



# Mini-Review: Cabozantinib in the Treatment of Advanced Renal Cell Carcinoma and Hepatocellular Carcinoma

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**Abstract:** Cabozantinib is an oral, tyrosine-kinase inhibitor with potent activity against VEGFR2 and MET, along with multiple other tyrosine kinases involved in cancer development and progression. Herein, we will focus on preclinical and clinical studies leading to the approval of cabozantinib in advanced renal cell carcinoma and hepatocellular carcinoma. Covered studies include NCT01100619, CABOSUN, METEOR, NCT00940225 and the CELESTIAL trial. Finally, we review future directions of cabozantinib development by highlighting some ongoing clinical trials.

**Keywords:** cabozantinib, renal cell carcinoma, hepatocellular carcinoma, kidney cancer, liver cancer, cabozantinib resistance mechanism

## Introduction

Receptor tyrosine kinases (RTKs) are key regulators of cellular proliferation, differentiation, survival, migration, and metabolism.<sup>1</sup> Mutations and other genomic alterations can lead to aberrant activation of RTKs, causing dysregulated cell signaling that promotes angiogenesis, proliferation, and protection from apoptosis; resulting in tumor growth and metastasis.<sup>1</sup> Vascular endothelial growth factor (VEGF) is one of the RTK subfamilies that plays a major role in angiogenesis.<sup>2</sup> Hypoxia, common within the tumor microenvironment, activates hypoxia-inducible factors (HIF-1 $\alpha$  and HIF- $\beta$ ) that up-regulate transcription of pro-angiogenic genes, including VEGF and its receptors VEGFR1 and VEGFR2.<sup>3</sup> Thus, VEGF is an attractive target in tumors that overexpress VEGF, or are dependent on this signaling pathway.

Multiple small molecule inhibitors or antibodies of VEGF are clinically available to treat multiple cancer types, including hepatocellular carcinoma and renal cell carcinoma. However, these therapies are not curative, and resistance inevitably develops. One resistance mechanism includes activation of the hepatocyte growth factor (HGF)-MET pathway, thereby restoring proliferation and angiogenesis, in a hypoxia-independent manner.<sup>4</sup>

Cabozantinib is an oral, small-molecule tyrosine kinase inhibitor (TKI) with potent activity against VEGFR2 and MET, along with other RTKs such as RET, KIT, AXL, TIE2, ROS1, TYRO3, MER, TRKB, and FLT3 that are involved in cancer development and progression.<sup>5,6</sup> The capsular formulation Cometriq<sup>®</sup> is approved for the treatment of medullary thyroid cancer, and Cabometyx<sup>®</sup> is approved in renal cell carcinoma and second-line treatment of hepatocellular

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carcinoma.<sup>7</sup> This review will discuss cabozantinib (Cabometyx®) treatment for both renal cell carcinoma and hepatocellular carcinoma.

## Development of Cabozantinib in Advanced Renal Cell Carcinoma

3p loss is the first genomic event in sporadic renal cell carcinoma for the majority of patients and is lost in greater than 90% of RCC. The 3p chromosome encodes for many tumor suppressors important for this disease, including Von Hippel Lindau (*VHL*), *PBRM1*, *BAP1* and *SETD2*. The *VHL* gene is the most commonly mutated gene (approximately 80%) in clear cell renal cell carcinoma (ccRCC).<sup>8</sup> Pathogenic loss of *VHL* function is an early event in the development of ccRCC.<sup>9</sup> It leads to constitutive stabilization and activation of hypoxia-inducible factor, resulting in excessive production of proangiogenic factors such as VEGF, FGF, and PDGF; downregulation of E-cadherin; induction of epithelial to mesenchymal transition; and activation of hepatocyte growth factor receptor (HGFR, encoded by *MET*) or alteration of downstream *MET* signaling.<sup>9</sup>

In cellular assays, cabozantinib has shown to potently inhibit *MET* and VEGFR2 phosphorylation at nanomolar concentrations, resulting in decreased in vitro cell invasion.<sup>5</sup> The IC<sub>50</sub> values of cabozantinib for *MET*, VEGFR2, *KIT*, *RET*, *AXL*, *TIE2*, and *FLT3* are 1.3, 0.035, 4.6, 5.2, 7, 14.3, and 11.3 nmol/L, respectively. Potent inhibition of these RTKs leads to disruption of angiogenesis, inhibition of tubule formation, tumor migration-causing disruptions in tumor vasculature, and extensive endothelial and tumor cell apoptosis.<sup>5</sup> In in vivo experiments, in H441 tumors that constitutively harbor phosphorylated *MET*, a single oral dose of 100 mg/kg cabozantinib resulted in *MET* inhibition within 8 hours.<sup>5</sup> In pre-clinical RCC models, cabozantinib has shown to rescue acquired sunitinib resistance by suppressing the expression and inhibiting the activation of *AXL* and/or *MET*.<sup>10</sup>

Cabozantinib has a long plasma half-life of approximately 120 hours and accumulates five-fold by day 15, with daily dosing based on the area under the curve of the plasma concentration-time function.<sup>7</sup> Cabozantinib plasma concentrations increase proportionally with increasing drug concentrations over the 20–60 mg tablet range, but only marginally when comparing the 60 mg dose to the 140 mg dose.<sup>11</sup> It is a substrate of CYP3A4 and multidrug resistance protein 2 (*MRP2*) in vitro. Therefore, inhibitors of CYP3A4 and *MRP2*, along with high-fat diet or hepatic impairment, can increase its systemic exposure.<sup>7,12,13</sup>

## Phase I Trials

A single-arm, open-label phase I trial (NCT01100619) enrolled 25 heavily pretreated metastatic ccRCC patients to evaluate the safety and tolerability of cabozantinib.<sup>14</sup> The most common grade 3 or worse side effects were hypophosphatemia (40%), fatigue (20%), hyponatremia (20%), diarrhea (12%), and lipase elevation (12%). Grade 3 or worse proteinuria (8%), palmar–plantar erythrodysesthesia (4%), pulmonary embolism (12%), and hypertension (4%) were also reported. Common grade 1 or 2 side effects also included hypothyroidism (48%) and hypertension (32%). These side effects are frequently seen with other VEGF antagonistic TKIs used in the treatment of metastatic ccRCC.<sup>15,16</sup> As summarized in Table 1, cabozantinib demonstrated a significant overall response rate (ORR) of 28% (7 of 25 patients), and a promising median progression-free survival (PFS) of 12.9 months and median overall survival (OS) of 15 months.<sup>14</sup>

## Phase III METEOR – the Registration Trial of Cabozantinib in Metastatic Renal Cell Carcinoma

The METEOR trial was a randomized phase III study that compared the efficacy of cabozantinib with everolimus in patients with advanced ccRCC who progressed after at least one VEGF-targeted therapy.<sup>17</sup> Of the 658 enrolled patients, 330 were randomized to the cabozantinib arm and 328 to the everolimus arm. The trial was powered for both the primary endpoint of PFS and the secondary endpoint of OS. Safety and ORR were other secondary endpoints. Median PFS and ORR were determined in the first 375 randomized patients. Both endpoints favored cabozantinib compared to everolimus (Table 1).<sup>17</sup> The median OS was 21.4 months with cabozantinib and 17.1 months with everolimus (HR 0.70; 95% CI 0.58–0.85;  $p=0.0002$ ).<sup>18</sup> For all subgroups evaluated, the point estimates favored cabozantinib over everolimus for both PFS and OS, including IMDC risk categories (favorable, intermediate and poor), age, the number of prior therapies, prior immune therapy use and presence of visceral metastasis among others.<sup>18,19</sup>

Cabozantinib improved PFS, OS, and ORR as compared to everolimus regardless of age group (<65, 65–74, ≥ 75 years).<sup>20</sup> A recent network meta-analysis further demonstrated that salvage cabozantinib may offer the best survival outcomes in elderly (≥ 65 years) metastatic RCC patients.<sup>21</sup> In another subgroup analysis, cabozantinib improved outcomes irrespective of prior antiangiogenic therapy (sunitinib or pazopanib) or prior use of checkpoint inhibitor therapy.<sup>22</sup> On survival analysis based on PD-L1 expression, cabozantinib improved survival outcomes regardless of the PD-L1

expression profile. In PD-L1 positive patients ( $\geq 1\%$ ), cabozantinib had a non-statistically significant longer median PFS (5.6 months vs 3.7 months; HR 0.66 95% CI 0.40–1.11) and longer median OS (18.4 months vs 13.9 months, HR 0.82; 95% CI 0.47–1.41) as compared to everolimus. In PD-L1 negative patients, cabozantinib showed a longer median PFS (8.5 months vs 4.1 months; HR 0.46, 95% CI 0.32–0.66) and OS (not reached vs 18.4 months, HR 0.58, 95% CI 0.38–0.88).<sup>23</sup> However, in the combined analysis of CABOSUN and METEOR trials, MET and/or PD-L1 expression were not found to be significant predictors of benefit from cabozantinib ( $P$  interaction  $> 0.20$ ).<sup>23</sup>

Cabozantinib and everolimus had similar grade 3 or higher adverse event rates, 71% and 61%, respectively.<sup>18</sup> The most common grade 3 or higher adverse events for cabozantinib were hypertension (15%), diarrhea (13%), fatigue (11%), and palmar-plantar erythrodysesthesia (8%). The most common grade 3 or higher adverse events for everolimus were anemia (17%), fatigue (7%), hyperglycemia (5%), and hypertension (4%). Dose reductions with cabozantinib occurred in 64% of

patients, while dose reductions with everolimus occurred in only 25% of patients. Treatment discontinuation due to adverse events was relatively similar between cabozantinib (13%) and everolimus (11%).

### Phase II CABOSUN Trial

The CABOSUN trial was a randomized phase II clinical trial evaluating first-line cabozantinib for International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk ccRCC patients.<sup>24,25</sup> The study randomized 157 patients with newly diagnosed mcrRCC 1:1 to cabozantinib ( $n=79$ ) or sunitinib ( $n=78$ ). PFS was assessed as the primary endpoint, and secondary endpoints included OS, ORR, and safety. Cabozantinib showed a superior median PFS of 8.6 months, as compared to 5.3 months with sunitinib (hazard ratio [HR] 0.48, 95% CI 0.31–0.74;  $p=0.0008$ ), per independent radiology review.<sup>25</sup> Cabozantinib, as compared to sunitinib, also showed a non-statistically significant higher median OS (26.6 months vs 21.2 months, HR 0.80; 95% CI

**Table I** Selected Cabozantinib Trials in Metastatic Clear Cell Renal Cell Carcinoma with Survival Results

Trial with Survival Results	NCT01100619 <sup>14</sup>	CABOSUN <sup>23,24</sup>		METEOR <sup>17-18</sup>	
Phase	I	II		III	
Primary Endpoint	Safety/Tolerability	PFS, as per IRC		PFS, as per IRC	
Treatment arms (number of patients)	Cabozantinib (N=25)	Cabozantinib (N=79)	Sunitinib (N=78)	Cabozantinib (N=330)	Everolimus (N=328)
mPFS (months) (95% CI)	12.9 (N/A)	8.6 (6.8–14.0)	5.3 (3.0–8.2)	7.4 (5.6–9.1)	3.8 (3.7–5.4)
HR of mPFS (95% CI); P-value	N/A	0.48 (0.31–0.74); 0.0008		0.58 (0.45–0.75); $<0.001$	
ORR (%) (95% CI)	28 (N/A)	20 (12–30.8)	9 (3.7–17.6)	17 (13–22)	3 (2–6)
mOS (months) (95% CI)	15.0 (N/A)	26.6 (14.6–NE)	21.2 (16.3–27.4)	21.4 (N/A)	17.1 (N/A)
HR of mOS (95% CI); P-value	N/A	0.80 (0.53–1.21); N/A		0.70 (0.58–0.85); 0.0002	
IMDC Favorable (%)	12	0	0	43	44
IMDC Intermediate (%)	80	81	81	43	40
IMDC Poor (%)	8	19	19	14	16
Any grade adverse events (%)	N/A	96	99	100	$>99$
Most common all grade adverse events (%)	Fatigue (80), Diarrhea (64), Hypophosphatemia (60)	Fatigue (85.9), Hypertension (80.8), Diarrhea (71.8)	Fatigue (81.9), Hypertension (68.1), Diarrhea (52.8)	Diarrhea (74), Fatigue (56), Nausea (50)	Fatigue (46), Anemia (38), Decreased appetite (34)
Most common grade 3–5 adverse events (%)	Hypophosphatemia (40), Fatigue (20), Hyponatremia (20)	Hypertension (28.2), Diarrhea (10.3), Palmar-Plantar Erythrodysesthesia (7.7)	Hypertension (22.2), Fatigue (15.3), Diarrhea (11.1), Thrombocytopenia (11.1)	Hypertension (15), Diarrhea (13), Fatigue (11)	Anemia (17), Fatigue (7), Hyperglycemia (5)

**Abbreviations:** PFS, progression-free survival; OS, overall survival; ORR, overall response rate; IRC, Independent Radiology Review Committee; IMDC, International Metastatic RCC Database Consortium; HR, hazard ratio; CI, confidence interval.

0.53–1.21), higher ORR (20% vs 9%), and similar grade 3 or higher adverse events (AEs, 68% vs 65%) (Table 1).<sup>25</sup>

Similar trends were observed upon stratifying patients based on MET expression. In patients with MET-positive tumors (defined as  $\geq 50\%$  of tumor cells staining 2+ or 3+ by immunohistochemistry), cabozantinib showed a higher median PFS of 13.8 months, as compared to 3.0 months with sunitinib (HR 0.32; 95% CI, 0.16–0.63). For MET-negative patients, the median PFS was 6.9 months with cabozantinib and 6.1 months with sunitinib (HR 0.67; 95% CI 0.37–1.23).<sup>25</sup> When stratified based on IMDC risk groups and the presence of bone metastases, cabozantinib was consistently favored.<sup>24</sup> In another subgroup analysis, improved survival with cabozantinib was observed in patients, regardless of the PD-L1 expression profile. In PD-L1 positive patients ( $\geq 1\%$  expression score), cabozantinib had a non-statistically significant longer median PFS (8.4 months vs 3.1 months; HR 0.46 95% CI 0.18–1.21) and similar OS (18.1 months vs 21 months, HR 0.85 95% CI 0.31–2.31), as compared to sunitinib. In PD-L1 negative patients, cabozantinib showed a longer median PFS (11 months vs 5 months; HR 0.47, 95% CI 0.26–0.86) and a non-statistically significant longer median OS (30.3 months vs 22.4 months, HR 0.71, 95% CI 0.39–1.29), as compared to sunitinib.<sup>23</sup>

## Cabozantinib in Hepatocellular Carcinoma

HGF is known to be a potent mitogen for primary hepatocytes, and the HGF/MET axis plays an important role in liver development and regeneration.<sup>26</sup> In vitro, MET knockdown was shown to prevent MHCC97-L cells from proliferating by arresting cells at the G<sub>0</sub>-G<sub>1</sub> phase.<sup>27</sup> In vivo, overexpression of the MET RTK allowed for its activation in an HGF-independent manner, and induced HCC.<sup>27</sup> Overexpression of mRNAs for the MET receptor has been noted in poorly differentiated tumors and in HCC patients with early tumor recurrence.<sup>28</sup> Sorafenib, a VEGFR inhibitor was the only approved first-line systemic therapy for HCC until 2018.<sup>29</sup> One of the common resistance mechanisms involves activation of the HGF/MET axis.<sup>30</sup> Therefore, the HGF/MET axis appears to be an attractive target in HCC treatment.

### Phase II Trials

In a phase II placebo-controlled, randomized discontinuation study, 41 HCC patients were enrolled based on a criteria of Child-Pugh A liver function and prior treatment with  $\leq 1$  systemic anticancer regimen.<sup>31,32</sup> All patients received daily cabozantinib during a 12-week lead-in phase. At week 12, patients

with stable disease (SD) were randomized to cabozantinib or placebo, patients with a partial response (PR) continued open-label cabozantinib treatment, and patients with progressive disease (PD) at or before week 12 discontinued treatment. Primary endpoints included ORR at week 12 (lead-in phase) and PFS (randomized phase). In the entire cabozantinib-treated population, safety, tolerability, PFS, and OS served as secondary endpoints. The results demonstrated promising activity of cabozantinib in HCC (Table 2). In the lead-in phase, the ORR was only 5%, and there were no complete responses. However, the disease control rate (partial response plus stable disease) was 66%. In the randomized phase, where patients were randomized to receive cabozantinib versus placebo after the 12-week treatment with cabozantinib, there was a numerical increase in the median PFS with cabozantinib (2.5 months, 95% CI 1.3–6.8 months) as compared to placebo (1.4 months, 95% CI, 1.3–4.2 months), although this difference was not statistically significant. The median PFS and OS from start of cabozantinib treatment for all patients enrolled in this trial were 5.2 and 11.5 months, respectively. Alpha-fetoprotein response (AFP, defined as a reduction from baseline by  $>50\%$  with AFP  $>20$  ng/mL at baseline) was observed in 35% (9 of 26 patients with  $\geq 1$  post-baseline AFP levels) of patients treated with cabozantinib. While the trial had 9 cohorts of various disease types, with an initial enrollment plan to randomize 70 patients per cohort, randomization was halted early due to promising activity in the cabozantinib arm and symptomatic progression in individual patients in the placebo arm.<sup>31</sup> These encouraging results in ORR, OS, and a high disease control rate led to the initiation of a phase III trial in HCC patients.

### Phase III CELESTIAL- the Registration Trial of Cabozantinib in Advanced HCC

The CELESTIAL trial was a double-blinded, randomized phase III trial that compared cabozantinib with placebo in previously treated, advanced HCC patients who were not amenable to curative treatment.<sup>33</sup> 707 HCC patients, all of whom had previously received sorafenib, were randomized in a 2:1 ratio to receive daily cabozantinib (n=470) or placebo (n=237). Treatment was given until disease progression or unacceptable toxicity were observed. The primary endpoint was OS, and secondary endpoints were PFS and ORR. Patients treated with cabozantinib had improved outcomes, with a significantly longer median OS, PFS, and ORR (Table 2). There was a higher percentage of patients alive at 6, 12, 18, and 24 months in the cabozantinib group as compared to the placebo group. Approximately 50% of patients in the cabozantinib arm, as compared to 13% in the placebo arm, had an AFP

**Table 2** Selected Clinical Studies of Cabozantinib in Hepatocellular Carcinoma

Trial with Survival Results	NCT00940225 <sup>31</sup>	CELESTIAL <sup>33</sup>	
Phase	II Randomized Discontinuation	III	
Primary Endpoint	Lead-in stage: ORR Randomized stage: PFS	OS	
Treatment arms	Cabozantinib (N=41)	Cabozantinib (N=470)	Placebo (N=237)
mPFS (months) (95% CI)	5.2 (N/A)	5.2 (4.0–5.5)	1.9 (1.9–1.9)
HR of mPFS (95% CI); P-value	N/A	0.44 (0.36–0.52); <0.001	
ORR (%) (95% CI)	5 (N/A)	4 (N/A)	<1 (N/A)
mOS (months) (95% CI)	11.5 (7.3–15.6)	10.2 (9.1–12.0)	8.0 (6.8–9.4)
HR of mOS (95% CI); P-value	N/A	0.76 (0.63–0.92); 0.005	
ECOG 0 (%)	44	52	55
ECOG 1 (%)	56	48	45
ECOG 2 (%)	0	<1	0
Any grade adverse events (%)	100	99	92
Most common all-grade adverse events (%)	Diarrhea (63), Hand-foot syndrome (56), Fatigue (56)	Diarrhea (54), Decreased appetite (48), Palmar-Plantar Erythrodysesthesia (46)	Fatigue (30), Abdominal pain (25), Diarrhea (19), Constipation (19)
Most common ≥ grade 3 adverse events (%)	Diarrhea (20), Hand-foot syndrome (15), Thrombocytopenia (15)	Palmar-Plantar Erythrodysesthesia (17), Hypertension (16), Diarrhea (10), Fatigue (10)	Increase AST (6), Ascites (5), Anemia (5)

**Abbreviations:** PFS, progression-free survival; OS, overall survival; ORR, overall response rate; HR, hazard ratio; CI, confidence interval.

response (patients with baseline AFP  $\geq 20$  ng/mL and  $\geq 20\%$  decrease from baseline) at week 8.<sup>34</sup> Common grade 3 or 4 AEs associated with cabozantinib included palmar-plantar erythrodysesthesia, hypertension, aspartate aminotransferase elevation, fatigue, and diarrhea.

The development of palmar-plantar erythrodysesthesia or grade 3 or greater hypertension was associated with prolonged OS and PFS, though there were some differences in baseline characteristics among comparator groups.<sup>35</sup> Regarding quality of life assessments, cabozantinib was associated with a slight decrease in health utility initially, but an overall increase in health utility with continued treatment.<sup>36</sup>

## Mechanisms of Resistance to Cabozantinib

Almost all patients ultimately develop resistance to cabozantinib. However, the current understanding of mechanisms of resistance to cabozantinib is limited and these mechanisms might be similar to those with other TKIs.<sup>37,38</sup> In a prior

study, ccRCC activation of the transcription factor SOX18 has shown to alleviate the inhibitory effects of cabozantinib.<sup>39</sup> Identified mechanisms of resistance in prostate cancer include (1) “preexisting” or “de-novo resistance” where tumor-induced bone secretes proteins termed “osteoclines” that activate integrin signaling and give a survival advantage to tumor cells,<sup>40</sup> (2) vascular heterogeneity contributing to formation of islet of resistant cells,<sup>41</sup> (3) YAP/TBX5-dependent induction of FGFR1 in tumor cells as a potential mechanism of acquired resistance,<sup>41,42</sup> and (4) upregulation of secreted proteins including pappalysin, IGFBP2, WNT 16, and DKK1 by osteoblasts which increase the tumorigenicity of prostate cancer cells.<sup>43</sup> In mutant TPR-MET transformed Ba/F3 cells, cabozantinib treatment has shown to give rise to a broad range of unique mutants, such as F1200 and G1163R, etc., that are associated with cabozantinib resistance.<sup>44</sup> In advanced RET-rearranged lung cancers, MDM2 amplification has been implicated in primary and acquired resistance to cabozantinib.<sup>45</sup> In NTRK1 gene



rearranged KM12 colorectal cancer cells, activation of IGF1R has shown to mediate resistance to cabozantinib, as have various NTRK1 mutations like G595R, G595L, L564H, F646I, and D679G.<sup>46</sup>

## Conclusions & Future Directions

Following the remarkable success of cabozantinib as a single agent, multiple ongoing clinical trials are evaluating the safety and efficacy of various combination regimens that include immune checkpoint inhibitors in advanced RCC and HCC. Tables 3–5 provide a summary of selected clinical studies.

In advanced or metastatic RCC, cabozantinib is being evaluated in combination with pembrolizumab (NCT03149822), avelumab (NCT03200587), and nivolumab (CheckMate 9ER, NCT03141177). COSMIC-313 (NCT03937219) is evaluating cabozantinib with

nivolumab and ipilimumab in patients with previously untreated advanced or metastatic RCC. The CANTATA (NCT03428217) study is analyzing cabozantinib in combination with the glutaminase inhibitor telaglenastat (CB-839) in RCC patients who progressed on one or two prior therapies in the advanced or metastatic setting. Cabozantinib as a second-line treatment in locally advanced or metastatic RCC patients who have progressed on first-line checkpoint inhibitors is being investigated in the CaboPoint (NCT03945773) trial. It is also being explored in non-clear cell RCC in combination with nivolumab (CA209-9KU, NCT03635892) and as a single agent post-immunotherapy (ANZUP, NCT03685448).

A large, multi-cohort Phase 1b study (NCT03170960) is evaluating the optimal dosing and efficacy of cabozantinib with atezolizumab in patients with locally advanced or

**Table 3** Ongoing Clinical Trials Investigating Novel Combination Treatment Regimens for RCC

Trial Name	Phase	Target Population	Treatment Arms	Primary Endpoint	Secondary Endpoint	Estimated Study Completion Date
NCT03149822	I/II	Metastatic RCC	Phase 1: Pembrolizumab (200 mg) + Cabozantinib (40 mg)	ORR	Maximum Tolerated Dose (MTD), toxicities, PFS, progression of overall disease, clinical benefit rate, recommended phase 2 dose, duration on treatment beyond treatment progression	June 2020
			Phase 1: Pembrolizumab (200 mg) + Cabozantinib (60 mg)			
			Phase 2: Pembrolizumab (200 mg) + Cabozantinib (recommended phase 2 dose)			
NCT03200587	Ib	Metastatic RCC	Avelumab + Cabozantinib (20, 40, or 60 mg)	Recommended phase II dose	PFS	September 2022
COSMIC-313 (NCT03937219)	III	Previously untreated intermediate- or poor-risk advanced or metastatic RCC	Cabozantinib + Nivolumab + Ipilimumab	PFS	OS	June 2024
			Placebo + Nivolumab + Ipilimumab			
NCT 03428217	II	Advanced or metastatic RCC	CB-839 + Cabozantinib	PFS (per IRC)	OS, PFS (per investigator)	September 2022
			Placebo + Cabozantinib			
CheckMate 9ER (NCT03141177)	III	Locally advanced or metastatic RCC with a clear-cell component with no prior systemic therapy for RCC.	Nivolumab + Cabozantinib	PFS	OS, ORR, AE, Serious AE	May 2024
			Nivolumab + Ipilimumab + Cabozantinib			
			Sunitinib			

**Table 4** Ongoing Clinical Trials Investigating Novel Combination Treatment Regimens for HCC

Trial Name	Phase	Target Population	Treatment Arms	Primary Endpoint	Secondary Endpoint	Estimated Study Completion Date
CheckMate 040 (NCT01658878)	I/II	Untreated, advanced HCC	Nivolumab	Safety & tolerability, ORR	Complete response rate, disease control rate, duration of response, time to response, time to progression, PFS, OS, PD-L1 expression, pharmacokinetics of Nivolumab	April 2022
			Nivolumab + Ipilimumab			
			Nivolumab + Cabozantinib			
			Nivolumab + Ipilimumab + Cabozantinib			
			Sorafenib			
NCT03299946	I	Locally advanced HCC	Cabozantinib + Nivolumab	Number of AE, number of patients who complete pre-op treatment and proceed to surgery	% of patients who obtain R0 resection, % of patients with complete response, % of patients with major pathologic responses, ORR, OS, disease-free survival	March 2022
COSMIC-312 (NCT03755791)	III	Advanced HCC without previous systemic therapy	Cabozantinib + Atezolizumab (experimental)	PFS (experimental vs control), OS	PFS (single-agent vs control)	December 2021
			Sorafenib (control)			
			Cabozantinib (single-agent)			
CLEARANCE (NCT03963206)	IV	Intermediate HCC (ineligible for chemoembolization), or advanced HCC (after failure of Sorafenib or another systemic therapy)	Cabozantinib (20, 40, or 60 mg)	OS	AE, daily median dose of cabozantinib, number of patients with each dose of cabozantinib	September 2021
NCT03586973	II	Advanced HCC in Japanese patients	Cabozantinib (post first-line progression on sorafenib)	24-week PFS rate	PFS, ORR, disease-control rate, OS	November 2020
			Cabozantinib (treatment-naïve)			

**Table 5** Ongoing Clinical Trials Investigating Novel Combination Treatment Regimens for Both RCC and HCC

Trial Name	Phase	Target Population	Treatment Arms	Primary Endpoint	Secondary Endpoint	Estimated Study Completion Date
NCT03170960	Ib	Locally advanced, metastatic, or recurrent solid tumor	Cabozantinib + Atezolizumab	MTD, ORR	Incidence and severity of AE	December 2020

metastatic solid tumors, including RCC and HCC. CheckMate040 (NCT01658878) is a phase 1/2 study evaluating the safety, tolerability, and efficacy of nivolumab or nivolumab in combination with other agents (cabozantinib, sorafenib, and ipilimumab) in patients with advanced HCC. Another study (NCT03299946) is exploring neoadjuvant

cabozantinib in combination with nivolumab, prior to definitive resection, in patients with locally advanced HCC. The COSMIC-312 (NCT03755791) trial is comparing the efficacy of cabozantinib in combination with atezolizumab versus the standard-of-care sorafenib as first-line treatment for advanced HCC.

Cabozantinib has proven to be an effective agent in HCC and RCC. At present, cabozantinib is undergoing rapid development through multiple innovative trials that are exploring new avenues such as neoadjuvant treatments, novel combination regimens, and rare RCC histologies. Most of these trials are also incorporating novel biomarker studies to further understand the pathogenesis of these diseases and optimal patient selection for these therapies. These clinical trials have the potential to change the standard of care for HCC and RCC in the near future.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

Neeraj Agarwal and Umang Swami are co-corresponding authors. Dr Benjamin L. Maughan reports personal fees from Exelixis, BMS, Astellas, Bayer Oncology, Janssen Oncology, Tempus, Peloton Therapeutics, Clovis, and Merck, during the conduct of the study. Dr Neeraj Agarwal reports consultancy to: Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Janssen, Merck, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics; research funding to his institution: Astra Zeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracoon. The authors report no other conflicts of interest in this work.

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