# Cabozantinib as a second-line treatment option in hepatocellular carcinoma

**Running Title:** Cabozantinib in HCC

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## Abstract

**Introduction**: Hepatocellular carcinoma (HCC) is one of the most frequent tumours affecting the gastrointestinal tract and a universal cause of morbidity and mortality. Cabozantinib is a strong multi-inhibitor of receptor tyrosine kinases approved for renal cell carcinoma that could be useful also for the treatment of HCC. **Areas covered**: This review describes the chemical structure, the pharmacologic properties and current knowledge of the efficacy of cabozantinib in the treatment of HCC based on data available from first phase and later phase clinical trials. The ongoing studies testing cabozantinib, either alone or in combination with other drugs, are also described. **Expert opinion**: Despite the recent achievements in the use of cabozantinib for patients diagnosed with hepatocellular carcinoma, data are still needed to allow clinicians to make better decisions on how to treat specific patient subgroups.

Article highlights:

- Cabozantinib is an oral agent that inhibits several receptor tyrosine kinases, including MET, VEGFR 1-3, AXL and RET
- Cabozantinib has statistically significantly prolonged both overall and progression-free survival in advanced HCC patients previously treated with sorafenib
- In the phase III CELESTIAL trial, cabozantinib was superior to placebo in all patient subgroups and efficacy endpoints
- Cabozantinib is a new second-line treatment option and, for advanced HCC patients, the only third-line treatment option
- Cabozantinib is normally well tolerated with manageable adverse events

## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent tumours affecting the gastrointestinal tract and is a universal cause of morbidity and mortality. Based on updated cancer statistics, in 2018 around 40,000 and 30,000 people were diagnosed and died, respectively, with HCC in the United States, with 82,000 and 77,000 as the corresponding numbers in Europe [1,2].

The main HCC risk factors are infections (hepatitis B and C viruses), alcohol abuse and nonalcoholic fatty liver disease (NAFLD) [3], but 30% of HCC cases are defined as cryptogenic with no risk factors (RS) associated. All of the RS cause chronic liver inflammation, considered to be a carcinogenic condition [4]. Of note, most RS can be prevented by vaccination (e.g. HBV), treated with drugs (e.g. antiviral agents against HCV infection), or managed via modification of diet and alcohol assumption habits (e.g. in order to prevent nonalcoholic steatohepatitis [NASH] [5]). The hepatocarcinogenic process of HCC, driven by chronic inflammation, fibroblastic deposition and carcinogens, paves the way for overexpression and/or constitutive activation of different pathways. The most aggressive HCCs exhibit poorer gene signatures and higher alpha-fetoprotein (AFP) levels [6].

## 2. Background

Although different treatment options are available for HCC (decided mainly by a patient's performance status, liver function and tumour size), including surgical resection, local ablation, transplantation and transarterial chemoembolization (TACE) [4,7,8], HCC remains one of the commonest causes of cancer-related death worldwide [9]. Sorafenib was the first multi-target tyrosine kinase inhibitor (TKI) to show efficacy in patients diagnosed with advanced HCC but with good liver function (Child-Pugh A score). Sorafenib was approved for the treatment of advanced disease following the SHARP randomized trial and subsequent randomized trial in the Asia-Pacific

region [10,11]. In these trials, relative to placebo sorafenib showed a remarkable improvement in time to progression (TTP) and overall survival (OS) and has remained the gold standard drug for more than ten years [10,11]. After some negative clinical trials where sorafenib efficacy was compared to compounds such as sunitinib, brivanib, linifanib, erlotinib and sorafenib plus doxorubicin versus sorafenib alone [12–16], in 2018 the REFLECT trial highlighted non-inferiority of lenvatinib with respect to sorafenib and that it had reached its primary endpoint [17]. As a result, lenvatinib has been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) [18,19]. Unfortunately, patients in the lenvatinib group reported grade 3 or higher adverse events such as hypertension, reduced appetite, and increased rate of weight loss compared with patients in the sorafenib group; conversely, patients in the sorafenib arm reported a higher hand-foot skin reaction [20]. Sorafenib and lenvatinib have different inclusion criteria – liver involvement, main portal vein inclusion, invasion of bile duct – leading to a challenging scenario for oncologists when enrolling a patient for a first-line treatment that might be based on toxicity profile, outcome priority and physician comfort with the drug. Unfortunately, most patients experience intrinsic and adaptive resistance after receiving first-line treatments, and therapy discontinuation often occurs due to notable toxicity and/or disease progression requiring second-line therapy.

Second-line HCC treatment options increased with the TKI regorafenib administered after sorafenib; regorafenib approval came from the RESORCE trial which showed a notable improvement in OS of 10.6 months compared with 7.8 months in the placebo group in patients that had tolerated sorafenib in first-line therapy [21].

The second-line treatment landscape for advanced HCC involved not only TKIs but also the IgG1 monoclonal antibody ramucirumab. Ramucirumab was deeply investigated in the REACH-2 trial [22], showing a 1.2 months improvement in median OS compared to placebo in patients with elevated baseline AFP levels (>400 ng/mL). The treatment background for HCC in the second-line setting is made more complex by the use of the immune checkpoint inhibitors (ICIs) nivolumab and pembrolizumab. While the latter failed to meet its primary endpoint [23,24], the former, after significant results reported in the Checkmate 040 trial [25], received accelerated approval from FDA as second-line treatment for advanced HCC. The second-line trials discussed above only evaluated patients pretreated with sorafenib. Data for patients pretreated with lenvatinib as first-line therapy are therefore lacking from these trials [26].

Initial efforts to provide a gold standard in a second-line setting were unsuccessful and new treatment options are urgently needed; the recent introduction of the novel drug cabozantinib has, however, improved the treatment landscape of advanced HCC.

## 3. Cabozantinib

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) that are involved in different pathological processes and that play a pivotal role in carcinogenesis, tumour growth, angiogenesis and metastasis [27]. Cabozantinib inhibits phosphorylation (activation) of vascular endothelial growth factor-2 (VEGFR-2), MET, AXL, KIT and FMS-like tyrosine kinase 3 (FLT3) in vitro [28] (Figure 1); cabozantinib showed similar inhibition of MET in tumour tissue and healthy liver plus VEGFR-2 inhibition in healthy lung tissue in mice [28,29].

**3.1. Pharmacodynamics:**

Cabozantinib inhibited angiogenesis in preclinical studies, blocking endothelial cell development in vitro, altering the vascularization pattern of VEGF- and MET-expressing tumours and decreasing the consistency of tumour microvessels in HCC xenografts [28,29]. Cabozantinib was anti-proliferative in some human cancer cell lines such as HCC and several xenograft tumour models in mice, and it increased the apoptosis ratio in tumour xenograft models [28,29]. It is noteworthy that a stronger effect has been reported for HCC xenografts positive for phosphorylated MET, so this protein status might be considered a susceptibility marker for cabozantinib [30]. Cabozantinib exerted a blocking effect on migration of hepatocyte growth factor (HGF)-induced and also reduced invasiveness of different tumour cell lines in vitro. It also impaired metastatic escape of HCC cells to the liver and lungs in rodents [28,29]. In line with these findings, treatment with sorafenib, which targets-VEGFR, corresponded with increased tumour size in a metastatic model, whereas cabozantinib, which targets both VEGFR- and MET, might play a crucial role in blockingmetastatic escape [30].

**3.2.Pharmacokinetics**:

Cabozantinib administration seems to be unaffected by sex, age or race. Healthy adults administered with a single tablet containing 20, 40, or 60 mg of the compound showed maximum plasma concentration within 3-4 hours, on average [32]; simultaneous consumption of food should be avoided [27,31]. Of note, cabozantinib tablets and capsules differ in efficacy, so these two formulations are not exchangeable [27,31]. In the EU and US, the recommended dose for HCC patients previously treated with sorafenib is 60 mg administered once daily, separate from meals [27,31]. The drug oral volume distribution is around 319 L with potent plasma protein binding properties (> 99.7%) [27]. According to in vitro studies, cabozantinib is metabolized by CYP3A4 whereas CYP2C9 only partially contributes [27,31]; elimination takes place mainly through the

faeces and urine with a plasma elimination half-life of around 55 h and an estimated average clearance of 5.5 L/h after oral administration of a 20-140 mg dose [27,31]. In the US, cabozantinib should be avoided in patients with serious hepatic functional alterations and cabozantinib is not recommended in EU patients with severe hepatic and renal impairment since compound safety and efficacy has not been evaluated in these patients [27,31]. Close monitoring and/or dosage reduction is required in patients with mild or moderate renal and hepatic impairment in the US and EU [27,31,33].

### 3.3. Drug interactions:

Since cabozantinib is metabolized by CYP3A4, medications which promote or inhibit CYP3A4 expression might lower or raise cabozantinib concentration in plasma [34]. When co-administration of cabozantinib with a potent CYP3A4 antagonist is required, close monitoring and dose reduction are necessary in the EU and the US, respectively [27,31]. Likewise, cabozantinib dosage should be increased when administered with potent CYP3A4 inducers in the US [27]. Due to its strong plasma protein binding property, cabozantinib might impair warfarin plasma concentration, leading to a close follow-up of the international normalization ratio [31]. In terms of contraception, steroids are not recommended even though it is unclear whether cabozantinib affects steroid pharmacokinetics [31]. Two additional interactions have been reported: drugs which impair the MRP2 transporter might increase plasma concentration of cabozantinib as it binds the transporter in vitro, so caution is advised in the EU; and, although no clear clinical effect is known, p-glycoprotein expression is reported to be impaired by cabozantinib, leading to raised CYP1A1 mRNA in vitro [27,31].

### 3.4. Clinical efficacy:

Preliminary clinical validation of cabozantinib came from a phase II randomized discontinued trial that involved 41 HCC patients (enrolled in 1 of the 9 cohorts), of which 22 were pretreated with

sorafenib and 19 were sorafenib naïve [35,36]. A daily 100 mg dose of cabozantinib was set as a 12-week induction treatment. After restaging, patients showing partial response (PR) continued the cabozantinib treatment, patients with stable disease (SD) were further randomized to placebo or cabozantinib, and patients with progressive disease (PD) up to week twelve discontinued treatment. At week 12, cabozantinib displayed an objective response ratio (ORR) of 5% and a disease control rate (DCR) of 66%. Patients with SD at week 12 (n=22) were split into two different subgroups: 12 were randomized to placebo and 10 to cabozantinib. Likely due to the small sample size, no notable difference in terms of progression-free survival (PFS) was reported between the two subgroups. Overall, among the 41 enrolled patients, the median PFS was 5.2 months and median OS was 11.5 months from the beginning of the study. Mild to moderate grade diarrhoea, weight loss and hand-foot skin reaction (HFSR) were the main adverse events reported [37].

On the heels of these preliminary but significant clinical outcomes, a phase III, randomized, international, double-blinded, controlled trial known as the CELESTIAL trial was conducted in 95 centres for 4 years. 707 HCC patients pretreated with sorafenib were enrolled and randomized at a 1:2 ratio to receive placebo (237) or cabozantinib (467). Eligibility required HCC diagnosis with preserved liver function (Child-Pugh A) and pretreatment with sorafenib (patients could have been administered with up to two previous systematic treatments and progressed on at least one of them). Patients were stratified in order to accomplish a suitable randomization ratio according to geographic region (Asia versus other), etiologic factors (HBV +/- HCV versus HCV without HBV versus other), presence of macrovascular invasion and extrahepatic disease. The study schedule included either daily 60 mg dose of cabozantinib or matched placebo administered as long as patients experienced acceptable toxicity or clinical benefit. The primary endpoint of an increased overall survival (OS) was achieved at the second pre-scheduled interim analysis with a median OS of 10.2

months in the cabozantinib arm and 8.0 months in the placebo arm (death HR: 0.76; 95% CI: 0.63-0.92; p=0.005); in the subgroup of patients in the second line, the mOS was 11.3 months for cabozantinib recipients and 7.2 months for placebo recipients (death HR 0.70; 95% CI: 0.55-0.88). The median progression-free survival (mPFS) was 5.2 months for cabozantinib recipients compared to 1.9 months for placebo recipients (HR 0.44; 95% CI: 0.36-0.52; p<0.001). Moreover, the secondary endpoint of disease control rate (DCR) fully endorsed the experimental arm with a DCR of 64% in the cabozantinib group and 33% in the placebo group (p=0.0086). Patients administered with cabozantinib reported tumour shrinkage, and 23% of patients with high AFP levels reported a decrease in AFP levels of at least 50% [38,39]. On the whole, patients with AFP levels >400 ng/mL (HR for OS 0.71) benefitted most compared to those with AFP levels <400 ng/mL (HR for OS: 0.81). Further investigations showed that cabozantinib benefit is unrelated to macrovascular invasion, disease stage, extrahepatic disease, age and previous TACE treatment [39–41]. Preclinical studies revealed that cabozantinib can increase tumour immunogenicity. Ongoing studies are therefore testing cabozantinib in combination with immune checkpoint inhibitors [42]. Table 1 summarizes the ongoing clinical trials for cabozantinib in HCC patients.

**3.5. Tolerability and adverse events:**

According to the CELESTIAL trial, orally administered cabozantinib has an overall reasonable tolerability profile in adult patients diagnosed with HCC, whilst adverse events (AE) often required supportive care and/or dose modification [36]. Most importantly, given that many AEs occur in the early stage of therapy and often impair liver function, close patient monitoring is warranted during the first eight weeks to establish whether dosage modification is necessary [31]. Disappointingly, treatment-emergent adverse events (TEAEs) took place in the majority of patients administered with both cabozantinib (99%) and placebo (92%); the commonest, with a reported incidence of more than 20%, were diarrhoea, decreased appetite, palmar-plantar erythrodysesthesia (PPE),

fatigue, nausea, hypertension, vomiting, rise of asthenia and AST plasma concentration [36]. TEAEs of grade 3 and 4 occurred in around two-fold more patients in the cabozantinib group than the placebo group (68% vs 37%); the most frequent were PPE (17% in the cabozantinib group vs 0% in the placebo group), hypertension (16% vs 2%), rise of AST plasma levels (12% vs 7%), diarrhoea (10% vs 2%) and fatigue (10 vs 4%) [36]. A few cabozantinib recipients (1.3%) reported grade 5 treatment-related adverse events: hepatorenal syndrome, pulmonary embolism, hepatic failure, portal vein thrombosis, upper gastrointestinal haemorrhage and broncoesophageal fistula (one patient each) [36]. As a consequence, patients in both cabozantinib and placebo groups underwent dose reduction by 62% and 13% respectively, and treatment was discontinued in 84% of cabozantinib recipients [31]. Table 2 reports the most important AEs with cabozantinib for HCC.

## 4. Discussion

Cabozantinib is a multiple RTK inhibitor. Several of the inhibited RTKs are involved in antiangiogenic drug resistance [43–45] and are considered poor prognostic factors [14,46,47]. Cabozantinib was approved largely according to results from the CELESTIAL clinical trial. Compared to placebo in this study, cabozantinib met the primary endpoint with an increased OS and PFS in sorafenib-pretreated patients, progressed after one systemic therapy and was administered with up to two systemic treatments for advanced malignancy. These findings were not affected by disease and/or patient characteristics. The tolerability profile of cabozantinib was considered acceptable with AEs requiring supportive care and dose modification. Based on the findings of this clinical trial [30,41,48], most of the current guidelines suggest cabozantinib for advanced HCC as a second-line treatment setting, even though patient characteristics may deviate slightly from guidelines [4,7].

**Expert opinion:**

Advanced HCC is a medical unmet need, with sorafenib the only approved first-line treatment and still the current standard of care [4,7,8]. Many drugs have failed to show efficacy in first and second-line randomized clinical trials (RCTs) [49]. Newer multiple RTK inhibitors are now approved, however, including lenvatinib as an additional first-line option and cabozantinib, regorafenib, ramucirumab, nivolumab and pembrolizumab for a second-line setting [6].

Second-line treatment options initially expanded with regorafenib, which targets stromal (FGFR, PDGFR-β), angiogenic (TIE2, VEGFR1-3) and oncogenic (RAF, KIT and RET) tyrosine kinase receptors [50]. In the RESOURCE trial, advanced HCC patients reported a substantial OS improvement (26 months vs 19.2 months in the experimental and placebo group respectively) when administered with regorafenib following sorafenib, showing similar side effects (due to similar molecular structures) with hypertension (15%), hand-foot skin reaction (13%) and fatigue (9%) the most common grade 3 or 4 AEs [21]. Although the sorafenib-regorafenib sequence might bring those with advanced HCC a comparable outcome to those diagnosed with intermediate-stage HCC, this similar prognosis was only possible for advanced HCC patients who tolerated and progressed on sorafenib as first-line therapy. Therefore, regorafenib should not be administered to sorafenib intolerant patients. The armamentarium of potential treatments for advanced HCC has been augmented with ramucirumab, a monoclonal antibody (IgG1) against VEGFR-2. According to the REACH-2 trial, where a statistically significant median OS improvement of 1.2 months was observed in the experimental arm when compared to the placebo arm, this novel agent might be used for advanced HCC patients who do not tolerate oral TKI, since ramucirumab is administered intravenously, and with elevated baseline AFP levels (>=400 ng/mL) [22]. Nonetheless, the predictive biomarker role of elevated AFP needs further research since varying values were used to categorize AFP concentration across

separate studies [21,36,51,52]. Treatment discontinuation occurred more frequently in the ramucirumab arm than in the placebo arm with hypertension (13%), hyponatremia (6%) and elevated aspartate aminotransferase (3%) the most common grade 3 or 4 AEs reported. The immune checkpoint inhibitors nivolumab and pembrolizumab (both humanized IgG4 monoclonal antibodies against PD-1 immune checkpoint) made the treatment scenario for advanced HCC more intricate. The accelerated FDA approval of nivolumab followed promising results from CheckMate 040 phase I/II trial where a DCR was achieved in 64% of patients, a complete response (CR) in 1% of patients and an ORR of 15% and 20% in the dose-escalation and dose-expansion cohort, respectively [25]. A further subgroup analysis for PD-L1 expression levels raised the possibility that PD-L1 may not be a predictive marker for checkpoint inhibitor treatment in HCC patients (patients with a PD-L1 < 1% and PD-L1 > 1% reported an ORR of 19% and 26% respectively). Given these data, nivolumab is currently being investigated in the CheckMate 459 trial, a phase III head-to-head study, as a second-line agent versus sorafenib in advanced HCC [25]. Pembrolizumab did not meet its primary endpoints (OS and PFS) in the confirmatory KEYNOTE-240 trial [23,53]. At present, whilst immune checkpoint inhibitors are strongly recommended for advanced HCC patients who poorly tolerate TKIs, the benefit from single-agent PD-1 immune checkpoint inhibitors is unclear for the advanced HCC setting.

Despite the progress made so far, the overall prognosis for advanced HCC patients remains poor. Furthermore, no clinical or biological marker is available to guide treatment choice, especially in the second-line treatment after sorafenib. In addition to novel “me-too” compounds, optimisation of treatment algorithms is urgently needed. Among the new drugs, cabozantinib is the most recently approved in the US and EU for treatment of advanced HCC patients previously treated with sorafenib, and cabozantinib is the only third-line treatment for patients with advanced HCC.

Promising OS and PFS results have been reported by the CELESTIAL trial which investigated a total of 707 hepatocellular carcinoma patients. The vast majority of clinical studies carried out over the last decade, however, enrolled heterogeneous groups of patients with no regard to the potential response biomarkers. Similarly, treatments have been advanced to phase III studies based on small phase II studies with too much weight placed on OS predictors endpoints for HCC such as overall survival ratio (OSR), progression-free survival (PFS) and time to progression (TTP) [48]. Additional stringent clinical studies are needed for cabozantinib, enrolling patients with more impaired hepatic function and worse performance status that those included in the CELESTIAL trial. Likewise, direct comparison of cabozantinib efficacy to other novel agents such as regorafenib and ramucirumab, and a bespoke cost-sustainability assessment, is required because only indirect comparisons have been conducted to date [54,55].

**Conflict of interest statement**

The authors declare that there are no conflicts of interest

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