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Review Article

The treatment of renal cell carcinoma with the c-met inhibitor cabozantinib: mechanisms and clinical trials

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Abstract: C-MET, a type of receptor tyrosine kinase, has been studied in relation to renal cell carcinoma (RCC) in recent years. After the signaling pathway of c-MET and its pathological role in RCC were revealed and clarified in several studies, c-MET became a promising therapeutic focus of RCC research. Cabozantinib-a c-MET inhibitor-has been approved as a treatment for RCC, and there are numerous studies investigating the effect of cabozantinib on the drug resistance of VEGF-TKI therapy in RCC. Cabozantinib is being examined for its treatment efficacy either in combination or in comparison with other cancer therapies, including immune checkpoint inhibitors and anti-angiogenesis therapy, in ongoing clinical trials. This article focuses on the treatment role and examines several clinical trials investigating how the therapeutic application of the c-MET inhibitor cabozantinib improves RCC.

Keywords: Cabozantinib, clinical trials, c-MET, kidney cancer, renal cancer

Introduction

In 2018, there were approximately 400,000 cases of kidney cancer diagnosed worldwide, with renal cell carcinoma (RCC) being the most prevalent type (approximately 90% of all cases) [1, 2]. RCC is categorized into three major subtypes: clear cell RCC (ccRCC, 75%), papillary RCC (10%), and chromophobe RCC (5%) [3]. RCC is characterized by enormous vascularized malignant tissues caused by the mutation of the von Hippel-Lindau (VHL) tumor suppressor gene, which is responsible for modulating the hypoxia-inducible factor (HIF) [3, 4]. The mutation of the VHL gene causes function loss in the production of VHL proteins, which drives the upregulation of HIF-1α and HIF-2α [5, 6]. As the HIF level increases, it promotes the transcription of the angiogenesis factors PDGF and vascular endothelial growth factor (VEGF) (which is the most important), ultimately inducing vascularization and tumorigenesis [7]. Recent reporting shows increasing incidences of RCC and decreases in mortality, with the latter possibly linked to the advancement of antiangiogenic therapy [8]. Previous antiangiogenic therapies targeted receptor tyrosine kinases (RTK) and their ligands, including the VEGF, PDGF, and VEGF receptors (VEGFR); however, resistance invariably occurred within a short period [9]. Previous studies found that VHL disruption also prompts the excessive expression of the RTK c-MET, which expresses increased renal malignancy compared to normal renal tissue [10]. C-MET provides an alternative pathway that bypasses the VEGFR pathway and drives angiogenesis, which is closely correlated with resistance to the VEGF tyrosine kinase inhibitor (TKI) and the poor prognoses of RCC patients [5, 11]. Cabozantinib, an RTK inhibitor, not only inhibits VEGFRs but also c-MET; thus, combining VEGF-targeted therapy with cabozantinib in RCC treatment can effectively inhibit metastasis and late-stage tumor progression [6, 7, 12, 13].

Here, we provide a comprehensive review of the pathology and the role of c-MET in RCC. We conducted a literature review of articles indexed in PubMed using the search terms “c-MET” and “renal cell carcinoma”.

The c-met pathway and its function

C-MET and its ligand, hepatocyte growth factor, initiate a signaling pathway

MET, a proto-oncogene located on chromosome 7q21-31, encodes RTK c-MET [14]. C-MET exists in the epithelial cells of numerous organs, including the liver, kidneys, intestines, lungs, pancreas, and stomach, as well as in the muscle tissue [15, 16]. Hepatocyte growth factor (HGF), a paracrine factor secreted by mesenchymal cells, is the only natural ligand for the c-MET receptor [14]. When the ligand HGF binds to the c-MET receptor, it activates a successive signaling pathway associated with cell proliferation, cell cycle progression, motility, and the epithelial-to-mesenchymal transition [14, 17, 18]. The HGF/c-MET pathway is also crucial during embryogenesis and tissue or organ regeneration [14, 17, 18]. The c-MET protein is a heterodimer that is composed of an extracellular α chain and a transmembrane β chain, which are linked by a disulfide bond [15, 18]. There is a semaphorin domain, a plexin-semaphorin-integrin domain, some immunoglobulin-plexin-transcription domains, a transmembrane domain, a juxtamembrane domain, a tyrosine kinase domain, and a carboxyl-terminal tail in the transmembrane chain (β chain) [15, 18, 19].

The c-MET signaling pathway and its association with carcinogenesis

In **Figure 1**, the downstream and crosstalk pathways of c-MET are summarized. The c-MET signaling pathway starts when HGF binds to the c-MET receptor, resulting in the formation of a homodimer [17, 19-22]. Next, two intracellular tyrosine residues are phosphorylated by the kinase domain itself, and autophosphorylations promote the recruitment of several effector or adaptor proteins, such as growth factor receptor-bound protein 2 (GRB2), GRB2-associated adaptor protein 1, and SRC homology domain 2, SRC homology domain 3, domain-containing protein, Son of Sevenless (SOS), proto-oncogene tyrosine-protein kinase SRC, phosphatidylinositol 3-kinase (PI3K), phospholipase Cγ, and SRC homology protein tyrosine phosphatase 2 [17, 19-22]. These effector proteins are related to many pathways, resulting in tumor progression when their expressions experience a loss of control [19, 23-25].

For the mitogen-activated protein kinase (MAPK) pathway, the phosphorylation of c-MET induces the recruitment of adaptor protein GRB2. Then, the SOS protein binds to it, activating the downstream GTP-binding protein Ras, which in turn activates Raf; Raf phosphorylates mitogen-activated protein kinase kinase kinase (MAP3K). MAP3K then phosphorylates mitogen-activated protein kinase kinase (MAP2K), and MAP2K promotes the phosphorylation of MAPK [15, 26, 27]. MAPK can phosphorylate transcription factors, such as c-Jun and c-Fos; after phosphorylation, these transcription factors bind to a DNA promoter, which promotes the transcription of cell cycle regulators, such as Cyclin D or p16INK4A [28, 29]. These gene products are responsible for the cellular proliferation, differentiation, and degradation of proteins and the matrix when experiencing a loss of control [18, 28, 30, 31]. Ras, a kind of GTPase, activates another GTP-binding protein called Rho; this phosphorylates p21-activated kinase, which is strongly associated with proto-oncogenic pathways, including AKT, C-MYC, and β-catenin [18, 32].

The PI3K signaling pathway is similarly activated by the autophosphorylation of the tyrosine kinase domain of c-MET [5, 14]. Adaptor proteins recruited by phosphorylated residues bind to PI3K, which converts the plasma membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP2) to the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3) via phosphorylation, resulting in the successive activation of AKT and the mammalian target of rapamycin (mTOR) [5, 14]. AKT promotes cell survival, cell proliferation, metastasis, glycolysis metabolism, and the cell cycle, inhibiting apoptosis. The mTOR kinase is strongly related to those signaling proteins and transcription factors, including EIF4E, Cyclin D, tuberous sclerosis complex 1 (TSC1), tuberous sclerosis complex 2 (TSC2), phosphatase and tensin homolog (PTEN), serine/threonine protein kinase 11 (LKB1), and tumor suppressor p53 [24, 33]. Transcription factor EIF4E assists the expression of Cyclin D, c-Myc, and VEGF, which promote cell cycle progression and angiogenesis, resulting in tumorigenesis [20, 34]. TSC1 and TSC2 are suppressors of

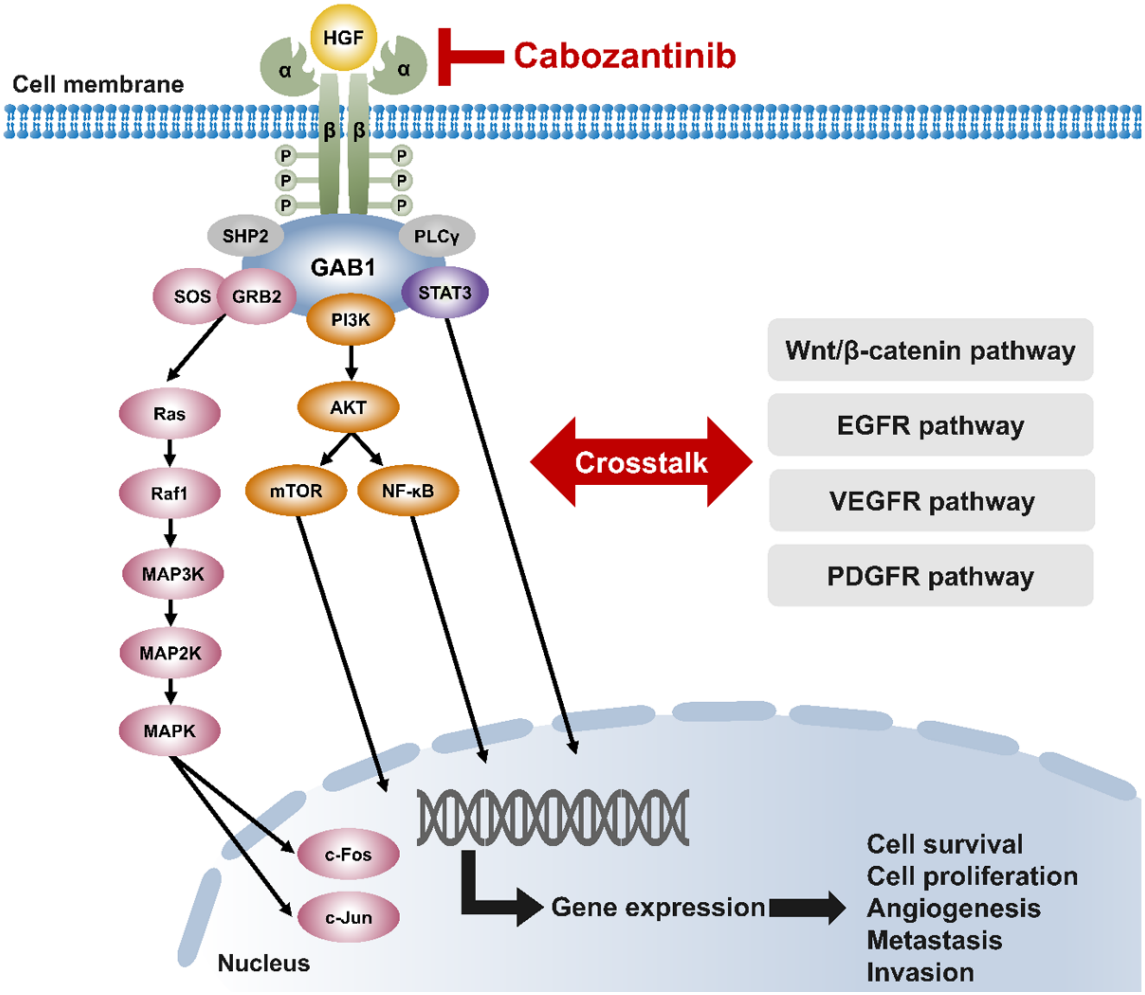

Figure 1. The C-MET downstream signaling pathway and the crosstalk pathway. Cabozantinib can block c-MET signaling cascades, preventing the drug resistance production of anti-angiogenesis therapies, including VEGF-targeted therapies.

the mTOR pathway, and their low expressions are found in some cancers [35]. PTEN is a phosphatase converted from PIP3 to PIP2, blocking the PI3K signaling pathway and inhibiting cell survival and proliferation [36]. The mutation of PTEN is correlated with tumor progression due to the loss of the tumor suppression function [37]. LKB1 is a kinase acting as a tumor suppressor, and it plays a critical role in human cancers [38, 39]. With the activation of PIP3 and the signaling protein, AKT translocates into the cell nucleus and phosphorylates transcription factor NF-κB. This factor affects both inflammatory cells and malignant cells, resulting in the inhibition of apoptosis and cell growth, and the promotion of the invasion process [24, 40].

The c-MET/HGF axis has been associated with other signaling pathways, such as the Wnt/β-catenin pathway, the epidermal growth factor receptor (EGFR) pathway, the VEGFR pathway, and the platelet-derived growth factor receptor pathway [15, 18]. Crosstalk between the c-MET pathway and the Wnt/β-catenin pathway is implicated in tumorigenesis; c-MET enhances nuclear translocation and accumulation in cytoplasms of β-catenin, stimulating the gene expressions of c-Myc, c-Jun, Cyclin D1, Fra-1, and MMP-7, which promote metastasis, proliferation, the loss of cell-cell contact, and aberrant cell migration [41-44]. Furthermore, the Wnt/β-catenin pathway displays the activation of the c-MET downstream pathway, including the MAPK and PI3K/mTOR signaling cas-

cades, and it is also related to carcinogenesis [45]. EGFR is an RTK and also forms homo/heterodimers for signaling transduction; additionally, this pathway is a crosstalk pathway of the c-MET pathway [46, 47]. EGFR can modulate the Ras/MAPK and PI3K/AKT pathways; therefore, EGFR mutation and c-MET amplification are closely related to drug resistance [18, 47]. The EGFR pathway can bypass c-MET to regulate the MAPK and PI3K pathways; in fact, c-MET can activate EGFR downstream cascades to boost cancer progression and cause EGFR tyrosine kinase inhibitor resistance [47, 48]. There are therapies simultaneously targeting both the c-MET and VEGF pathways due to their inseparable involvement [49]. In terms of inducing angiogenesis, c-MET controls the VEGF pathway with its downstream cascades, such as PI3K and Ras/MAPK, and is a signal transducer and activator of transcription-3 (STAT3) [50, 51]. The MAPK and PI3K pathways trigger the synthesis of hypoxia-inducible factor-1 (HIF-1), binding to the hypoxia-response element and promoting VEGFR translation. STAT3 is a transcription factor that activates the VEGF gene [50, 51]. The interaction between c-MET and VEGFR ultimately results in TKI resistance and the production of tumor blood vessels [52].

Renal cell carcinoma and the c-met inhibitor cabozantinib

The mechanism of cabozantinib

Cabozantinib, a multiple tyrosine kinase inhibitor, is the first-line therapy for moderate- or high-risk metastatic RCC, and it is also a second-line therapy for the treatment of advanced ccRCC and non-ccRCC after the first-line immune checkpoint inhibitor fails [53-55]. Cabozantinib inhibits RTKs, such as c-MET, AXL, RET, and VEGFR1-3, and as a treatment for RCC, cabozantinib is beneficial for decreasing the drug resistance of VEGF-targeted therapy due to c-MET's and AXL's involvement in drug resistance [13, 56]. Metastatic RCC tumors frequently develop drug resistance to VEGF-targeted therapy (e.g., sunitinib) because c-MET and AXL provide alternative downstream pathways instead of VEGF downstream cascades to some extent [57, 58].

CYP3A4, the most abundant cytochrome P450 (CYP450) enzyme in the human liver, is implicated in the metabolism of several drugs; for example, cabozantinib is a substrate of CYP3A4 [6]. Therefore, regarding the administration of CYP3A4 inducers or inhibitors (e.g., rifampicin/ketoconazole), it is worth noting when there is concomitant use of cabozantinib, the CYP3A4 inducer causes a decrease in the exposure of cabozantinib, and the CYP3A4 inhibitor causes an increase in the exposure of cabozantinib [6, 14]. Moreover, there have been studies analyzing CYP3A4 gene variations that have helped investigate the enzymatic properties of CYP3A4 and have clarified the metabolic ability of cabozantinib in individuals [59].

Cabozantinib: treatment and clinical trials for RCC

We used the keywords "Cabozantinib" and "Renal cell carcinoma" to find clinical trials at ClinicalTrials.gov. These clinical trials were in either combination or comparison with cabozantinib and other anti-cancer drugs. All types and stages of RCC were included in the clinical trials, which are described below and in **Tables 1** and **2**.

Cabozantinib was approved by the U.S. Food and Drug Administration for the treatment of advanced RCC in 2016 [60]. This approval was based on the CABOSUN study, which was a phase 2, randomized clinical trial comprising 157 patients [61]. Researchers compared the efficacy and safety of sunitinib to cabozantinib as first-line therapies for moderate- or high-risk metastatic RCC. The progression-free survival (PFS) was significantly longer when patients were treated with cabozantinib (8.2 versus 5.6 months, respectively), and the objective responsive rate was higher for cabozantinib than it was for sunitinib (33% versus 12%, respectively) [61]. Furthermore, there was no difference in the grade 3/4 adverse events (AEs). The results of this trial caused cabozantinib to replace sunitinib as a first-line treatment for mRCC patients [61].

In recent years, immune checkpoint inhibitors have been shown to be effective therapies for advanced RCC. Several studies have compared cabozantinib with immune checkpoint inhibitors. In a systematic review of the literature, cabozantinib has been indirectly compared with the immune checkpoint inhibitor

Table 1. A list of currently recruiting trials for RCC using cabozantinib

Identifier	Study Title	Conditions	Interventions	Estimated Enrollment	Start Date	Estimated Study Completion Date
NCT04022343	Neoadjuvant Cabozantinib in Treating Patients With Locally Advanced Kidney Cancer	Renal Cell Carcinoma	Drug: Cabozantinib	17	6-Aug-19	31-Aug-23
NCT02761057	Cabozantinib S-Malate, Crizotinib, Savolitinib, or Sunitinib Malate in Treating Patients With Locally Advanced or Metastatic Kidney Cancer	Renal Cell Carcinoma	Drug: Cabozantinib Drug: Cabozantinib S-malate Drug: Crizotinib Drug: Savolitinib Drug: Sunitinib Drug: Sunitinib Malate	180	5-Apr-16	1-Jan-21
NCT03634540	A Trial of PT2977 in Combination With Cabozantinib in Patients With Clear Cell Renal Cell Carcinoma (ccRCC)	Renal Cell Carcinoma; (and 8 more...)	Drug: PT2977 in combination with Cabozantinib tablets	118	21-Sept-18	1-Sept-21
NCT03937219	Study of Cabozantinib in Combination With Nivolumab and Ipilimumab in Patients With Previously Untreated Advanced or Metastatic Renal Cell Carcinoma	Renal Cell Carcinoma	Drug: Cabozantinib Biological: Nivolumab Biological: Ipilimumab Drug: Cabozantinib-matched placebo	676	25-Jun-19	Jun-24
NCT03866382	Testing the Effectiveness of Two Immunotherapy Drugs (Nivolumab and Ipilimumab) With One Anti-cancer Targeted Drug (Cabozantinib) for Rare Genitourinary Tumors	Renal Cell Carcinoma; Metastatic Renal Cell Carcinoma; (and 37 more...)	Drug: Cabozantinib Drug: Cabozantinib S-malate Biological: Ipilimumab Biological: Nivolumab	186	12-Apr-19	28-Feb-23
NCT03798626	Gevokizumab With Standard of Care Anti-cancer Therapies for Metastatic Colorectal, Gastroesophageal, and Renal Cancers	Renal Cell Carcinoma; (and 2 more...)	Drug: Gevokizumab Drug: Bevacizumab Drug: Modified FOLFOX6 Drug: FOLFIRI Drug: Ramucirumab Drug: Paclitaxel Drug: Cabozantinib	172	22-May-19	18-Dec-23
NCT03793166	Immunotherapy With Nivolumab and Ipilimumab Followed by Nivolumab or Nivolumab With Cabozantinib for Patients With Advanced Kidney Cancer, The PDIGREE Study	Clear Cell Renal Cell Carcinoma; (and 6 more...)	Drug: Cabozantinib Biological: Ipilimumab Biological: Nivolumab Other: Quality-of-Life Assessment Other: Questionnaire Administration	1046	9-May-19	15-Sept-21
NCT03729245	A Study of NKTR-214 in Combination With Nivolumab Compared With the Investigator's Choice of a Tyrosine Kinase Inhibitor (TKI) Therapy (Either Sunitinib or Cabozantinib Monotherapy) for Advanced Metastatic Renal Cell Carcinoma (RCC)	Renal Cell Carcinoma; Metastatic Renal Cell Carcinoma	Biological: NKTR-214 Drug: Sunitinib Biological: Nivolumab Drug: Cabozantinib	600	28-Dec-18	Jun-24
NCT03463681	A Study of Cabozantinib in Patients With Advanced or Unresectable Renal Cell Carcinoma (BREAKPOINT)	Metastatic Renal Cell Carcinoma	Drug: Cabometyx	49	11-Jun-18	Jun-20
NCT03200587	Cabometyx and Avelumab in Patients With Metastatic Renal Cell Carcinoma (mRCC)	Renal Cell Carcinoma	Drug: Avelumab Drug: Cabozantinib	20	21-Feb-18	Sept-22
NCT03149822	Study of Pembrolizumab and Cabozantinib in Patients With Metastatic Renal Cell Carcinoma	Metastatic Renal Cell Carcinoma	Drug: Cabozantinib Drug: Pembrolizumab	55	28-Sept-17	Jun-20
NCT02867592	Cabozantinib-S-Malate in Treating Younger Patients With Recurrent, Refractory, or Newly Diagnosed Sarcomas, Wilms Tumor, or Other Rare Tumors	Renal Cell Carcinoma; (and 35 more...)	Drug: Cabozantinib Drug: Cabozantinib S-malate Other: Pharmacological Study	146	8-May-17	30-Jun-21

NCT02496208	Cabozantinib S-malate and Nivolumab With or Without Ipilimumab in Treating Patients With Metastatic Genitourinary Tumors	Renal Cell Carcinoma; (and 35 more...)	Drug: Cabozantinib Drug: Cabozantinib S-malate Biological: Ipilimumab Biological: Nivolumab	152	9-Jul-15	30-Sept-19
NCT03647878	Study of Cabozantinib in Patients With Advanced or Metastatic Renal Cell Carcinoma Under Real-life Clinical Setting in 1st Line Treatment (CABOCARE)	Advanced or Metastatic Renal Cell Carcinoma	Drug: Cabozantinib	105	24-Sept-18	30-Aug-22
NCT03635892	A Study of Nivolumab In Combination With Cabozantinib in Patients With Non-Clear Cell Renal Cell Carcinoma	Renal Cell Carcinoma; (and 6 more...)	Drug: Cabozantinib Drug: Nivolumab	57	13-Aug-18	Aug-18
NCT03354884	Cabozantinib in Collecting Ducts Renal Cell CarcInoma (BONSAI)	Collecting Duct Carcinoma (Kidney)	Drug: Cabozantinib	23	12-Jan-18	Jun-20
NCT03541902	Cabozantinib or Sunitinib Malate in Treating Participants With Metastatic Variant Histology Renal Cell Carcinoma	Renal Cell Carcinoma; (and 8 more...)	Drug: Cabozantinib Drug: Sunitinib Malate	84	15-May-18	31-Jul-20
NCT03685448	ANZUP - Non-clear Cell Post Immunotherapy Cabozantinib (UNICAB)	Renal Cell Carcinoma; (and 6 more...)	Drug: Cabozantinib	48	11-Apr-19	30-Apr-24

Table 2. A list of current but not yet recruiting (first four) and active RCC trials (two have results) using cabozantinib

Identifier	Study Title	Conditions	Interventions	Estimated Enrollment	Start Date	Estimated Study Completion Date
NCT04134390	Study of Cabozantinib Efficacy, Safety and Tolerability in Metastatic Renal Carcinoma in Aged Fragile Patients: CABOMAYOR Study (CABOMAYOR)	Old Age; Debility Renal Carcinoma Metastatic	Drug: Cabozantinib	50	Nov-19	Dec-22
NCT04071223	Testing the Addition of a New Anti-cancer Drug, Radium-223 Dichloride, to the Usual Treatment (Cabozantinib) for Advanced Renal Cell Cancer That Has Spread to the Bone	Advanced Renal Cell Carcinoma; (and 8 more...)	Drug: Cabozantinib Drug: Cabozantinib S-malate; (and 3 more...)	210	13-Sept-19	15-Jun-21
NCT03967522	Evaluation of Cabozantinib in Metastatic Renal Cell Carcinoma (mRCC) With Brain Metastases (CABRAMET)	Metastatic Renal Cell Carcinoma	Drug: Cabozantinib	77	Sept-19	Mar-24
NCT03945773	Study of Cabozantinib as 2nd Line Treatment in Subjects With Locally Advanced or Metastatic Renal Cell Carcinoma (RCC) With a Clear-Cell Component Who Progressed After 1st Line Treatment With Checkpoint Inhibitors (CaboPoint)	Locally Advanced or Metastatic Renal Cell Carcinoma	Drug: Cabozantinib	250	30-Sept-19	1-Jan-23
NCT03339219	A Phase 2 Study of Cabozantinib in Japanese Patients With Advanced Renal Cell Carcinoma	Advanced Renal Cell Carcinoma	Drug: Cabozantinib	35	13-Dec-17	22-Aug-20
NCT03141177	A Study of Nivolumab Combined With Cabozantinib Compared to Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 9ER)	Renal Cell Carcinoma	Biological: Nivolumab Drug: Cabozantinib Drug: Sunitinib Biological: Ipilimumab	638	11-Jul-17	14-May-24
NCT02293980	A Phase 1, Dose-Escalation Trial of PT2385 Tablets In Patients With Advanced Clear Cell Renal Cell Carcinoma	Renal Cell Carcinoma; (and 4 more...)	Drug: PART 1: PT2385 Tablets Drug: PART 2: PT2385 Tablets in combination with nivolumab Drug: PART 3: PT2385 Tablets in combination with cabozantinib	110	Nov-14	Aug-20
NCT03428217	CANTATA: CB-839 With Cabozantinib vs. Cabozantinib With Placebo in Patients With Metastatic Renal Cell Carcinoma (CANTATA)	Advanced Renal Cell Carcinoma Metastatic Renal Cell Carcinoma	Drug: CB-839 Drug: Cabozantinib Drug: Placebo	416	27-Mar-18	30-Sept-22
NCT01865747	A Study of Cabozantinib (XL184) vs. Everolimus in Subjects With Metastatic Renal Cell Carcinoma (METEOR) (Has Result)	Renal Cell Carcinoma	Drug: Cabozantinib tablets Drug: Everolimus (Afinitor) tablets	658	Jun-13	Jun-19
NCT01835158	Cabozantinib-s-malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer (Has Result)	Clear Cell Renal Cell Carcinoma Metastatic Kidney Carcinoma; (and 2 more...)	Drug: Cabozantinib S-malate Other: Laboratory Biomarker Analysis Drug: Sunitinib Malate	157	8-Jul-13	18-Apr-16

nivolumab for the treatment of metastatic RCC [62, 63]. This study used data from two clinical trials: a randomized, open-label, phase 3 study of nivolumab versus everolimus in mRCC (ClinicalTrials.gov Identifier: NCT01668784) and a trial focused on the comparison of cabozantinib (XL184) and everolimus in the treatment of mRCC patients (ClinicalTrials.gov Identifier: NCT01865747). The patients in both aforementioned clinical trials underwent anti-angiogenic therapy [62].

Another study compared the clinical and cost-effectiveness of axitinib, cabozantinib, everolimus, nivolumab, and sunitinib for the treatment of patients with advanced mRCC who were previously treated with VEGF-targeted therapy [64]. This study collected clinical information from several databases, including Medline, Embase, and The Cochrane Library [64]. In this systematic review, the researchers evaluated data from randomized, controlled trials (RCTs) and non-RCTs and conducted crucial clinical indicators of five drugs: OS, PFS, and ORR (all are presented with 95% credible intervals) [64]. According to the first statistical analysis study, cabozantinib's effects were significantly greater on PFS, although there was no difference in the effect on OS. In the second study, cabozantinib was preferable because it controlled tumor growth and prolonged survival [62, 64].

There are many clinical trials in progress (**Tables 1** and **2**). These studies are implicated in many aspects of RCC and cabozantinib. For example, brain metastasis is a delicate problem for mRCC treatment due to low drug penetration at the blood-brain barrier [65]. In a recent study and case report, cabozantinib seemed to be an outstanding option for the treatment of brain metastasis in mRCC patients [65, 66]. Peverelli et al. analyzed patients with brain metastases who underwent cabozantinib treatment and discovered no brain-related or any neurological AEs in the patients [66]. However, these studies were limited by a small sample size, leaving insufficient evidence of cabozantinib's efficacy on brain metastasis in mRCC patients. At the time of this writing, there is an ongoing phase 2, open-label clinical trial evaluating the efficacy of cabozantinib on mRCC in patients with brain metastases (ClinicalTrials.gov Identifier: NCT03967522).

Researchers have also focused on the efficacy of combining cabozantinib with other drugs (mostly those in the immunotherapy category) in the treatment of mRCC patients. For example, a phase 3, double-blind trial conducted in the U.S. is evaluating cabozantinib versus a placebo in combination with nivolumab and ipilimumab using previously untreated mRCC patients of moderate or high risk (ClinicalTrials.gov Identifier: NCT03937219). In addition to nivolumab and ipilimumab, a phase 1b, open-label clinical trial is testing the clinical activity (PFS) of cabozantinib in combination with avelumab and establishing their safety, tolerability, and AEs in subjects with mRCC (ClinicalTrials.gov Identifier: NCT03200587). Pembrolizumab, an immune checkpoint blockade targeting PD-1, is also being combined with cabozantinib in a phase 1-2 clinical trial, where researchers are trying to evaluate cabozantinib in combination with pembrolizumab (ClinicalTrials.gov Identifier: NCT03149822) [67]. Additionally, two studies are respectively testing PT2977 and PT-2385, both HIF-2α inhibitors, in combination with cabozantinib for the treatment of RCC (ClinicalTrials.gov Identifier: NCT03634540/NCT02293980).

There are clinical trials investigating cabozantinib for first-line and second-line therapies after the failure of immune checkpoint inhibitors. To examine the real-life safety and efficacy of cabozantinib as a first-line therapy, an observational, non-interventional study is trying to evaluate dose reduction and terminations due to AEs (ClinicalTrials.gov Identifier: NCT03647878). Cabozantinib is also in use as a second-line therapy for mRCC patients whose disease progressed after the use of first-line immunotherapy; the safety and efficacy of cabozantinib is being evaluated in a phase 2, open-label clinical trial (ClinicalTrials.gov Identifier: NCT03945773). The many ongoing clinical trials testing cabozantinib as an mRCC treatment will likely lead to improvements in the treatment of RCC.

In conclusion, c-MET is overexpressed in all RCC subtypes and plays a crucial role in metastasis and advanced RCC [4, 68]. The c-MET inhibitor cabozantinib is a novel, promising treatment for every stage of metastatic RCC. Cabozantinib seems to have potential in the treatment of mRCC patients in combination with other anti-cancer drugs. We believe that

further study will reveal new uses for this drug against this often-fatal malignancy.

Disclosure of conflict of interest

None.

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