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Exposure-response modeling of cabozantinib in patients with renal cell carcinoma: Implications for patient care

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ABSTRACT

Cabozantinib is an oral tyrosine kinase inhibitor (TKI) approved for the treatment of patients with advanced renal cell carcinoma (RCC) at a dose of 60 mg/day. As with other TKIs, cabozantinib is associated with high interpatient variability in drug clearance and exposure that can significantly impact safety and tolerability across a patient population. To optimize cabozantinib exposure (maintaining efficacy and tolerability) for the individual, patients may require treatment interruption with dose reduction (40 mg/day and then 20 mg/day). In the pivotal Phase 3 METEOR trial, cabozantinib significantly improved overall survival, progression-free survival and the objective response rate compared with everolimus in patients with advanced RCC who had received previous treatment with a VEGFR TKI. Dose reductions were common for patients receiving cabozantinib (60%) but effective as only 9% discontinued treatment due to adverse events (AEs). In this review, we discuss pharmacometric analyses that evaluated the impact of cabozantinib dose on efficacy and safety outcomes during the METEOR study. Exposure-response models demonstrate that the risk of experiencing adverse events and dose reduction is increased in patients with low cabozantinib clearance versus typical clearance and decreased in patients with high clearance. Dose reduction of cabozantinib to manage AEs is predicted to have minimal impact on efficacy as AEs are more likely to occur in patients with low clearance and higher exposure to cabozantinib. These analyses further support a dose modification strategy to optimize cabozantinib exposure for individual patients.

Introduction

The vascular endothelial growth factor (VEGF) pathway is an established target in clear-cell renal cell carcinoma (RCC) with a number of VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) approved for the treatment of patients with advanced disease. As our understanding of RCC biology has advanced, new targets have emerged. Cabozantinib is an oral TKI that inhibits VEGFR as well as the novel targets MET and AXL, which are implicated in RCC growth, metastasis, and therapeutic resistance [1]. Based on positive data from the phase 3 METEOR study (ClinicalTrials.gov, NCT01865747) in patients previously treated with at least one antiangiogenic agent and the randomized phase 2 CABOSUN study (NCT01835158) in treatment-naïve patients with intermediate- or poor-risk disease [2–5], cabozantinib has become a standard of care for advanced RCC [6,7]. In these studies, cabozantinib demonstrated clinical benefit over existing standards of care with a safety and tolerability profile that was manageable with dose modification.

Dose modification is a common strategy with TKI therapy to balance efficacy and tolerability. TKIs, including cabozantinib, are associated with high interpatient variability in drug clearance [8–13]. Variability in clearance leads to wide ranges in steady-state exposure to the drug. Generally, patients start TKI treatment at the recommended dose, and if needed, the dose is reduced to address overexposure and resolve intolerable adverse events (AEs). However, there is some concern that dose reduction may impact efficacy. It is, therefore, essential to develop informed strategies to optimize the dose for the individual patient.

Pharmacometric analyses have been used to support and guide

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dosing strategies with TKIs [14–16]. Pharmacometrics integrates pharmacology, statistics, and computational modeling [14]. Population pharmacokinetic (popPK) models characterize PK parameters across a patient population and identify factors associated with variability in exposure [17], while exposure–response (ER) models predict the relationship of drug exposure with efficacy, safety, and tolerability and the potential clinical implications of dose modification [15].

To better inform dosing strategies with cabozantinib, popPK and ER models were developed to evaluate the relationship of cabozantinib dose, clearance, and exposure with efficacy, safety, and tolerability during the METEOR study [18–21]. These analyses support dose modification as the principal strategy to manage tolerability of cabozantinib while maintaining efficacy [22,23]. In this review, we present an overview of previously published pharmacometric analyses of cabozantinib in patients with advanced RCC and discuss the implications of these analyses in terms of patient care and appropriate dose modification.

Clinical outcomes of cabozantinib in RCC

For both the METEOR and CABOSUN studies, cabozantinib was administered orally at a dose of 60 mg/day, with dose interruptions and reductions to 40 and 20 mg/day recommended to manage AEs [2,4]. The 60-mg/day dose was selected based on the activity, safety, and tolerability of cabozantinib in a phase 1 trial of patients with previously treated metastatic RCC and studies of cabozantinib in other solid tumors [24,25]. Supplementary Table 1 summarizes outcomes from key clinical studies of cabozantinib in RCC. In the pivotal phase 3 METEOR study, cabozantinib was compared with the mammalian target of rapamycin (mTOR) inhibitor everolimus in patients with advanced RCC who had received prior therapy with a VEGFR TKI (N = 658) [2,3]. Cabozantinib improved progression-free survival (PFS) as assessed by independent review committee (IRC) relative to everolimus (median 7.4 vs 3.9 months; hazard ratio [HR] 0.51; 95% confidence interval [CI] 0.41–0.62; $p < 0.0001$), as well as overall survival (OS) (median 21.4 vs 16.5 months; HR 0.66; 95% CI 0.53–0.83; $p = 0.00026$) and the objective response rate (ORR) (17% vs 3%; $p < 0.0001$) [3]. In the phase 2 CABOSUN study, cabozantinib was compared with sunitinib as a first-line treatment in intermediate and poor-risk patients (per International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] criteria) with metastatic RCC (N = 157) [4,5]. PFS assessed by IRC was significantly longer with cabozantinib than with sunitinib at 8.6 versus 5.3 months (HR 0.48; 95% CI 0.31–0.74; $p = 0.0008$), with a corresponding ORR of 20% versus 9% [5].

The safety and tolerability profile of cabozantinib was consistent across the METEOR and CABOSUN studies. In the METEOR study, the most commonly reported AEs of any grade were diarrhea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), palmar-plantar erythrodysesthesia (PPE, 42%), and hypertension (37%); and the most common grade 3/4 AEs were hypertension (15%), diarrhea (11%), fatigue (9%), and PPE (8%) [2]. Cabozantinib dose reductions were frequently employed to manage AEs [2–5]. In METEOR, 40% of patients receiving cabozantinib maintained the 60-mg/day dose, while 60% required at least 1 dose reduction to 40 mg/day and 20% required a second dose reduction to 20 mg/day [2,26]. AEs that led to cabozantinib dose reduction included diarrhea (16%), PPE (11%), fatigue (10%), and hypertension (8%). While dose reductions were more frequent with cabozantinib than with everolimus (60% vs 25%), the rates of discontinuation due to AEs were similar (9% vs 10%).

Results from the METEOR and CABOSUN studies supported approval of cabozantinib by the United States Food and Drug Administration for the treatment of patients with advanced RCC, and approval by the European Medicines Agency for the treatment of patients with advanced RCC previously treated with a VEGF-pathway inhibitor or treatment-naïve patients with intermediate- or poor-risk disease [6,7].

Table 1
Cabozantinib PK parameters estimated from popPK base model for patients with RCC and single dose PK data from healthy volunteers [18,26,27]

Parameter	RCC PopPK* 60-mg/day dose	Healthy Volunteers 60-mg dose (single-dose study)
$t_{1/2}$	99 h	111 h
CL/F	2.23 L/h	2.35 L/h
Coefficient of variability	46%	67%
Vc/F	319 L	363 L

CL/F, plasma clearance; h, hour; popPK, population pharmacokinetics; RCC, renal cell carcinoma; $t_{1/2}$, terminal elimination half-life; Vc/F, apparent volume of distribution of central compartment.

* Based on pooled data from healthy volunteers (N = 63) and patients with RCC enrolled in the cabozantinib arm of METEOR with 2 measurable pharmacokinetic samples (N = 282). PK parameters were estimated from the PopPK Model.

Pharmacokinetics of cabozantinib in patients with RCC

Cabozantinib PK has been characterized in healthy volunteers and in patients with various solid tumors, including RCC. In healthy volunteers receiving a single 20-, 40-, or 60-mg dose of cabozantinib, maximum plasma concentrations were reached in 3 to 4 h with a mean maximum plasma concentration of 343 ng/mL at the 60-mg dose [8,27]. With daily oral dosing, the median time to steady-state cabozantinib concentration in patients with solid tumors is approximately 15 days with a 4- to 5-fold mean cabozantinib accumulation (based on area under the curve) compared with single-dose administration [28].

Cabozantinib clearance is variable. Cabozantinib is metabolized primarily by the cytochrome P450 (CYP) 3A4 pathway and to a far lesser extent by CYP2C9, with a relatively long terminal half-life (99–120 h). Food intake, hepatic impairment, and concomitant use of medications that inhibit or induce the CYP3A4 pathway are known to affect cabozantinib plasma concentrations [29–32]. In healthy volunteers administered 60 mg, the average clearance was 2.35 L/h with a coefficient of variability (CV) of 67% [27].

Generally, the PK characteristics of cabozantinib in patients with advanced RCC are consistent with those of healthy volunteers (Table 1). As part of the METEOR study, plasma samples were obtained for PK assessments from patients assigned to the cabozantinib treatment arm, and a popPK model was developed using data from METEOR patients along with healthy volunteers [18,33]. The estimated terminal half-life for patients with RCC was 99 h. Cabozantinib clearance was variable, with a predicted range of 0.51 to 7.24 L/h (Fig. 1**A**) [21] and an estimated CV of 46% [26]. In a multiple covariate model, baseline patient characteristics such as age, body mass index, and baseline laboratory parameters including hemoglobin, bilirubin, alanine aminotransferase, serum albumin, and creatinine clearance did not have a statistically significant effect on clearance. Asian race and female gender were associated with lower cabozantinib clearance compared with their respective counterparts (reductions of − 27% and − 21%, respectively); however, these were deemed not clinically significant given the variability in clearance for the overall population [18,26].

The relationship of cabozantinib clearance with dosing was explored using data from METEOR [21]. From the popPK model, clearance for a typical white male patient was estimated at 2.23 L/h [18]. Additional clearance values of 1.3 and 3.3 L/h were chosen to represent patients with low and high clearance characteristics, respectively (Fig. 1**A**) [21]. At the 60-mg/day dose, the average plasma concentration of cabozantinib at steady state was estimated to be 1122 ng/mL for patients with typical cabozantinib clearance (Fig. 1**B**), with the concentration increasing by + 71% (1923 ng/mL) for patients with low clearance but decreasing by − 32% (758 ng/ml) for patients with high clearance [21]. A stepwise dose reduction to 40 or 20 mg/day for a

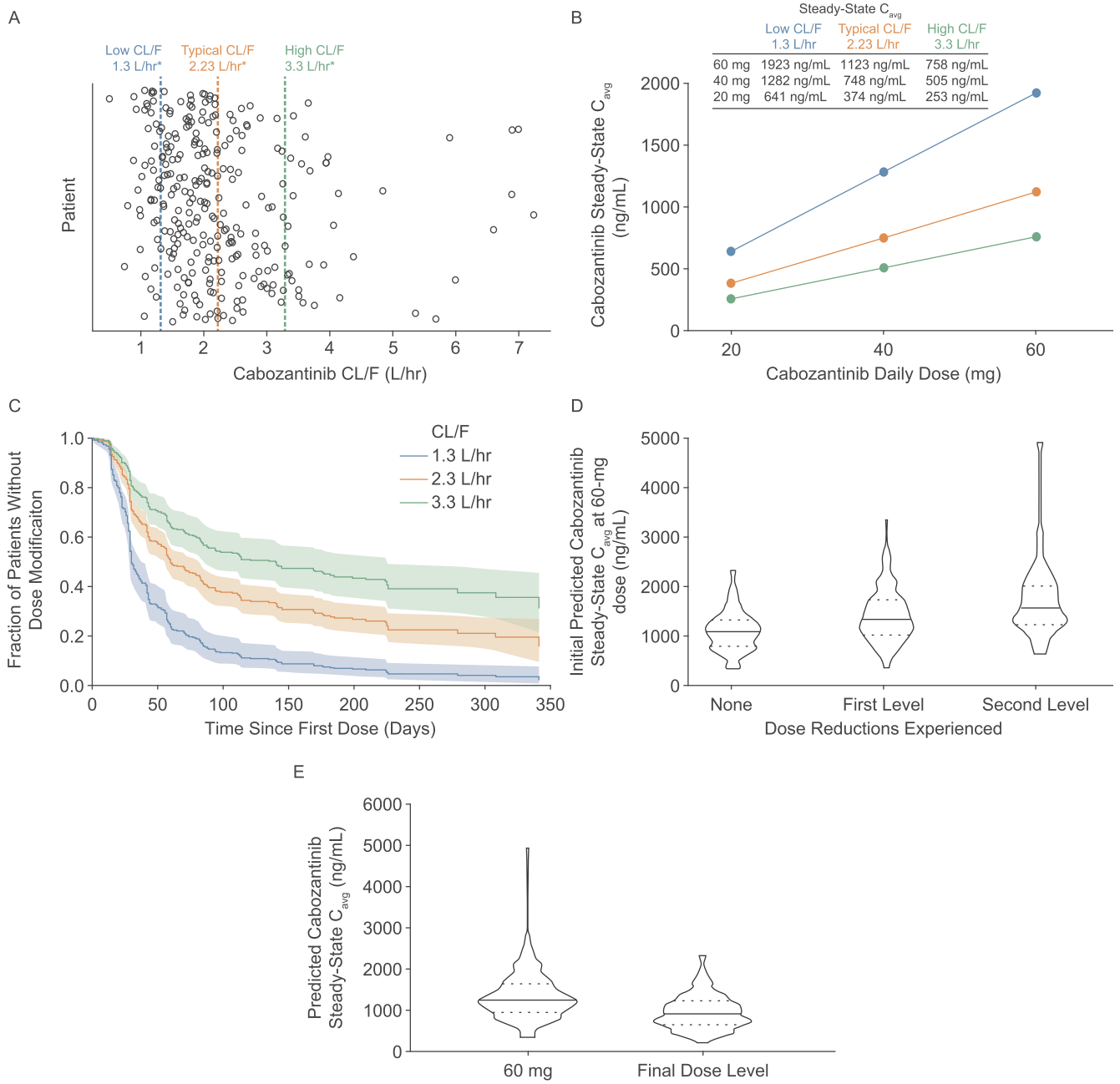

Fig. 1. Cabozantinib in RCC – relationship of clearance with dosing. (A) Distribution of calculated cabozantinib clearance values in patients from the METEOR study (N = 282), with values modeled for low, typical, and high clearance indicated [21]; (B) Predicted cabozantinib concentrations at varying doses with different population PK-derived clearance values (N = 282) [21]; (C) Predicted fractions of patients without dose modification for selected values of cabozantinib clearance at a dose of 60 mg/day (N = 317) (*Lacy et al.* [20], *reprinted under the terms of the Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/; the figure has been modified from the original*); (D) Distribution of predicted steady-state cabozantinib C_{avg} at 60-mg/day dosing for patients in METEOR based on their history of dose reduction (median and quartiles shown) (data on file); (E) Predicted steady-state cabozantinib C_{avg} for all patients at the 60-mg/day dose and at the final dose level experienced (median and quartiles shown) (data on file). *Based on popPK analyses. C_{avg}, average plasma concentration; CL/F, plasma clearance; PK, pharmacokinetics; popPK, population PK; RCC, renal cell carcinoma.

patient with lower clearance would bring exposure to a more typical level.

The probability of dose modification during METEOR increased as clearance decreased; patients with low clearance had a high rate of dose modifications during the initial weeks of cabozantinib treatment (Fig. 1**C**) [20]. Furthermore, the subgroups of patients who dose-reduced to 40- or 20-mg/day dose levels showed higher initial exposure compared with those who did not (data on file) (Fig. 1**D**). With dose reductions, predicted median cabozantinib exposure across the entire treated population was lowered from a median of 1340 ng/mL at the initial 60-mg/day dose to a median of 957 ng/mL when estimated at the final dose level of each patient (Fig. 1**E**), with a corresponding reduction in the standard deviation from 566 ng/mL to 414 ng/mL (data on file).

Cabozantinib Exposure-Response modeling

Initial ER models were developed to characterize the relationship of cabozantinib dose with outcomes during METEOR for patients with typical baseline characteristics and clearance [20]. Given the scope of

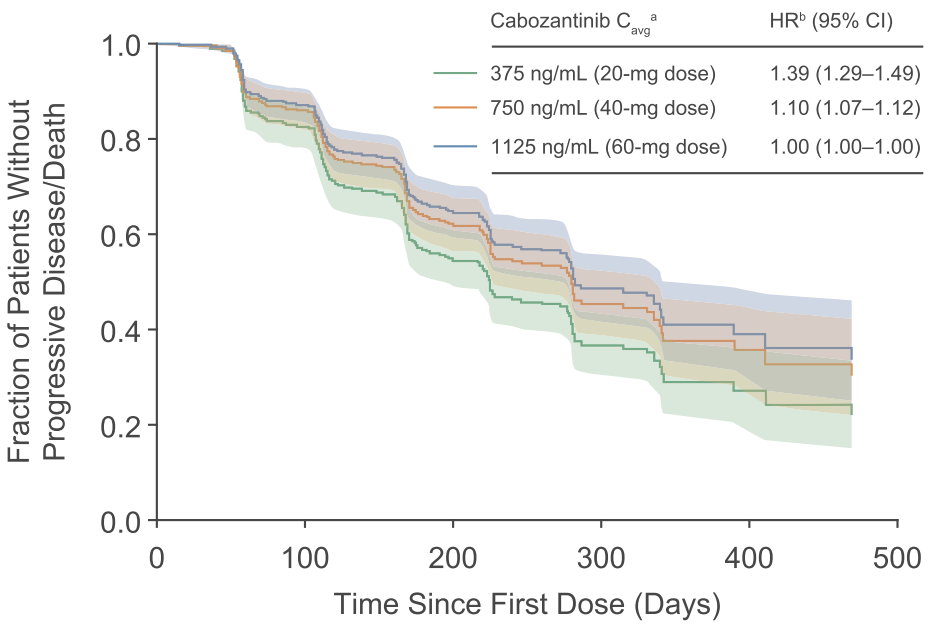

Fig. 2. Kaplan–Meier estimates of progression-free survival for simulated doses of cabozantinib for a typical white male patient with cabozantinib clearance of 2.23 L/h. *Lacy et al.* [20], *reprinted under the terms of the Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/; the figure has been modified from the original.* Predicted PFS for typical individual predicted steady-state average cabozantinib concentration at 20-mg/day (green), 40-mg/day (orange), and 60-mg/day (blue) doses with 95% CIs; based on 172 events in 315 RCC patients from the METEOR study with at least 1 measurable cabozantinib concentration. Time-varying average cabozantinib concentration was estimated over the 3 weeks prior to a PFS event (C_{avg3w}); the relationship between C_{avg3w} and PFS was evaluated using nonlinear models over a range of EC_{50} values (concentration that gives half-maximal response) for C_{avg3w}. An EC_{50} of 100 ng/mL resulted in the best model fit and was used to generate the predicted PFS curves and is considerably lower than the predicted steady-state average cabozantinib concentrations associated with doses of 20 mg, 40 mg, and 60 mg (375, 750, and 1125 ng/mL, respectively). [a]Cabozantinib concentrations correspond to model-predicted typical individual steady-state average concentrations for the 20-, 40-, and 60-mg/day once-daily dosing regimens. [b]HR relative to a 1125-ng/mL cabozantinib concentration calculated over the 3 weeks prior to time of event. Estimated PFS EC_{50} = 100 ng/mL based on best nonlinear ER model. C_{avg}, average plasma concentration; CI, confidence interval; EC_{50}, concentration of the drug that gives the half-maximal response; HR, hazard ratio; PFS, progression-free survival; RCC, renal cell carcinoma.

this review, we have limited our discussion on ER methodology, but detailed methods are described by Lacy et al. [20]. Cox proportional hazard models estimated hazards for PFS and select AEs across the 60-, 40-, and 20-mg/day dosing options. Given the variability in cabozantinib clearance and its relationship with exposure and dose modification, ER models were then extended to evaluate the relationship of cabozantinib dose with outcomes across the spectrum of patients with varying clearance values. The models compared 60- and 40-mg/day doses in patients with low (1.3 L/h), typical (2.23 L/h), and high clearance (3.3 L/h) [20,21].

For the typical patient, starting cabozantinib at a lower dose of 20 or 40 mg/day was predicted to increase the hazard of disease progression or death compared with a 60-mg/day dose (Fig. 2) [20]. A dose of 20 mg/day was predicted to have notable impact, with a +39% hazard increase for PFS compared with a dose of 60 mg/day, while the predicted hazard increase for a dose of 40 mg/day versus 60 mg/day was limited at +10%. Results from tumor response models were consistent with PFS estimates. The predicted ORR for patients with typical clearance was 8.7% at a 20-mg/day dose, 15.6% at 40 mg/day, and 19.1% at 60 mg/day; and in a tumor growth model, the predicted median change in tumor size from baseline was −4.5%, −9.1%, and −11.9%, respectively [20].

Exposure-response models for safety focused on select AEs associated with dose modification, including PPE (grade ≥ 1), fatigue/asthenia (grade ≥ 3), diarrhea (grade ≥ 3), and hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg). For the typical patient, a higher cabozantinib dose was predicted to increase the risk of AEs [19–21]. Based on a 60-mg/day versus a 40-mg/day dose, the HR was 1.49 (95% CI 1.27–1.75) for PPE, 1.42 (95% CI 1.11–1.82) for fatigue/asthenia, 1.36 (95% CI 1.15–1.60) for hypertension, and 1.33 (95% CI 1.04–1.70) for diarrhea; corresponding HRs for a 60-mg/day versus a 20-mg/day dose were 2.21 (95% CI 1.60–3.06), 2.01 (95% CI 1.22–3.31), 1.85 (95% CI 1.33–2.57), and 1.78 (95% CI 1.08–2.91). There was no apparent ER relationship for nausea/vomiting (grade ≥ 3) or stomatitis (grade ≥ 3).

When ER modeling is extended to include both lower and higher cabozantinib clearance values, the impact of dose modification on outcomes becomes more well defined. Reducing the dose is predicted to have a modest impact on PFS (HR = 1.06) for patients with lower clearance, while substantially improving AE tolerability (Fig. 3). The hazard rate of PPE, for example, was predicted to decrease by −49% with a dose of 40 mg/day versus 60 mg/day for patients with low cabozantinib clearance. Conversely, for patients with higher clearance, use of the 40-mg/day dose has a more noticeable impact on PFS compared with 60 mg/day (HR = 1.13), with a corresponding decrease of −24% in the hazard rate of PPE [21].

It is important to note the limitations inherent to ER analyses, for example, the effects of unrecognized confounders and imbalances within subgroups [34]. Best practice necessitates the use of data from controlled, randomized trials for ER analysis; however, clinical trial populations may differ considerably from those seen in the clinic, who are often older and have more comorbidities and interpatient variation. Nevertheless, ER modeling is a powerful tool for benefit-risk evaluation and can help to maximize the utility of clinical trial data, including in a regulatory setting. ER models from METEOR formed part of the clinical development of cabozantinib and were considered by regulatory bodies when formulating label recommendations [26,35]. Taken together, ER models support a dose modification strategy to improve tolerability with cabozantinib while maintaining efficacy. Significant AEs likely reflect lower clearance and overexposure to cabozantinib; dose reduction is predicted to significantly improve AE tolerability in these patients, while having a minimal effect on efficacy. Box 1 summarizes key points of the benefit-to-risk profile of cabozantinib described in the ER models.

Optimizing the cabozantinib dose for an individual Patient: Practical strategies for dosing

Clinicians are faced with a number of challenges for treating individual patients with advanced RCC. Patients are often older, present with comorbidities, and are receiving multiple concomitant medications [36–38]. The cabozantinib label provides guidance on dosing and dose modification based on adverse events, food intake, concomitant medications, and hepatic impairment (Box 2). Prior to starting patients on cabozantinib, it is important for clinicians to conduct a thorough medical examination, including an assessment of medical history,

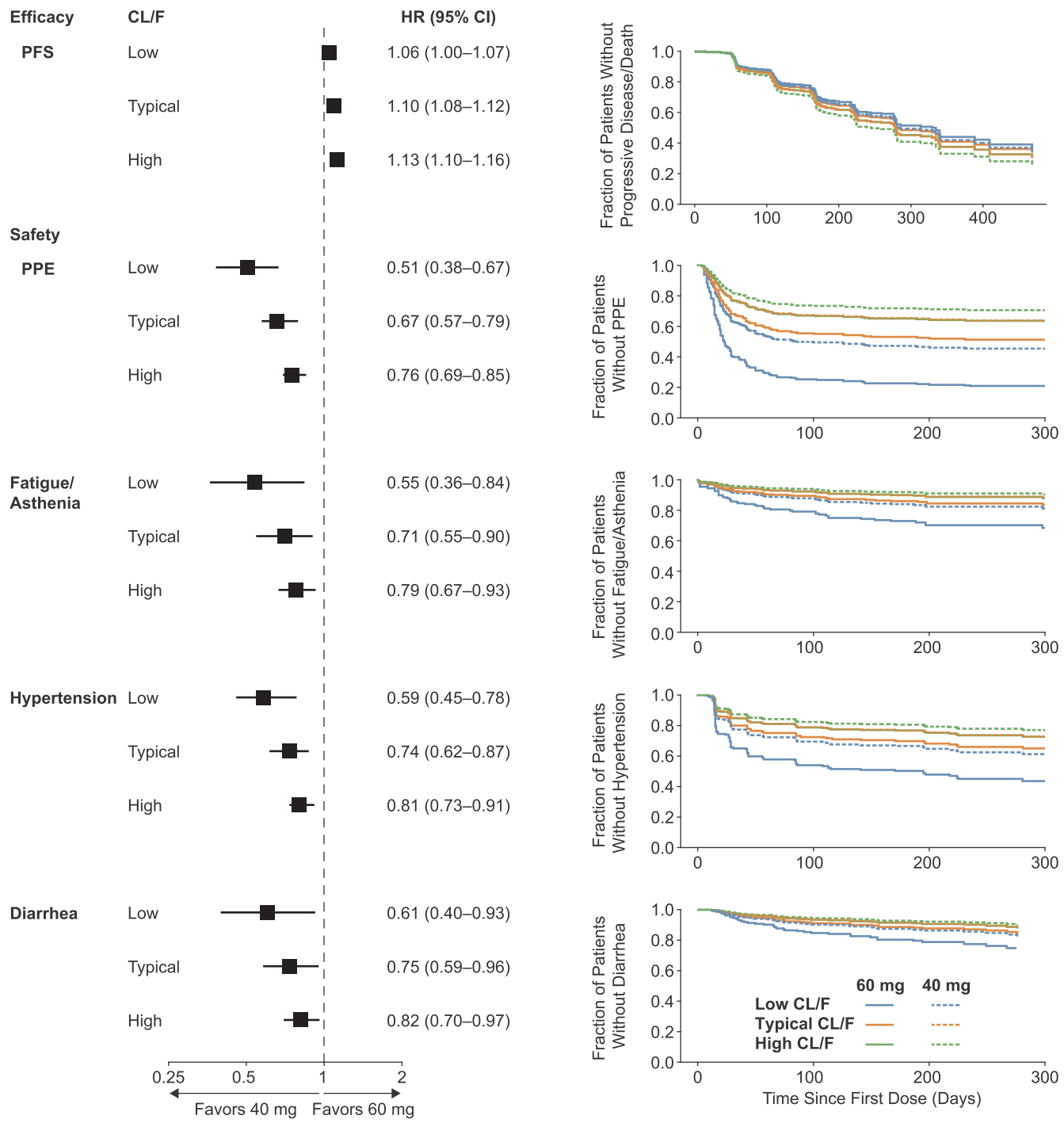

Fig. 3. Estimated hazard of PFS and selected adverse events and corresponding Kaplan–Meier estimates for doses of cabozantinib (40 mg/day vs 60 mg/day) as assessed by predicted clearance values. *Survival curves reproduced with permission from Jonasch et al.* [21]. Based on: 172 events in 315 patients for PFS; 137 events for PPE (grade ≥ 1), 42 events for fatigue/asthenia (grade ≥ 3), 103 events for hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg), and 38 events for diarrhea (grade ≥ 3) in 318 patients. Clearance values: Low, 1.3 L/h; typical, 2.23 L/h; and high, 3.3 L/h. AE, adverse event; CI, confidence interval; CL/F, plasma clearance; HR, hazard ratio; PFS, progression-free survival; PPE, palmar-plantar erythrodysesthesia.

current medications, and any prior experience with TKI treatment. Clinicians should identify concomitant medications that induce or inhibit the CYP3A4 pathway [6,7]. Strong CYP3A4 modifiers should be avoided, and patients should be switched to alternate medications that have no or minimal CYP3A4 modification whenever possible. If concomitant use with a strong CYP3A4 modifier cannot be avoided, then the cabozantinib dose should be adjusted as indicated per the US label (note the European Summary of Product Characteristics does not include recommendations for dose adjustments based on potential CYP3A4 interactions).

Because of the interpatient variability in clearance (CV of 46%) and exposure, clinicians should anticipate that many patients receiving cabozantinib will require dose modifications to manage exposure and tolerability. The most common AEs associated with cabozantinib generally emerge within 3–5 weeks of treatment initiation and are likely a marker of low cabozantinib clearance and high exposure [26,39]. As shown in the Kaplan–Meier curves (Fig. 3), PPE emerges rapidly in patients with low cabozantinib clearance. During METEOR, median

Box 1
Cabozantinib Exposure-Response (ER) Summary and Recommendations.

- ER modeling provides further support for treating patients with the highest tolerable dose of cabozantinib, balancing efficacy and tolerability.
- There is considerable interpatient variability in cabozantinib clearance and exposure. Because cabozantinib is administered at a fixed dose, clinicians should consider variability in cabozantinib clearance to optimize the dose for each patient during therapy.
- ER models predict improved efficacy with higher doses of cabozantinib but also increased risk of adverse events (AEs).
- **Patients with high cabozantinib clearance** are less likely to experience an AE that requires dose modification during the early months of treatment. These patients should be maintained at the 60-mg/day dose as tolerated.
- **Patients with typical cabozantinib clearance** are likely to experience an AE that requires dose modification during the early months of treatment. The dose should be reduced to 40 mg/day when needed to improve tolerability. ER modeling predicts that dose reduction to 40 mg/day will not have a clinically significant impact on efficacy. Further dose reduction to 20 mg/day may be necessary to improve long-term tolerability for a minority of treated patients.
- **Patients with low cabozantinib clearance** are at high risk of experiencing an AE that requires dose modification during the early months of treatment. These patients may require a second-level dose reduction to 20 mg/day. At 20 mg/day, cabozantinib exposure for a patient with low clearance is comparable to exposure for a patient with typical clearance receiving 40 mg/day or for a patient with high clearance receiving 60 mg/day.
- Dose reduction to 20 mg/day may negatively impact efficacy for patients with high or typical cabozantinib clearance. The 20-mg/day dose should be used only in patients for whom 40 mg/day is intolerable; this intolerability is likely associated with low clearance and dose reduction should have a minimal effect on efficacy.

time to first occurrence was 3.0 weeks (interquartile range [IQR], 2.0–6.1) for hypertension, 3.4 weeks (IQR, 2.3–6.1) for PPE, and 4.9 weeks (IQR, 2.7–8.1) for diarrhea [26]. Corresponding to the early onset of AEs, the median time to first dose reduction was 7.9 weeks (range, 1.4–50.7), and median time to second dose reduction was 13.3 weeks (range, 4.1–45.3) [26]. Given that the time to steady-state concentration for cabozantinib is ~ 15 days with a relatively long half-life of ~ 99 h, dose interruption until resolution or improvement is appropriate prior to dose reduction. Clinicians should be mindful that some AEs can be more readily managed with supportive care than others. The ratio of patients requiring a dose reduction for an AE to the total number of patients experiencing the AE (any grade) was 38/139 (27%) for PPE, 54/245 (22%) for diarrhea, 25/122 (20%) for hypertension, and 33/186 (18%) for fatigue [26].

It is important for clinicians to discuss with their patients the objectives of treatment and the balance between efficacy (prolonged survival, tumor control, and potential symptom relief) and treatment side effects [2–5]. Patients need to be aware that AEs can impact quality of life and to understand how to recognize the signs of the more common events. Patients should understand that adverse effects need to be addressed promptly and may require dose interruptions, reductions, or possibly treatment discontinuation. Patients need reassurance that dose reductions are unlikely to have a clinically significant impact on efficacy but should improve tolerability so that they can remain on treatment.

A number of prophylactic and supportive care measures can be implemented to mitigate the risk and severity of some of the more common side effects, including PPE, fatigue, gastrointestinal events, and hypertension [39,40]. Clinicians should identify any potential drug–drug interactions with concomitant medications prior to treatment initiation [39,41,42]. Cabozantinib does not have a clinically significant effect on QTc interval; and therefore, coadministration with QTc-prolonging agents such as antiemetic therapy with serotonin inhibitors is not contraindicated. Clinicians should consider monitoring patients with a history of QT interval prolongation or at-risk patients (eg, patients with relevant cardiac disease) during cabozantinib treatment [6,7,29,41,43].

Currently, there is no strong evidence to support dose adjustments based on age, sex, or race [18,33]. However, in a subgroup analysis of METEOR outcomes by age, AEs emerged more rapidly in a small subgroup of elderly patients (n = 27) receiving cabozantinib compared with younger patients; and elderly patients required more frequent dose reductions. The median time to a grade ≥ 3 AE was 3.4 weeks for patients ≥ 75 years of age versus 16.1 weeks for patients 65–74 years of age, and the corresponding rates of dose reduction were 85% versus 61% [44]. These data suggest reducing the initial dose of cabozantinib based on age may be warranted, but additional data are needed to support a clinical recommendation. Regardless, hepatic function should be assessed as elderly patients can have reduced liver mass and hepatic function [45], and older patients should be closely monitored for

Box 2
Cabozantinib Dosing Recommendations [6,7]

- The approved dose for cabozantinib is 60 mg/day, which should be maintained during the course of treatment as tolerated.
- Cabozantinib should be administered at least 1 h before or at least 2 h after eating.
- Grade 1/2 adverse events (AEs) can often be managed with supportive care. Cabozantinib should be held if a patient experiences an intolerable grade 2 AE, a grade 3/4 AE, or osteonecrosis of the jaw (a rare [< 1%] but serious event). Once the AE has resolved to grade 1 or to baseline level, cabozantinib should be restarted at a dose reduced by 20 mg/day. If the previous dose was 20 mg/day, patients should be restarted at 20 mg/day or cabozantinib should be discontinued.
- Clinicians should be aware of factors that can modify cabozantinib exposure. Cabozantinib is metabolized by the CYP3A4 pathway; therefore, patients receiving concomitant strong CYP3A4 inhibitors should have their dose lowered by 20 mg/day, while those receiving concomitant strong CYP3A4 inducers should have the dose increased by 20 mg/day. If the concomitant medication is discontinued, the cabozantinib dose should be adjusted appropriately after a 2–3-day washout period.
- Per the US FDA prescribing information, patients with moderate hepatic impairment (Child-Pugh B) should have their dose reduced to 40 mg/day given the potential for increased exposure, and these patients should be closely monitored. (Note that the European Summary of Product Characteristics does not recommend dose adjustments for moderate hepatic impairment due to limited data). Cabozantinib should be avoided in patients with severe hepatic impairment (Child-Pugh C).
- Dose adjustments are not recommended for patients with mild hepatic impairment or mild to moderate renal impairment. Cabozantinib use has not been established in patients with severe renal impairment.

emerging AEs. A number of descriptive studies have reported outcomes in patients treated with cabozantinib using modified dosing strategies [46–48]. However, more retrospective and prospective data are needed to support definitive randomized controlled trials to evaluate novel dosing strategies with cabozantinib, such as a dose-escalation approach. As the clinical data set for cabozantinib in RCC grows, future studies should continue to assess the impact of comorbidities and concomitant medications (eg, CYP3A4 modifiers) on dosing and clinical outcomes.

Conclusions

Clinical data and ER modeling support cabozantinib at a dose of 60 mg/day for the treatment of patients with advanced RCC, with a dose modification strategy to manage AEs. Because of interpatient variability in cabozantinib clearance, clinicians should anticipate that many patients may experience AEs during the early months of treatment. Grade 1 or 2 AEs can often be managed with supportive care alone, but intolerable grade 2 or grade 3/4 AEs require prompt dose interruption and subsequent reduction. Judicious use of dose modification in patients experiencing adverse events is expected to improve overall tolerability with a minimal impact on efficacy outcomes. The dose should be adjusted as indicated for patients receiving concomitant medication with strong CYP3A4 inducers or inhibitors, or for patients with moderate hepatic impairment (per the US Food and Drug Administration prescribing information [6]). Clinicians may also consider patient age prior to starting cabozantinib. Adverse events may occur earlier in older patients, and these patients should be monitored closely and dose reductions implemented expeditiously.

Several ongoing clinical trials will evaluate cabozantinib in combination with checkpoint inhibitors including nivolumab ± ipilimumab (NCT03635892, NCT03937219), pembrolizumab (NCT03149822), and atezolizumab (NCT03170960), in patients with advanced RCC. Dose escalation studies will define the optimal dosing regimen for each combination, and future analyses will seek to maximize the benefit/risk profile of cabozantinib within the evolving treatment paradigm for advanced RCC.

Declaration of interest

DC has received fees for consulting and/or advisory roles with Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Ipsen, Janssen Oncology, Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Roche/Genentech, and Sanofi; institutional research funding from Janssen Oncology; and travel/accommodations and/or expenses from Bristol-Myers Squibb, Pfizer, and Roche. JPM has received fees for consulting and/or advisory roles with Astellas Korea, Bayer, Bristol Myers-Squibb, Janssen China R&D, Novartis, Pfizer, and Roche; and research funding from Roche. FB is an Ipsen Pharma employee (Medical R&D Department). NT is an Ipsen employee. LN is an employee of Exelixis, Inc., and also owns Exelixis stocks. DOC is an employee of Exelixis, Inc., owns Exelixis stocks, and receives shared royalties from a UCSF patent. EJ has received fees for consulting and/or advisory roles with Eisai, Exelixis, Genentech/Roche, Novartis, and Pfizer; research funding from Exelixis, Novartis, Peloton Therapeutics, Pfizer; and travel/accommodations and/or expenses from Pfizer.

Author Contributions

All authors contributed to the conception of the manuscript and intrepretation of data. DC, DOC, and EJ contributed to the drafting of the manuscript. All authors provided critical review and revisions, and all authors approved the final version of the manuscript for submission and publication.

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Appendix A. Supplementary data

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