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REVIEW

Cabozantinib in the treatment of advanced renal cell carcinoma: design, development, and potential place in the therapy

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Abstract: The treatment of metastatic renal cell carcinoma (mRCC) has markedly improved over the last few years with the introduction of several targeted agents in clinical practice. Nevertheless, either primary or secondary resistance to inhibition of VEGF and mTOR pathways has limited the clinical benefit of these systemic treatments. Recently, a better understanding of the involvement of MET and its ligand HGF in many biological processes made this signaling pathway an attractive therapeutic target in oncology, particularly in mRCC. Herein, we review the development of cabozantinib, a recently approved inhibitor of multiple tyrosine kinase receptors, including MET, VEGFRs, and AXL, which has proven to increase progression-free survival and overall survival when compared to everolimus in mRCC patients who had progressed after VEGFR-targeted therapy. Finally, we discuss the potential role of cabozantinib within the current treatment landscape for mRCC.

Keywords: cabozantinib, XL-184, metastatic renal cell carcinoma, VEGF-inhibitor, c-Met, targeted therapy

Introduction

Renal cell carcinoma (RCC) accounts for ~330,000 cases diagnosed each year and 140,000 deaths worldwide.[1] Most cases are localized; however, one-third of patients present with an advanced disease at diagnosis and ~30% of subjects eventually develop metastatic disease after nephrectomy. The VHL protein plays a major role in RCC, being downregulated due to gene inactivation or epigenetic silencing. As a consequence, the hypoxia-inducible factors (HIFs) are stabilized and VEGF, MET, and AXL genes are upregulated.[2,3] This effect on VEGF can explain the angiogenic drive of clear-cell RCC (ccRCC), and expression of MET or AXL can be associated with an invasive tumor phenotype and poor prognosis.[3,4–6] Preclinical evidence also showed that MET and AXL upregulation in ccRCC can also occur in response to VEGFR tyrosine kinase inhibitor (TKI) therapies, underlying a potential role for MET and AXL in the development of secondary resistance. Moreover, overexpression of angiopoietin, FGF, MET, and HGF has been associated with the mechanisms of resistance to VEGF inhibitors.[7–9] Therapeutic strategies for metastatic disease are mostly based on VEGF inhibitors such as sunitinib, pazopanib, bevacizumab, sorafenib, and axitinib and mTOR inhibitors, including temsirolimus and everolimus. Nevertheless, despite an impressive improvement of outcome with targeted agents, complete remissions are rarely achieved and either primary or secondary resistance eventually develops. In addition, cross talk between the MET and VEGFR pathways is involved

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in tumor neoangiogenesis and progression but is implicated in the resistance to anti-VEGFR agents. The recently approved cabozantinib is able to target both the VEGF and c-Met pathways in order to overcome resistance to TKIs while maintaining VEGF inhibition. This review focused on the clinical development of this novel agent and the potential placement among other approved drugs to treat metastatic renal cell carcinoma (mRCC).

MET pathway and renal cancer

The MET proto-oncogene is located on chromosome 7q21–31 and encodes a tyrosine kinase receptor. The MET RTK is expressed on the surface of epithelial and endothelial cells, where it can be bound specifically by its ligand, the HGF. HGF is an inactive serine protease analog that is produced in cells of mesenchymal origin. MET and HGF are involved in many physiological and pathological processes, such as fetal development, including liver, placenta and muscle formation, as well as in the nervous system development.[10] After birth, HGF–MET pathway appears to be activated in epithelial–mesenchymal transition, as well as in liver, renal, and skin regeneration. MET signaling is also involved in tumor growth, invasion, resistance to systemic treatments, and angiogenesis. Furthermore, it plays an important role in RCC where MET expression is associated with poor prognosis and higher Fuhrman grade as well as advanced disease.[11] The results of MET signaling pathway activated from several mechanisms, including chromosomal rearrangement, germline or somatic mutations, gene amplification, MET protein overexpression, and increased HGF expression, or by alternate activation of other pathways affecting MET.[12] Moreover, MET along with VEGFR-2 plays a synergistic role in promoting tumor angiogenesis and metastatic phenotype. Mutations in the HGF and MET genes are associated with bilateral type I papillary renal carcinoma (pRCC) in hereditary pRCC syndrome that generally has a better prognosis. Type I pRCC presents a higher expression of MET when compared with the type II subtype, which generally presents poor pathological features with a poorer prognosis.[13] The trisomy of chromosome 7 is a common occurrence in pRCC, and several activating missense mutations of the MET gene have been described, both in sporadic and hereditary forms.[14] MET expression is significantly higher in both type I and type II pRCCs than in clear-cell histology, justifying MET inhibitors as a therapeutic strategy in advanced pRCC.[15,16] Moreover, mutations or loss of the VHL gene under hypoxic conditions lead to accumulation of HIFs: as a result, different HIF target genes are upregulated, including

VEGF, PDGF, TGF-a, and MET. HGF signaling is increased by hypoxia; thus, MET pathway contributes to invasive phenotype of VHL-negative renal carcinoma. Recently, Ciamporcero et al[17] evaluated the impact of either monotherapy or combination strategies targeting the VEGF and MET pathways in ccRCC mice models. Sunitinib-sensitive and sunitinib-resistant models of human ccRCC patient-derived xenograft were used to test these drugs. Immunodeficient SCID male mice (eight per group) were implanted with high c-Met expressing 786-O tumor cells and treated with either a VEGFR TKI, axitinib (36 mg/kg, two times per day); a c-Met inhibitor, crizotinib (25 mg/kg, one time per day); or combination. This drug combination was further tested in a human ccRCC low c-Met expressing patient-derived xenograft, RP-R-01, in both VEGF-targeted therapy-sensitive and therapy-resistant models. The antitumor effect in both models was increased with the combination therapy, independent of MET expression. It was concluded that combined VEGF and HGF–MET pathway blockade might improve the outcome of RCC patients. Similarly, Shojaei et al[18] observed that the addition of an MET inhibitor was able to overcome sunitinib resistance in mouse models with increased HGF expression that was resistant to sunitinib.

Preclinical models of cabozantinib activity

Cabozantinib (XL-184) was designed and synthesized as an oral small inhibitor of multiple tyrosine kinase receptors with activity toward VEGF (VEGFR-2) and Met and also RET, KIT, AXL, TIE2, and FLT3 (Fms-like tyrosine kinase), which are also involved in tumor pathogenesis.[19,20] Met and VEGFR-2 play a synergistic role in promoting tumor angiogenesis and metastatic spread and are overexpressed in hypoxic condition. Moreover, KIT and RET inhibitions make XL184 clinically effective in medullary thyroid cancer (MTC).[19] Hypoxic conditions due to VEGF pathway inhibition can induce c-Met expression, which may eventually promote tumor invasion, survival, and metastasis. Drugs targeting only VEGF and its receptors can hence induce Met, leading to the development of angiogenesis and cancer progression. Cabozantinib inhibits both the receptor tyrosine kinases, thus hampering the overexpression of these factors and causing an increase in tumor cell death associated with a decreased vascularization as shown in an MDA-MB-231 breast cancer xenograft model.[19] These antiangiogenic effects translated into a proapoptotic effect able to hamper tumor growth in xenograft cancer models, including breast, lung cancer,

and glioblastoma.[21] Cabozantinib showed to play a role in bone metastasis models since HGF, MET, and VEGFRs are expressed on either osteoblasts or osteoclasts, regulating their proliferation, migration, and survival.[22,23] Bone metastases from prostate cancer seem to overexpress MET as compared to soft tissue metastases,[13] and preclinical xenograft prostate cancer models showed responses to cabozantinib in nude mice.[24] Activity of cabozantinib in patients with bone metastases from RCC has been confirmed in a Phase III trial.[25]

Phase I development of cabozantinib

The Phase I study was a dose-escalation trial done on the patients with advanced solid tumors to evaluate primary end points such as safety, pharmacokinetics, and maximum tolerated dose, and secondary end points such as response evaluation criteria in solid tumors (RECIST), pharmacodynamics, RET mutational studies, and biomarker analyses. A total of 85 patients were enrolled, including 37 patients with MTC and two with RCC (one pRCC and one ccRCC). Ten patients (29%) experienced partial response, and seven patients had unconfirmed response. Fifteen patients (41%) had a stable disease with a duration of at least 6 months.[26] The adverse events (AEs) occurring with cabozantinib were the same as those with the other drugs targeting RTKs, including VEGFR-2, KIT, and RET. Following these results, a Phase Ib drug–drug interaction study was designed to evaluate safety, tolerability, and efficacy of cabozantinib in 25 mRCC patients treated with at least one or two prior lines of systemic therapy. Cabozantinib was administered in doses up to 140 mg daily, which was associated with a single dose of rosiglitazone at day 22. All the patients received at least one or two prior lines of therapy, with 68% of patients receiving two or more prior systemic agents and 32% receiving four or more prior lines of therapy, including anti-VEGF treatment (88%), mTOR inhibitor therapy (60%), and both agents (52%). The majority of patients (84%) were classified as intermediate risk group per Heng criteria; only 4% were in the favorable risk group, while 12% were in the poor risk group. Bone metastases were present in four patients (16%).[18] Seven of these patients

(28%) had an objective response, and 13 (52%) had stable disease as per the RECIST criteria. At a median follow-up of 14.7 months (range 11.2–21.8 months), the median progression-free survival (PFS) was 12.9 months, while the overall survival (OS) was 15.0 months with a median follow-up of 28.3 months (range 24.8–35.5 months; Table 1). Three out of four patients with bone metastases showed a response, and two received effective palliation of bone pain from treatment. The safety profile was similar to other TKIs with grades 3–4 adverse AEs, including fatigue (16%), diarrhea (12%), hypophosphatemia (36%), and hyponatremia (20%).[27] Based on tolerability and activity associated with doses of cabozantinib <140 mg in this study, a daily dose of 60 mg was selected for subsequent trials. These preliminary data have led to the design of randomized trials of cabozantinib in the first-line setting (NCT01835158)[28] after development of resistance to a VEGFR TKI.[25] More recently, positive results of both single-agent nivolumab, a novel monoclonal antibody that inhibits the interaction between PD-1 receptor expressed by activated T-cells and its ligand PD-L1 on the surface of tumor cells, which prevent T-cell activation (in the Phase III CheckMate-025 trial, where mRCC patients previously treated with at least one anti-VEGF treatment were randomly assigned to receive nivolumab or everolimus, the median OS was 5.4 months longer with nivolumab with an objective response rate (ORR) of 25% vs 5% for everolimus),[29] and cabozantinib (METEOR trial) in mRCC have provided the rationale for an ongoing Phase I combination trial of nivolumab and cabozantinib (NCT02496208).[30]

Phase II studies of cabozantinib

Cabozantinib has demonstrated clinical activity in different tumor types, including medullary and papillary thyroid cancers, melanoma breast cancer, lung cancer, ovarian cancer, hepatocellular carcinoma, and castration-resistant prostate cancer. In a Phase II randomized discontinuation study in men with castration-resistant prostate cancer (XL184-203), cabozantinib showed an increase in PFS as compared with placebo (median PFS 23.9 weeks vs 5.9 weeks).[31] The ORR at 12 weeks was 5%, and the stable disease was reported in 75%. The majority of subjects (67%) achieved a bone

Table 1 Summary of the published clinical trials and outcome measures for cabozantinib therapy

Study	Description	Patients (n)	Primary end point	OS	Median PFS	ORR
Shojaei et al[18]	Phase Ib drug–drug interaction study	25	Safety and tolerability	15.0 months	12.9 months	PR 28%
Choueiri et al[16]	Phase III randomized on C vs E	658	PFS	C 21.4 months E 16.5 months	C 7.4 months E 3.8 months	C: PR 21% E: PR 5%

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; PR, partial response; C, cabozantinib; E, everolimus.

scan response, including four patients showing a complete response and 62% with a partial response. Sixty-four percent of patients reported a 30% decrease in the average daily pain compared with baseline when considering patients with a baseline pain of at least 4 on a 0–10 scale. Disease control rates were also observed in other cohorts, including 38% in non-small cell lung cancer, 48% in breast cancer, 46% in melanoma, 47% in ovarian cancer, and 66% in hepatocellular carcinoma. Based on the success of Phase Ib study on RCC, a randomized Phase II study comparing cabozantinib versus sunitinib in the first-line intermediate or poor risk mRCC patients (CABOSUN) is being conducted by Alliance for Clinical Trials in Oncology. The primary end point is PFS. The study met its enrollment target of 150 patients, and the results are due to be released in late 2016.[32] Another randomized Phase II study is enrolling mRCC patients to receive multiple MET kinase inhibitors, including cabozantinib, crizotinib, volitinib, or sunitinib, in metastatic papillary renal carcinoma (PAPMET) with the primary end point of PFS.[33]

Pivotal Phase III study of cabozantinib in mRCC

Based on these encouraging results, a randomized, open-label, Phase III study comparing cabozantinib with everolimus in patients with mRCC progressing after VEGFR TKI therapy was conducted.[16] In this study, 658 patients were randomized 1:1 to receive 60 mg of cabozantinib or 10 mg of everolimus daily and stratified based on the number of prior VEGFR TKI therapies and the risk criteria of Memorial Sloan Kettering Cancer Center (MSKCC). No cross-over was allowed. The primary end point was PFS, and the secondary end points were OS and ORR. The median PFS was 7.4 months (95% confidence interval [CI] 5.6–9.1) in the cabozantinib arm and 3.08 months (95% CI 3.7–5.4) in the everolimus arm with a rate of disease progression or death of 42% lower with cabozantinib (HR 0.58, 95% CI 0.45–0.75, $P<0.001$). In a post hoc analysis, the median PFS was 9.1 months (95% CI 5.6–11.2) with cabozantinib and 3.7 months (95% CI 1.9–4.2) with everolimus in a subgroup of patients who received sunitinib as their only prior systemic anti-VEGF treatment. The overall response rate was 21% with cabozantinib as compared to 5% with everolimus. Stable disease occurred as the best response in 62% of patients in each group, while progressive disease occurred in 14% of patients treated with cabozantinib and 27% of patients treated with everolimus. At the prespecified interim analysis of OS, a trend toward longer OS with cabozantinib was observed, but the second interim analysis crossed the boundary for declaration of statistical significance for OS. The median OS was 21.4 months for patients receiving cabozantinib versus 16.5 months for those receiving everolimus (HR =0.66, 95% CI 0.53–0.83, P=0.0003) with a 34% reduction in the rate of death (Table 1).

Safety and tolerability

Most frequently reported grade 3 AEs in the Phase Ib study were fatigue (20%), diarrhea (12%), hypophosphatemia (40%), and hyponatremia (20%). Other grade 3 AEs reported included decreased appetite (4%), palmar-plantar erythrodysesthesia (PPE; 4%), hypertension (4%), and vomiting (4%). Fatigue (16%) and diarrhea were the most common relevant AEs noted with cabozantinib along with electrolyte abnormalities, including hypophosphatemia (36%) and hyponatremia (20%), in patients treated in the Phase II renal cancer trial. The dose used in the renal cancer trial was 140 mg daily; however, a number of toxicities were dose dependent. The frequency of drug discontinuation due to toxicities reported in the larger randomized discontinuation trial was 16%. A dose de-escalation study was conducted with continued assessment of efficacy in metastatic prostate cancer patients. The dose of 40 mg showed equivalent efficacy and lower toxicity, thus leading to the choice of the lower starting dose of 60 mg daily in the Phase III prostate cancer trials. In advanced renal cancer, a similar study should be conducted. In the Phase III METEOR trial, the most common AEs of any grade reported were diarrhea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), and PPE (42%). The most common grades 3–4 AEs in the cabozantinib arm were hypertension (15%), diarrhea (11%), and fatigue (9%), while anemia (16%), hyperglycemia (5%), and fatigue (7%) were reported with everolimus. One patient in the cabozantinib group experienced a grade 5 treatment-related AE (death not otherwise specified). The most common AEs leading to dose reduction with cabozantinib were diarrhea (16%), PPE (11%), and fatigue (10%), while those with everolimus were pneumonitis (4%), stomatitis (3%), and fatigue (3%). Dose reduction occurred in 60% and 25% of patients treated with cabozantinib and everolimus, respectively. Treatment discontinuation due to AEs occurred in 9% of subjects receiving cabozantinib and in 10% of those receiving everolimus.[16]

Conclusion

Increasing evidence for the role of MET in the development of resistance to anti-VEGF targeting agents led to the

development of cabozantinib as an orally bioavailable multikinase inhibitor that has shown a significant improvement in PFS and OS of patients with mRCC after failure of TKIs compared to everolimus. The drug has recently received the approval of the US Food and Drug Administration. Based on the information from the recently reported trial, its position among other agents will be as a second-line therapy option for mRCC subjects progressing after at least one VEGF-TKI treatment. The overall PFS and that reported in patients receiving cabozantinib after sunitinib showed the best outcome for a single agent used for mRCC treatment. Besides, the PFS reported in the same study with everolimus was similar to that reported in the Phase III RECORD 1 study.[34] This supports the METEOR study that suggests that the characteristics of this study population may not be more favorable in comparison to previous studies. Significant side effects (diarrhea, fatigue, nausea, decreased appetite, PPE, and hypertension) have been observed with cabozantinib therapy, resulting in ~60% of patients undergoing a dose reduction in the Phase III trial versus everolimus. As a result, the management of the toxicity of patients receiving cabozantinib may be a potential key driver for treatment choice. Focusing on special populations such as patients with bone metastases from RCC would be a strategy to achieve improved efficacy in patients where currently approved drugs have shown less efficacy. Moreover, association studies are evaluating the effect of the combination of cabozantinib with checkpoint inhibitors in patients with mRCC.[30] The ability of cabozantinib to cross the blood–brain barrier[21] as shown in glioblastoma warrants investigation in mRCC. Targeting the MET and VEGFR pathways simultaneously represents a promising approach for RCC treatment since this will target multiple pathways. Cabozantinib has demonstrated an improvement in PFS, ORR, and OS of pretreated mRCC patients. The peculiar safety profile of cabozantinib requires a prompt management of AEs in order to minimize dose reduction and optimize outcome. Clinical trials to evaluate specific subpopulations such as patients with bone and brain metastases from mRCC need further evaluation.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. 2012;62(4):220–241.
2. Harschman LC, Choueiri TK. Targeting the hepatocyte growth factor/c-Met signaling pathway in renal cell carcinoma. *Cancer J*. 2013;19(4):316–323.
3. Rankin EB, Fuh KC, Castellini L, et al. Direct regulation of GAS6/AXL signaling by HIF promotes renal metastasis through SRC and MET. *Proc Natl Acad Sci U S A*. 2014;111(37):13373–13378.
4. Bommi-Reddy A, Almeciga I, Sawyer J, et al. Kinase requirements in human cells: III. Altered kinase requirements in VHL-/- cancer cells detected in a pilot synthetic lethal screen. *Proc Natl Acad Sci USA*. 2008;105(43):16484–16489.
5. Gibney GT, Aziz SA, Camp RL, et al. c-Met is a prognostic marker and potential therapeutic target in clear cell renal cell carcinoma. *Ann Oncol*. 2013;24(2):343–349.
6. Koochekpour S, Jeffers M, Wang PH, et al. The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. *Mol Cell Biol*. 1999;19(9):5902–5912.
7. Saylor PJ, Escudier B, Michaelson MD. Importance of fibroblast growth factor receptor in neovascularization and tumor escape from antiangiogenic therapy. *Clin Genitourin Cancer*. 2012;10(2):77–83.
8. Fernando NT, Koch M, Rothrock C, et al. Tumor escape from endogenous, extracellular matrix-associated angiogenesis inhibitors by up-regulation of multiple proangiogenic factors. *Clin Cancer Res*. 2008;14(5):1529–1539.
9. Eder JP, Vande Woude GF, Boerner SA, LoRusso PM. Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. *Clin Cancer Res*. 2009;15(7):2207–2214.
10. Garajová I, Giovannetti E, Biasco G, et al. c-Met as a target for personalized therapy. *Transl Oncogenomics*. 2015;7(suppl 1):13–31.
11. Pàez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell*. 2009;15(3):220–231.
12. Maroun CR, Rowlands T. The Met receptor tyrosine kinase: a key player in oncogenesis and drug resistance. *Pharmacol Ther*. 2014;142(3):316–338.
13. Albiges L, Guegan J, Le Formal A, et al. MET is a potential target across all papillary renal cell carcinomas: result from a large molecular study of pRCC with CGH array and matching gene expression array. *Clin Cancer Res*. 2014;20(13):3411–3421.
14. Giubellino A, Linehan WM, Bottaro DP. Targeting the Met signaling pathway in renal cancer. *Expert Rev Anticancer Ther*. 2009;9(6):785–793.
15. Fay AP, Signoretti S, Choueiri TK. MET as a target in papillary renal cell carcinoma. *Clin Cancer Res*. 2014;20(13):3361–3363.
16. Choueiri TK, Vaishampayan U, Rosenberg JE, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. *J Clin Oncol*. 2013;31(2):181–186.
17. Ciamporcero E, Miles KM, Adelaiye R, et al. Combination strategy targeting VEGF and HGF/c-met in human renal cell carcinoma models. *Mol Cancer Ther*. 2015;14(1):101–110.
18. Shojaei F, Lee JH, Simmons BH, et al. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. *Cancer Res*. 2010;70(24):10090–10100.
19. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther*. 2011;10(12):2298–2308.
20. Aftab DT, McDonald DM. MET and VEGF: synergistic targets in castration-resistant prostate cancer. *Clin Transl Oncol*. 2011;13(10):703–709.
21. Gordon MS, Vogelzang NJ, Schoffski P, et al. Activity of cabozantinib (XL184) in soft tissue and bone: results of a phase II randomized discontinuation trial (RDT) in patients (pts) with advanced solid tumors. *J Clin Oncol*. 2011;29(suppl abstract 3010):196s.
22. Knudsen BS, Gmyrek GA, Inra J, et al. High expression of the Met receptor in prostate cancer metastasis to bone. *Urology*. 2002;60(6):1113–1117.
23. Grano M, Galimi F, Zambonin G, et al. Hepatocyte growth factor is a coupling factor for osteoclasts and osteoblasts in vitro. *Proc Natl Acad Sci U S A*. 1996;93(15):7644–7648.
24. Dai J, Zhang H, Karatsinides A, et al. Cabozantinib inhibits prostate cancer growth and prevents tumor-induced bone lesions. *Clin Cancer Res*. 2014;20(3):617–630.

25. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1814–1823.

26. Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol*. 2011;29(19):2660–2666.

27. Choueiri TK, Pal SK, McDermott DF, et al. A phase I study of cabozantinib (XL184) in patients with renal cell cancer. *Ann Oncol*. 2014;25(8):1603–1608.

28. ClinicalTrials.gov [webpage on the Internet]. Cabozantinib-s-malate or Sunitinib Malate in Treating Patients with Previously Untreated Locally Advanced or Metastatic Kidney Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT01835158. Accessed June 17, 2016.

29. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803–1813.

30. ClinicalTrials.gov [webpage on the Internet]. Cabozantinib-s-malate and Nivolumab with or without Ipilimumab in Treating Patients with Metastatic Genitourinary Tumors. Available from: https://clinicaltrials.gov/ct2/show/NCT02496208. Accessed June 17, 2016.

31. Smith DC, Smith MR, Sweeney C, et al. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. *J Clin Oncol*. 2013;31(4):412–419.

32. ClinicalTrials.gov [webpage on the Internet]. Cabozantinib-s-malate or Sunitinib Malate in Treating Patients with Previously Untreated Locally Advanced or Metastatic Kidney Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT01835158. Accessed June 17, 2016.

33. ClinicalTrials.gov [webpage on the Internet]. Cabozantinib-S-Malate, Crizotinib, Volitinib, or Sunitinib Malate in Treating Patients With Locally Advanced or Metastatic Kidney Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT02761057. Accessed June 17, 2016.

34. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449–456.