all safety endpoints in prior RCC ER models. However, AUC_{AT} was not a significant exposure for all endpoints evaluated in RCC ER analysis. Therefore, AUC_{AT} was not included in this HCC ER analysis. In addition, treatment effects (binary as active or placebo arms) were considered for all clinical endpoints. Supplementary Table S1 provides a summary of exposure metrics used for analyses for each clinical endpoint.

Exploratory data analysis

Kaplan–Meier (KM) plots were generated to initially explore the relationship between cabozantinib exposure and clinical endpoints. During the exploratory steps for model development, the KM plots were prepared for efficacy and safety endpoints stratified by tertiles of individual model predicted C_{avg}AT. The exposures used in the exploratory phase were predicted using the PPK model and actual dosing data collected during the study. For time to first dose modification, KM plots were stratified by tertiles of individual model predicted CL/F.

Cox proportional hazards model

The Cox proportional hazards (CPH) models quantitated the relative hazard for each clinical endpoint. Only the time to the first event was considered for safety analyses due to the challenges in both implementation and interpretation of results when incorporating different types of supportive care measures (e.g., administration of antidiarrheal medication) following the first event.

The general form of the CPH model is given by the expression:

$$h(t, X(t)) = h_o(t) \cdot \exp(\beta \cdot X(t)) \quad (1)$$

where $h(t, X(t))$ denotes the hazard at time t, $h_o(t)$ is the background hazard function, β is a vector of the regression coefficients, and $X(t)$ is a matrix of covariates which may vary with time. Tied event times were handled by the exact method. The CPH model is a semi-parametric model in that the outcome variable (e.g., survival time) does not rely on distributional specifications (e.g., Weibull, exponential, log-logistic, lognormal) as required in parametric models. In addition, the baseline survival (or hazard) function $h_o(t)$ does not need specification. With these advantages, the CPH model is robust in that the results will closely approximate the results of a correct parametric model.

Model development

The impact of cabozantinib exposure on the relative hazard was evaluated in the base model stage of development. In CPH models, explanatory effects (e.g., exposure) are typically added in a linear fashion to the log hazard. The linear functional form was used to represent the initial base model; however, nonlinearity in the ER relationship was also evaluated. Maximum effect (E_{max})-type models were evaluated across a range of fixed values for the exposure measure (e.g., C_{avg}) that results in one half of the maximum

drug effect (EC_{50}). EC_{50} values were preset over a grid of fixed values ranging 1–3000 ng/mL for cabozantinib concentration and 0.1–6 L/h for CL/F. When EC_{50} is fixed, the model is linear and can be assessed in the PHREG procedure in SAS. The E_{max} model with the lowest partial likelihood determined which value was selected for the EC_{50}. Both functional forms of linear Eq. 2 and nonlinear Eq. 3 were explored:

$$h(t, X_{ex}(t)) = h_o(t) \cdot exp(\beta_{ex1} \cdot X_{ex}(t)) \quad (2)$$

$$h(t, X_{ex}(t)) = h_o(t) \cdot exp\left(\beta_{ex2} \cdot \frac{X_{ex}(t)}{X_{ex}(t) + EC_{50}}\right) \quad (3)$$

where $X_{ex}(t)$ is the cabozantinib exposure measure which may vary with time t, β_{ex1} represents the slope in the log-linear model, β_{ex2} represents the maximum drug effect in the E_{max} model, and EC_{50} represents a range of fixed values for the exposure at which half of the maximal effect is achieved. A step function was also used to assess the cabozantinib treatment effect independent of drug exposure.

Specific exposure metrics were evaluated for each clinical endpoint. Model development was guided by several criteria including: changes in the partial likelihood for hierarchical models, relative precision of the parameter estimates between competing models, and various diagnostics of the residuals (martingale, deviance, and Schoenfeld residuals).

Covariate effects

Covariate effects were assessed for the efficacy (OS and PFS) models only. Covariates were added to the base model simultaneously to form a full model. Clinical judgment and mechanistic plausibility were used to determine which covariates should be evaluated. The covariates evaluated included: baseline Eastern Cooperative Oncology Group (ECOG) score (0 or $\geq$ 1), hepatitis etiology (hepatitis B virus or hepatitis C virus), and presence or absence of extrahepatic spread of disease and/or macrovascular invasion.

Following development of a stable full model, a covariate reduction procedure was conducted to identify the most parsimonious model. The SELECTION = SCORE option in the PHREG procedure within SAS was used to assess changes in the log likelihood for all combinations of covariate effects. To find the most parsimonious model across the different number of covariates, Schwarz's Bayesian Criterion (SBC) was calculated and the model with the smallest SBC was selected to be the most parsimonious model. A backward elimination procedure was used to identify a parsimonious final model for each efficacy endpoint.

Simulations

Using the PPK model [9] and the final CPH model for each endpoint, simulations were performed to predict HR for starting cabozantinib doses of 60, 40, and 20 mg in order to understand the relationship between clinically relevant cabozantinib exposures for each dose level in hepatocellular carcinoma patients and incidence of efficacy and safety endpoints.

Results

Clinical events and total number at risk

The number of efficacy and safety events and the number of patients at risk in CELESTIAL trial are listed for efficacy and safety endpoints in Table 1. In total, there were 467 subjects that had at least one documented cabozantinib dose. Of those 467 subjects, 452 subjects had at least one measurable PK concentration such that individual PK parameters and exposure could be predicted. For the placebo arm, a total of 237 patients received at least one dose of placebo for inclusion in the analysis.

Summary of covariate data

A summary of the covariates considered for efficacy ER analyses is provided in Supplementary Table S2. Since Hepatitis C (HCV) co-infected with Hepatitis B (HBV) was less than 5% in both placebo (N = 4) and cabozantinib (N = 8) arms, HBV/HCV-coinfected patients were grouped into HBV. Therefore, the HBV etiology consists of HBV with and without HCV in the analysis. Co-infected HBV/HCV on treatment was not evaluated due to small sample size with this etiology. Baseline ECOG values greater than or equal to one were collapsed into one category due to only one patient with ECOG = 2. Distribution of covariates between cabozantinib treatment and placebo arms are comparably similar.

Population pharmacokinetic model

The PPK model characterized the pooled PK data by a two-compartment model with dual first- and zero-order absorption processes and first-order elimination. Individual observed cabozantinib concentration data collected from CELESTIAL trial were overlaid with observed mean data, population predictions, and individual predictions (Fig. 1a) [9]. Results for the estimated parameters and covariate effects included hepatocellular carcinoma cancer type and liver dysfunction per the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria were

Table 1 Summary of number of events and number of subjects at risk in efficacy and safety analysis datasets

Endpoints		Cabozantinib arm		Placebo arm		Total	
		Number of events	Number of subjects at risk	Number of events	Number of subjects at risk	Number of events[d]	Number of subjects at risk[d]
Efficacy	Overall survival (death)	112	272	35	89	147	361
	Progression-free survival (progressive disease or death)	299	419	185	223	484	642
Safety	Fatigue[a]	77	452	14	237	91	689
	Nausea/vomiting[a]	10	452	6	237	16	689
	Palmar-plantar erythrodysesthesia syndrome[b]	217	452	12	237	229	689
	Diarrhea[a]	46	452	4	237	50	689
	Hypertension[c]	124	452	13	237	137	689
	Alanine/aspartate aminotransferase elevation[a]	64	452	16	237	80	689
	Total bilirubin elevation[a]	13	452	4	237	17	689
	Dose Modification	369	452	74	237	369[e]	452[e]

[a]Adverse event of Grade 3 or higher

[b]Adverse event of Grade 1 or higher

[c]Systolic blood pressure (BP) > 160 mmHg or Diastolic BP > 100 mmHg

[d]Total number of events and number at risk include subjects with at least one measurable cabozantinib concentration and subjects receiving at least one dose of placebo

[e]Only cabozantinib treated patients were evaluated in the analysis for dose modification

reported in a separate manuscript [9]. Using the updated PPK model, predicted cabozantinib concentration time curve from 0 to 24 h post-dose at steady-state for 3 dose levels (20, 40 and 60 mg daily dose) was generated for patients in CELESTIAL trial (Fig. 1b). Predicted steady state average concentration versus dose stratified by sex showed no remarkable differences between male and female (Fig. 1c). The average steady state concentration by liver dysfunction based on the NCI-ODWG criteria showed minimal exposure differences between normal and mild liver dysfunction in hepatocellular carcinoma patients (Fig. 1d). Limited data, however, was available for patients classified with moderate and severe liver dysfunction.

Cox proportional hazard models

The parameter summary and predicted hazard ratio with 95% confidence interval (95% CI) are provided in Tables 2 and 3, respectively, for each efficacy and safety endpoint for the CPH models. Cabozantinib concentrations corresponding to model predicted typical individual steady state C_{avg} are 383 ng/mL (for 20 mg), 766 ng/mL (for 40 mg), and 1148 ng/mL (for 60 mg). N/V and total bilirubin elevation endpoints were not included due to the small frequency of events (< 5%) and none of these models resulted in statistically significant changes compared to the model without cabozantinib exposure, which indicated no evidence to suggest exposure or treatment as important predictors for these outcomes. Examples of residuals versus exposures for endpoints with exposure effect in the final ER models are found in the Supplementary Figure S1 (A–D).

Efficacy endpoints

Overall survival

The OS endpoint included only patients that received cabozantinib or placebo treatment for at least 12 weeks. Total patients included 52% (N = 361) of the 689 eligible patients. The total number of death events was 147 out of the 361 patients. The linear, nonlinear, and step function models produced similar, statistically significant reduction changes in the negative 2 log likelihood (Δ-2LL) compared to the model without cabozantinib exposure; therefore, the simplest linear model was selected as the base model to use for covariate assessment and to compute HR for C_{avg}. Based on the SBC criteria, the most parsimonious model was the structural covariate model with C_{avg}OS (Table 2). Time-to-event curves for OS corresponding to the model prediction for typical individual steady-state C_{avg} for 20 mg, 40 mg, and 60 mg once daily dosing regimens are

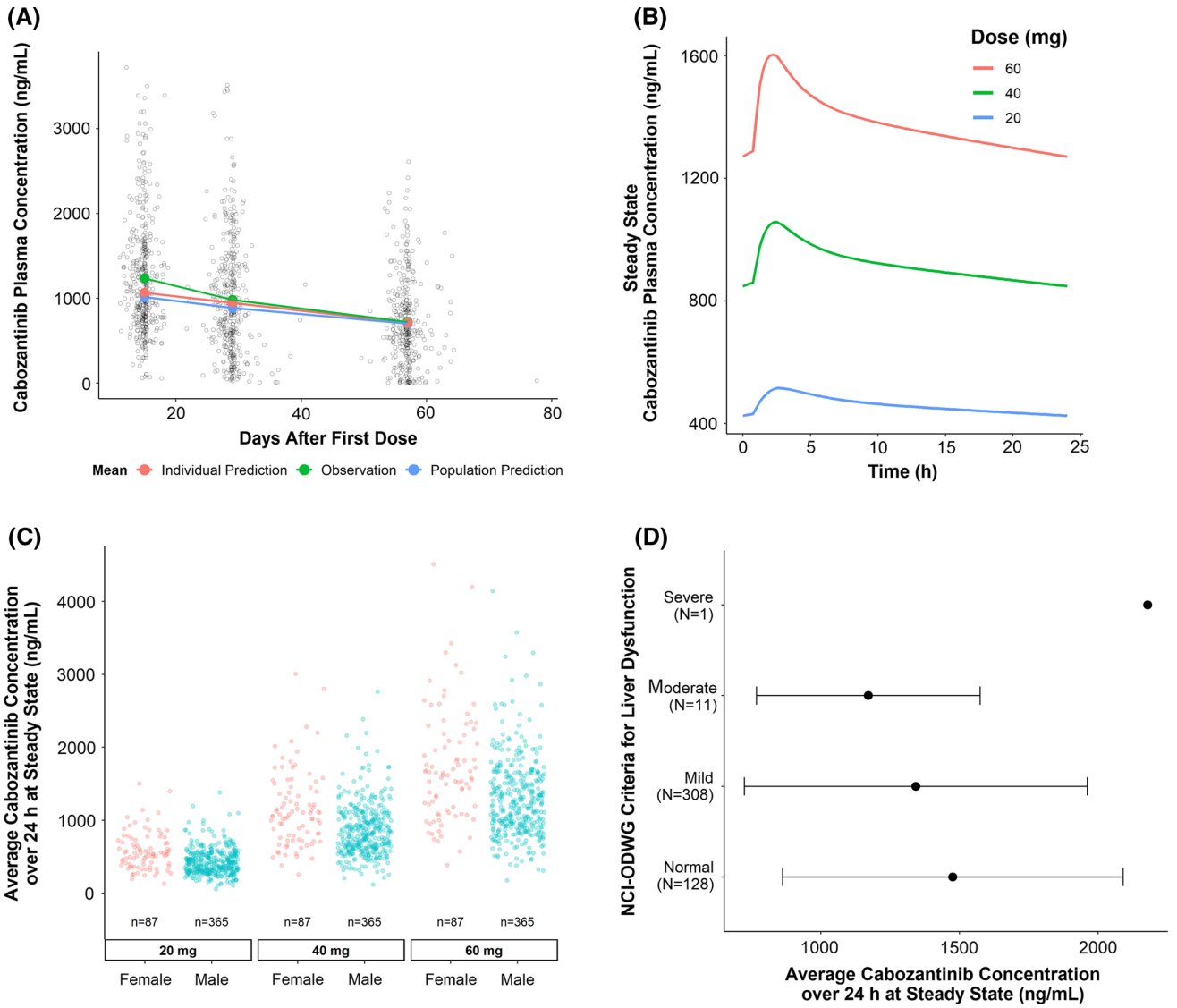

Fig. 1 Population pharmacokinetic model predictions for CELESTIAL trial patients. **a** Individual observed cabozantinib pharmacokinetic data (open circles) from days after first dose overlaid with observed arithmetic mean data, population predictions, and individual predictions. **b** Predicted cabozantinib concentration time curve from 0 to 24 h post-dose at steady state for 20, 40 and 60 mg daily dose. **c** Predicted average cabozantinib concentration over 24 h at steady state versus 20, 40, and 60 mg daily dose stratified by sex. **d** Mean and standard deviation of predicted average cabozantinib concentration over 24 h for 60 mg at steady state stratified by National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for liver dysfunction

illustrated in Fig. 2. The plot shows improved OS with increasing cabozantinib concentration for those subjects that received cabozantinib for at least 12 weeks. The predicted HR for OS (representing risk of death) were 0.84 (95% CI, 0.73 to 0.96) for 40 mg and 0.70 (95% CI, 0.54 to 0.92) for 60 mg based on predicted exposures relative to a 20 mg dose (Table 3).

Progression-free survival

The PFS endpoint included 642 patients (93% of 689) with an evaluable baseline and at least one post-baseline tumor assessment. Total disease progression or death events were 484 from the 642 patients. $C_{avg}3W$ and $C_{avg}AT$ were two possible cabozantinib exposure measures evaluated in the linear and nonlinear models for PFS. The nonlinear model using $C_{avg}3W$ as the cabozantinib exposure measure had the lowest Δ-2LL value and was selected as the final base model (Table 2). Figure 3 illustrates the impact of selected cabozantinib exposure values on the predicted time-to-event curves. The predicted HR for PFS (representing risk of disease progression or death) were 0.73 (95% CI, 0.70 to 0.77) for 40 mg and 0.62 (95% CI, 0.58 to 0.67) for 60 mg

Table 2 Cox proportional hazard models and parameters

Endpoint	Model	Exposure metric	EC_{50}	Parameter	Estimate	Standard error	P-value
Overall survival	Linear	C_{avg}OS		β_{CavgOS}	-4.65×10^{-4}	1.79×10^{-4}	0.01
	Non-linear	C_{avg}3W	500	β_{EXNL}	− 1.67	0.20	< 0.0001
Progression-free survival				β_{HepB}	0.55	0.13	< 0.0001
				$\beta_{EXNL*HepB}$	− 0.59	0.31	0.057
Dose modification	Log-linear	logCLF		β_{logCLF}	− 0.84	0.13	< 0.0001
Palmar-plantar erythrodysesthesia syndrome	Non-linear	C_{avg}2W	500	β_{EXNL}	4.47	0.42	< 0.0001
Diarrhea	Non-linear	C_{avg}2W	200	β_{EXNL}	2.53	0.66	0.0001
Hypertension	Non-linear	C_{avg}1D	500	β_{EXNL}	2.94	0.41	< 0.0001
Fatigue	Step function: Placebo versus cabozantinib	Treatment		β_{TRT}	0.94	0.29	0.001
Alanine/aspartate aminotransferase elevation	Step function: Placebo versus cabozantinib	Treatment		β_{TRT}	0.60	0.28	0.03

β_{CavgOS} the change in the log hazard ratio per unit change in C_{avg}OS, β_{EXNL} maximum change in the log hazard ratio, β_{logCLF} the change in the log hazard ratio per unit change in logCLF, β_{TRT} change in the log hazard ratio due to treatment, $C_{avg}1D$ average cabozantinib concentration calculated over the 24 h prior to time of response measure, $C_{avg}2W$ average cabozantinib concentration calculated over the two weeks prior to time of response measure, $C_{avg}3W$ average cabozantinib concentration calculated over the three weeks prior to time of response measure, $C_{avg}OS$ average cabozantinib concentration over the 28 days prior to the Week 12 landmark, EC_{50} concentration producing half of the maximum effect, *EXNL* (Exposure Metric)/(EC50 + (Exposure Metric)), *EXNL*HepB* statistical interaction between HepB and EXNL, *HepB* hepatitis B virus etiology, *logCLF* log apparent clearance

based on predicted exposures relative to a 20 mg dose (Table 3).

Covariate effects

No significant covariates were identified in addition to the C_{avg}OS structural covariate for the OS model. The most parsimonious model for PFS included the following three covariates: average cabozantinib exposure over the previous 3 weeks (β_{EXNL}), hepatitis B virus etiology (β_{HepB}), and their interactions ($\beta_{EXNL*HepB}$). Patients with increasing cabozantinib concentrations were predicted to have a decreased rate of progressive disease or death (i.e., a decreasing hazard ratio with increasing concentration). In addition, hepatocellular carcinoma patients with hepatitis B virus etiology were predicted to have a higher background rate of progressive disease or death. However, the difference in HR between patients with and without hepatitis B virus was predicted to diminish with increasing cabozantinib concentration as illustrated in Supplementary Figure S2.

Safety endpoints

Dose modifications A total of 452 patients were included in the analysis to understand the relationship between individual predicted cabozantinib CL/F and the rate of dose modifications. Based on Δ-2LL value, the linear model using log transformed CL/F performed better than the linear model with untransformed CL/F but was comparable to the nonlinear model. The log-linear CL/F model was selected over the nonlinear model. Figure 4 illustrates the impact of selected cabozantinib CL/F values on the predicted time-to-event curves. The median individual predicted CL/F for CELESTIAL patients was 1.95 L/h. One unit up (= 2.95 L/h) and one unit down (= 0.95 L/h) from 1.95 L/h was used to demonstrate high (∼ 50% increased) and low (∼ 50% decreased) CL/F, respectively, as compared to the median CL/F. The time-to-event curves show the predicted fraction without dose modifications over time for CL/F values of 0.95, 1.95 and 2.95 L/h. A statistically significant relationship between individual predicted cabozantinib clearance and the rate of dose modifications showed decreased cabozantinib clearance and the corresponding increased cabozantinib exposure were predicted to increase the rate of dose modifications. HR were 1.82 (95% CI, 1.52 to 2.19) for 0.95 L/h and 0.71 (95% CI, 0.64 to 0.79) for 2.95 L/h for dose modifications based on predicted CL/F relative to 1.95 L/h (Table 3). For a typical patient with a median cabozantinib CL/F of 1.95 L/h, the model predicted that 50% of patients on cabozantinib treatment would undergo the first dose modification by 28 days.

Table 3 Predicted hazard ratios

Treatment or exposure measure	Hazard ratio	95% Confidence interval
Overall survival		
20 mg	1.00	(1.00, 1.00)
40 mg	0.84	(0.73, 0.96)
60 mg	0.70	(0.54, 0.92)
Progression-free survival		
20 mg	1.00	(1.00, 1.00)
40 mg	0.73	(0.70, 0.77)
60 mg	0.62	(0.58, 0.67)
Dose modification		
CL/F = 0.95 L/h	1.82	(1.52, 2.19)
CL/F = 1.95 L/h	1.00	(1.00, 1.00)
CL/F = 2.95 L/h	0.71	(0.64, 0.79)
Palmar-plantar erythrodysesthesia syndrome		
60 mg	1.00	(1.00, 1.00)
40 mg	0.66	(0.62, 0.72)
20 mg	0.31	(0.25, 0.38)
Diarrhea		
60 mg	1.00	(1.00, 1.00)
40 mg	0.86	(0.80, 0.93)
20 mg	0.61	(0.48, 0.78)
Hypertension		
60 mg	1.00	(1.00, 1.00)
40 mg	0.76	(0.71, 0.82)
20 mg	0.46	(0.37, 0.57)
Fatigue		
Placebo	1.00	(1.00, 1.00)
Cabozantinib	2.57	(1.45, 4.55)
Alanine/aspartate aminotransferase elevation		
Placebo	1.00	(1.00, 1.00)
Cabozantinib	1.82	(1.05, 3.15)

Cabozantinib concentrations corresponding to model predicted typical individual steady-state average concentrations are 383 ng/mL for 20 mg, 766 ng/mL for 40 mg, and 1148 ng/mL for 60 mg. CL/F = apparent clearance

Adverse events A nonlinear model with exposure measure $C_{avg}2W$ for PPE and diarrhea and $C_{avg}1D$ for HTN was selected as the final model due to its statistically significant in Δ-2LL compared to the model without cabozantinib exposure. The parameter estimates indicated that decreases in C_{avg} result in decreases in the rate of PPE, diarrhea, and HTN (Table 2). Figure 5(a–c) shows predicted fractions of subjects without PPE (A), diarrhea (B), or HTN (C) over time for predicted steady state C_{avg} at various daily doses. HR were 0.31 (95% CI, 0.25 to 0.38) for 20 mg and 0.66 (95% CI, 0.62 to 0.72) for 40 mg for PPE, 0.61 (95% CI, 0.48 to 0.78) for 20 mg and 0.86 (95% CI, 0.80 to 0.93) for 40 mg for diarrhea, and 0.46 (95% CI, 0.37 to 0.57) for 20 mg and 0.76 (95% CI, 0.71 to 0.82) for 40 mg for HTN from predicted exposures relative to a 60 mg dose (Table 3).

A statistically significant cabozantinib treatment effect, but not cabozantinib plasma concentration effect, was detected for fatigue and ALT/AST elevation endpoints. A higher rate of event for fatigue with HR 2.57 (95% CI, 1.45 to 4.55) and for ALT/AST elevation with HR 1.82 (95% CI, 1.05 to 3.15) was predicted for cabozantinib compared to placebo treatment.

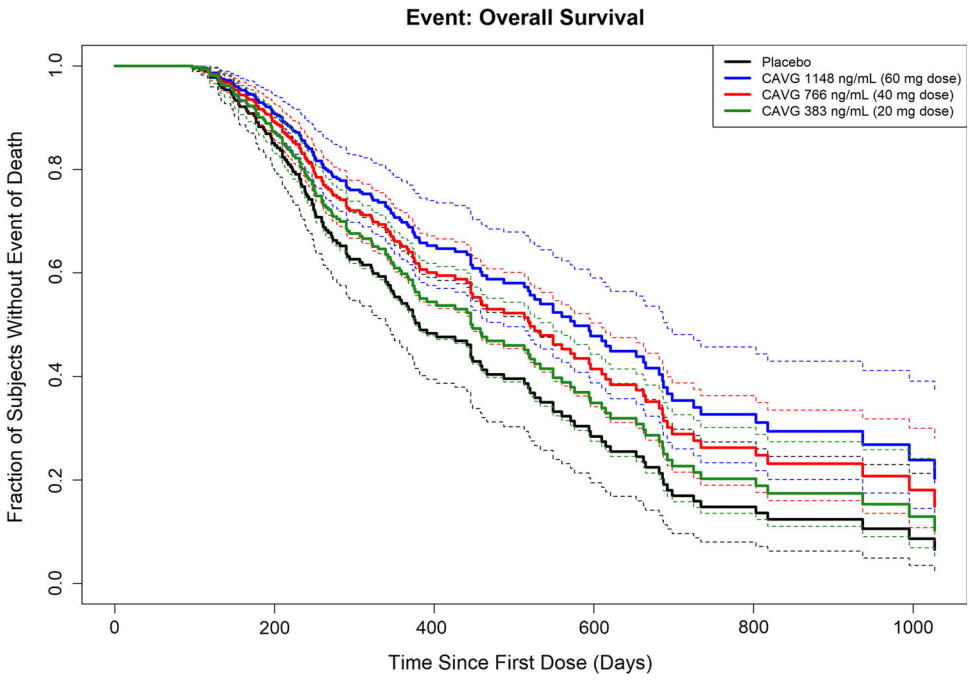

Fig. 2 Predicted time-to-event curves for overall survival. The solid line represents the fraction of subjects at each dose level without death over time. The dashed lines represent 95% confidence intervals. CAVG indicates predicted average cabozantinib concentration at steady state corresponding to dose level 20, 40, or 60 mg

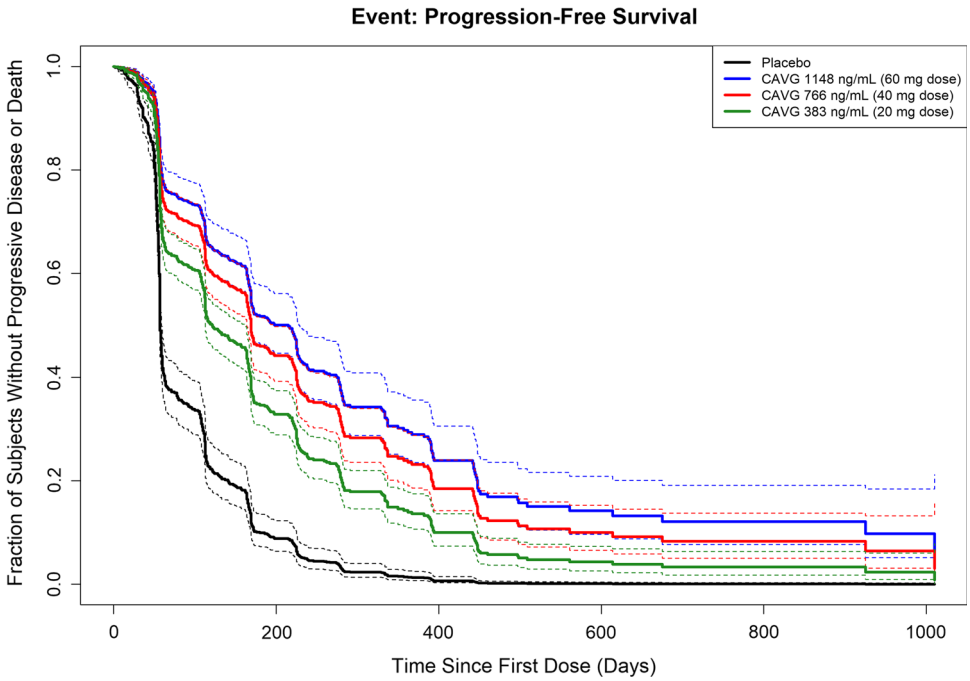

Fig. 3 Predicted time-to-event curves for progression-free survival. The solid line represents the fraction of subjects at each dose level without progression of disease or death over time. The dashed lines represent 95% confidence intervals. CAVG indicates predicted average cabozantinib concentration at steady state corresponding to dose level 20, 40, or 60 mg

Discussion

The CELESTIAL trial investigated cabozantinib's efficacy and safety in hepatocellular carcinoma patients. Patients received a cabozantinib dose of 60 mg or placebo once daily and could reduce the dose, as necessary, to first 40 mg then to 20 mg based on tolerability. ER models were developed to understand the relationship of cabozantinib exposure and the likelihood of selected efficacy and safety endpoints and the rationale for dose modification for hepatocellular carcinoma patients. The ER modeling was a sequential two-step PK/PD fitting process. First, actual dosing history from hepatocellular carcinoma patients from CELESTIAL was used in the PPK model to predict individual PK parameters and exposures. Second, these PK parameters and exposures were used to develop CPH models for each endpoint. Using the final ER models, simulations were performed for starting cabozantinib doses

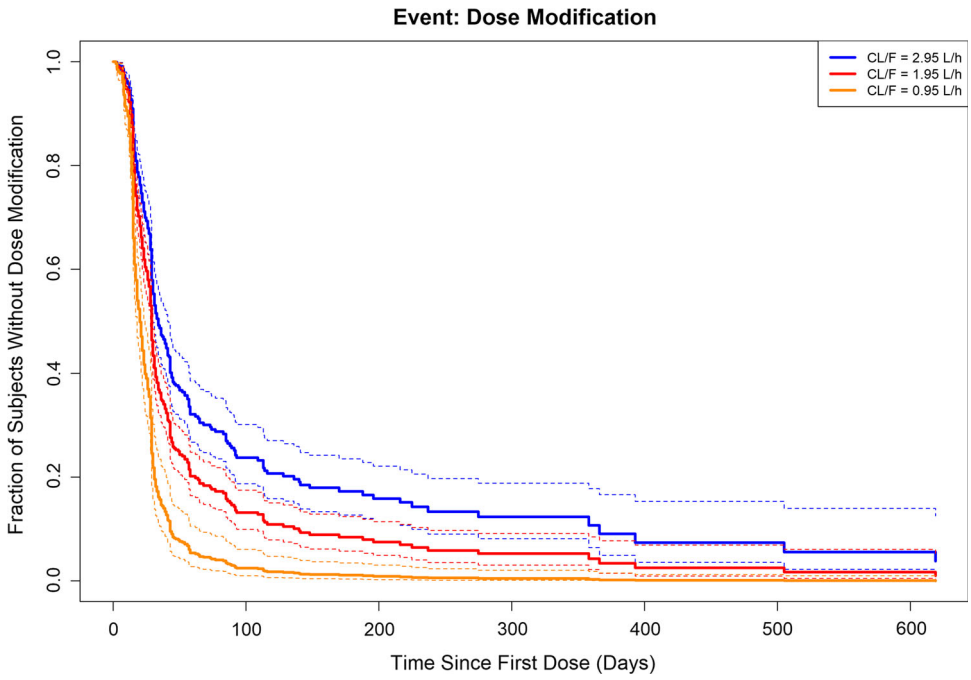

Fig. 4 Predicted time-to-event curves for dose modification for selected values of cabozantinib apparent clearance. The solid line represents the fraction of subjects at each selected value (0.95, 1.95, or 2.95 L/h) of cabozantinib apparent clearance (CL/F) without dose modification over time. The dashed lines represent 95% confidence intervals

of 60, 40, and 20 mg to predict the likelihood of efficacy and safety endpoints in hepatocellular carcinoma patients. These simulations were based on ideal condition of no dose modifications (no dose reductions or hold).

A total of 689 eligible patients from the CELESTIAL trial were included in the ER analysis. Requirements for the cabozantinib arm (N = 452) included at least one documented cabozantinib dose and at least one measurable PK concentration, which was needed to derive PK parameters and exposure for ER analysis. For the placebo arm (N = 237), patients were required to receive at least one dose of placebo. OS and PFS endpoints have different eligibility for inclusion in the analysis population. OS endpoint evaluated survival in only patients that lived long enough to receive at least 12 weeks of treatment. In contrast, PFS endpoint required a baseline tumor assessment and at least one evaluable post-baseline tumor assessment. The analysis population for OS included 52% (N = 361) of the 689 eligible patients, while the PFS population included 93% (N = 642) of the 689 eligible patients. Therefore, some patients in the OS analytic dataset were not in the PFS. Although dose modification was evaluated for both cabozantinib treated and placebo arms in CELESTIAL, the ER analysis for dose modification only included patients in the cabozantinib treated arm.

For efficacy, the relationship of OS and PFS with C_{avg} was statistically significant. With increasing plasma cabozantinib exposure, OS was longer and the rate of cancer progression or death decreased. Patients with hepatocellular carcinoma dosed at 60 mg daily of cabozantinib will result in steady state average concentration of 1148 ng/mL with predicted median overall survival of 576 days compared to 381 days if treated with placebo. For safety, statistically significant relationships were identified between C_{avg} and PPE, diarrhea and HTN. Cabozantinib treatment effect, but not C_{avg} effect, was found statistically significant for fatigue and ALT/AST elevation. A statistically significant relationship was identified between individual predicted cabozantinib clearance and the rate of dose modifications. Decreases in cabozantinib clearance were predicted to increase the rate of dose modifications. Higher cabozantinib exposures were predicted to increase likelihood of AE and subsequent dose reductions appeared to decrease the risk of AE.

Patients with higher clearance values eliminate cabozantinib faster and therefore have lower cabozantinib exposure. The increased cabozantinib clearance and the corresponding decreased cabozantinib exposure are predicted to decrease the rate of dose modifications. For example, a patient with a cabozantinib clearance of 0.95 L/h is predicted to have a 1.82 times greater risk of dose modification relative to a patient with an apparent clearance of 1.95 L/h.

To demonstrate that the rate of dose modifications was predicted to increase in patients with lower cabozantinib apparent clearance (CL/F), 28 days was selected as the cutoff since this was the duration it took for 50% of patients with typical CL/F of 1.95 L/h to undergo dose modification based on the model. The analytic dataset for dose modification for cabozantinib included 452 patients with individual predicted CL/F from the PPK model, event status, duration to first dose modification (dose hold or

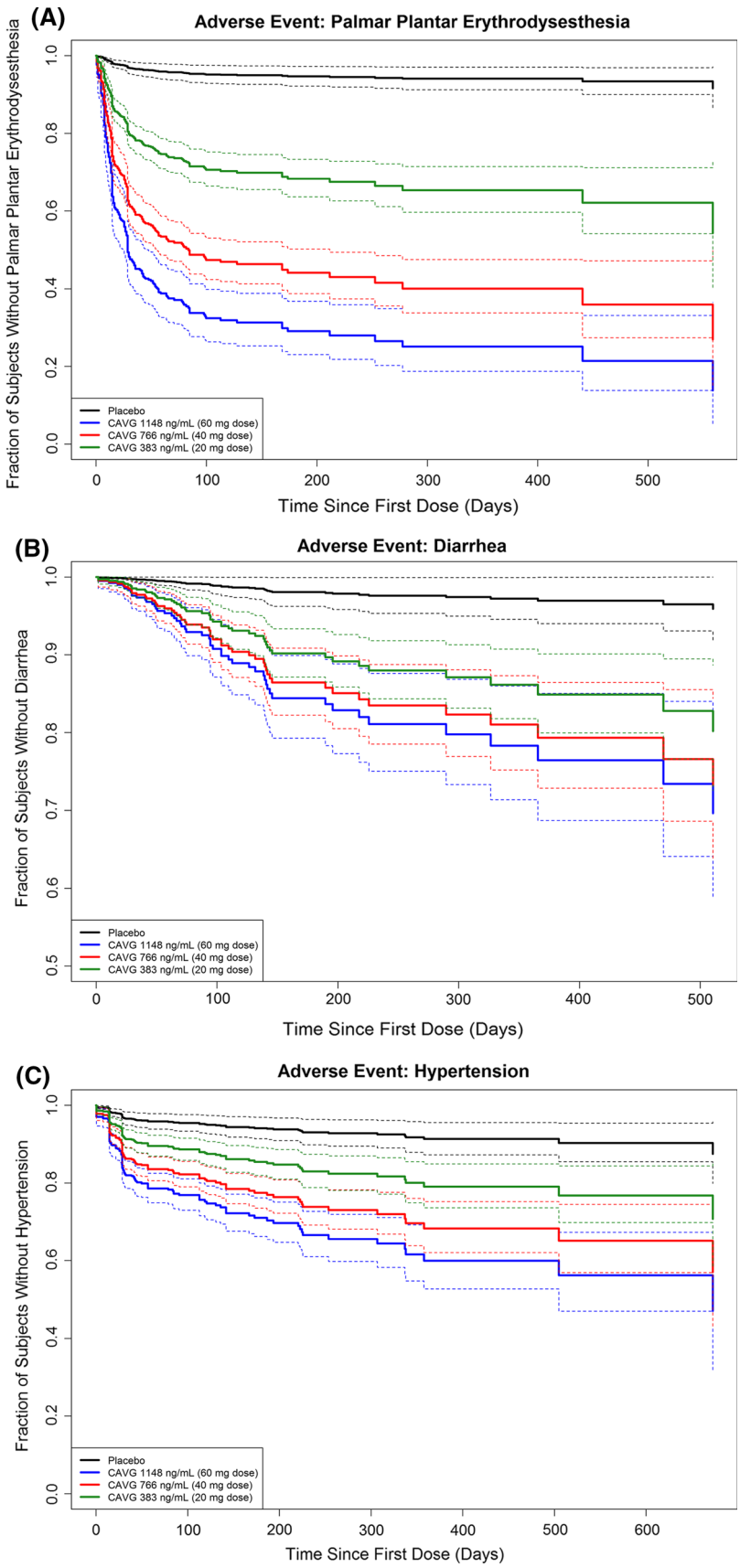

Fig. 5 Predicted time-to-event curves for **a** Palmar-plantar erythrodysesthesia syndrome, **b** diarrhea, and **c** hypertension. The solid line represents the fraction of subjects at each dose level without the indicated adverse event over time. The dashed lines represent 95% confidence intervals. CAVG indicates predicted average cabozantinib concentration at steady state corresponding to dose level 20, 40, or 60 mg

reduction), and censorship (study cutoff date or drug discontinuation date not attributed to adverse events). Before 28 days, 208 patients had dose modification event and their median CL/F was 1.74 L/h; 31 patients with median CL/F of 1.86 L/h were censored before 28 days. After 28 days, 161 patients with median CL/F of 2.16 L/h had dose modification; 52 patients with median CL/F of 2.53 L/h were censored after 28 days. The data clearly demonstrated that individual cabozantinib apparent clearance is related to the time to first dose modification.

These findings on individual predicted cabozantinib apparent clearance and the rate of dose modifications are consistent with previous ER analyses in patients with medullary thyroid cancer (MTC) and RCC [10, 11]. In addition, the ER relationship was significant for PPE, diarrhea, and HTN among RCC and hepatocellular carcinoma analyses.

Starting at 60 mg and dose-reducing appropriately provides patients with a chance to receive the therapeutic benefit of cabozantinib while also providing a way to limit the potential toxicity. Based on the PPK model, cabozantinib displays high inter-individual variability for CL/F at approximately 46% coefficient of variation [9]. For hepatocellular carcinoma patients with higher cabozantinib CL/F (lower exposures relative to patients with lower CL/F), the 60 mg dose provides an opportunity to achieve optimal clinical benefits relative to 40 and 20 mg starting doses. For hepatocellular carcinoma patients with lower cabozantinib CL/F, dose modifications from 60 mg due to AE would also provide patients opportunities to achieve therapeutic exposures for the clinical benefits and the doses can be reduced to manage AE. If all hepatocellular carcinoma patients were to initiate cabozantinib at a lower dose, patients with higher CL/F might not reach therapeutic drug concentration and would less likely to benefit from cabozantinib treatment.

Many pre-specified efficacy and safety endpoints in this ER analysis were based upon the previous knowledge of cabozantinib in other clinical indications. Although no relationship was determined for exposure or treatment for N/V or total bilirubin elevation endpoints, the frequencies of events for these endpoints were too small to ascertain an ER relationship.

The results of ER modeling and simulations of cabozantinib from patients in the CELESTIAL trial reflect the FDA labeling of 60 mg once daily of cabozantinib in hepatocellular carcinoma patients until disease progression or unacceptable toxicity [5]. Therapy is withheld for intolerable grade 2 adverse reactions, grade 3 or 4 adverse reactions, or osteonecrosis of the jaw. Dose reductions in 20 mg increments may resume upon resolution/improvement of AE.

Conclusions

Based on the ER analyses in hepatocellular carcinoma patients from the CELESTIAL trial, the cabozantinib exposure at the approved 60 mg daily dose is predicted to provide longer OS and a decreased rate of cancer progression or death compared to the predicted exposures at 40 mg or 20 mg starting doses. Higher cabozantinib exposure was predicted to increase the likelihood of AEs and subsequent dose reduction appeared to decrease these risks.

Compliance with ethical standards

Disclosures Steven Lacy, Linh Nguyen, and Benjamin Duy Tran are stockholders and current employees of Exelixis, Inc.

References

1. Global Burden of Disease Liver Cancer Collaboration (2017) The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol 3:1683–1691. https://doi.org/10.1001/jamaoncol.2017.3055
2. Samonakis DN, Kouroumalis EA (2017) Systemic treatment for hepatocellular carcinoma: still unmet expectations. World J Hepatol 9:80–90. https://doi.org/10.4254/wjh.v9.i2.80
3. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou Y-C, Joly AH (2011) Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 10:2298–2308. https://doi.org/10.1158/1535-7163.MCT-11-0264
4. Karagonlar ZF, Koc D, Iscan E, Erdal E, Atabey N (2016) Elevated hepatocyte growth factor expression as an autocrine c-Met activation mechanism in acquired resistance to sorafenib in hepatocellular carcinoma cells. Cancer Sci 107:407–416. https://doi.org/10.1111/cas.12891
5. Cabometyx® (cabozantinib) tablets (2019) US prescribing information. Exelix. Inc., Alameda, California. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208692s003lbl.pdf. Accessed 9 Jan 2019
6. Cabometyx® (cabozantinib) tablets (2018) Summary of product characteristics. Ipsen Pharma, Boulogne-Billancourt, France. https://www.medicines.org.uk/emc/product/4331/smpc. Accessed 1 Feb 2019
7. Abou-Alfa GK, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo B-Y, Cicin I, Merle P, Chen Y, Park J-W, Blanc J-F, Bolondi L, Klumpen H-J, Chan SL, Zagonel V, Pressiani T, Ryu M-H, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK (2018) Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 379:54–63. https://doi.org/10.1056/NEJMoa1717002
8. Lacy S, Hsu B, Miles D, Aftab D, Wang R, Nguyen L (2015) Metabolism and disposition of cabozantinib in healthy male volunteers and pharmacologic characterization of its major

metabolites. Drug Metab Dispos 43:1190–1207. https://doi.org/10.1124/dmd.115.063610
9. Nguyen L, Chapel S, Tran BD, Lacy S (2019) Updated population pharmacokinetic model of cabozantinib integrating various cancer types including hepatocellular carcinoma. J Clin Pharmacol 59:1551–1561. https://doi.org/10.1002/jcph.1467
10. Lacy S, Nielsen J, Yang B, Miles D, Nguyen L, Hutmacher M (2018) Population exposure-response analysis of cabozantinib efficacy and safety endpoints in patients with renal cell carcinoma. Cancer Chemother Pharmacol 81:1061–1070. https://doi.org/10.1007/s00280-018-3579-7
11. Miles D, Jumbe NL, Lacy S, Nguyen L (2016) Population pharmacokinetic model of cabozantinib in patients with medullary thyroid carcinoma and its application to an exposure-response analysis. Clin Pharmacokinet 55:93–105. https://doi.org/10.1007/s40262-015-0295-x