

Development of cabozantinib for the treatment of prostate cancer

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Abstract: Cabozantinib (XL184) is a multitargeted receptor tyrosine kinase with predominantly *MET* and vascular endothelial growth factor inhibition properties. It is currently approved by the US Food and Drug Administration for the treatment of progressive metastatic medullary thyroid cancer. The agent has a convenient once-daily oral dosing schedule and has demonstrated encouraging activity in metastatic castrate-resistant prostate cancer (CRPC). A Phase I/II trial demonstrated responses in soft tissue, visceral disease, and bone metastases in CRPC. An objective response rate of 5%, a stable disease rate of 75%, and a median progression-free survival of 6 months was observed. As compared with the 140 mg daily dose used in thyroid cancer, a lower dose of 60 mg daily is currently being utilized in prostate cancer studies due to the fact that toxicity could be reduced without compromising efficacy. Randomized trials are ongoing in comparison with prednisone or with mitoxantrone and prednisone in pretreated metastatic CRPC. Cabozantinib has demonstrated a unique mechanism of action and preliminary efficacy in the crowded therapeutic field of prostate cancer. Since multiple therapies have recently demonstrated overall survival benefit in metastatic CRPC, cabozantinib will likely face some challenges in clinical application. At present, in this rapidly evolving field, it is unclear what proportion of patients with prostate cancer will be eligible to receive this therapy. The cost of cabozantinib is likely to be another deterrent, especially if it remains more expensive than other oral therapies, such as abiraterone and enzalutamide. Defining the role of *MET* overexpression and *RET* mutations as biomarkers in prostate cancer may help to guide patient selection, and enrich and enhance the future applications of this targeted novel agent.

Keywords: XL184, castrate-resistant, vascular endothelial growth factor, *MET*, tyrosine kinase, metastasis

Core evidence clinical impact summary for cabozantinib

Perspective	Favorable evidence	Problems/concerns
Physician/ disease oriented	Preclinical rationale	Comparison trials with control group are still in progress
	Clinical efficacy	Durability of remissions
	Distinct mechanism of action	Difficult to carve a niche in a crowded therapeutics field
	Preclinical rationale	No associated identifiable biomarker to guide therapy
	Clinical efficacy	A limited proportion of patients will receive seventh line therapy (six systemic agents currently approved by the US FDA)
	Nonoverlapping toxicities with other agents, especially chemotherapy	Response assessment is challenging as PSA can be discordant with response and bone scan response quantification is not yet validated for this agent
	Combination trials are planned/ongoing	
	Possibility of complete response on bone scan	

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(Continued)		
Perspective	Favorable evidence	Problems/concerns
Patient-oriented	Convenient oral once-daily dosing Pain control Off narcotic pain medications Possibility of CR	No proven survival benefit as yet Toxicities such as hypertension, fatigue are not trivial Cost
Economic impact/costs of agents	Midrange cost as compared with other agents with OS benefit Cabozantinib costs \$9,900 per month (current known cost, may be different for dose used in prostate cancer if approved by the US FDA) Sipuleucel T costs \$31,000 per injection, course of three injections Alpharadin costs \$11,500 per injection, course of six injections	Can we justify the cost especially if it is used just for pain control? Mitoxantrone which has palliative benefit alone without OS benefit is now generic and costs about \$42 Very hard to cover out of pocket expenses Cost is high as compared with following agents showing OS benefit: Enzalutamide, \$7,450 Cabazitaxel, \$5,598.29 Abiraterone, \$5,000 Docetaxel, \$2,483
Abbreviations: CR, complete response; US FDA, US Food and Drug Administration; OS, overall survival; PSA, prostate-specific antigen.		

Introduction

The world of prostate cancer therapeutics has undergone a major overhaul in the last 5 years. Numerous agents with multiple, nonoverlapping mechanisms of action have achieved US Food and Drug Administration (FDA) approval for the indication of metastatic castrate-resistant prostate cancer (CRPC).^{1–5} Cabozantinib (Cometriq®; Exelixis Inc., South San Francisco, CA, USA) faces the challenge of entering a crowded marketplace. It does, however, demonstrate the unique phenomenon of complete response or normalization of bone scans in metastatic prostate cancer.⁶ This type of transformation on bone scan has not been observed, even with androgen deprivation therapy, which to this day remains the most effective front-line systemic therapy for prostate cancer. Despite recent advances, there is an ongoing clinical need to develop better therapies for advanced prostate cancer, to improve the chance of achieving long-term remission. Higher levels of *MET* expression are noted in prostate cancer cells, as compared with benign prostatic hyperplasia, which correlates directly with a higher grade of cancer.⁷ The resistance pathways in metastatic disease consist of hypoxia, leading to overexpression of *MET* and an increase in vascular endothelial growth factor (VEGF) levels, resulting in increasing angiogenesis and invasion.⁷ The clinical efficacy of cabozantinib is well established in medullary thyroid cancer by level I evidence from a well conducted, randomized, placebo-controlled, double-blind clinical trial.⁸

Cabozantinib has dual VEGF and Met inhibition properties and fits the current need for a distinctive novel target in prostate cancer therapy.⁷ Although a preliminary anticancer effect was noted in metastatic CRPC, the clinical efficacy of cabozantinib cannot be accepted until the results of randomized trials are available. The potential clinical and economic impact if cabozantinib is approved by the US FDA for use in metastatic CRPC is summarized above.

Mechanism of action

Importance of *MET* in cancer

In medullary thyroid cancer, the pathways of *MET*, *RET*, and VEGF appear to be pathophysiological for disease progression and proliferation. *MET* is activated by hepatocyte growth factor and both are broadly expressed in adult tissues and implicated in postnatal physiological and pathophysiological processes.

Upregulated hepatocyte growth factor and Met expression is observed in several injured tissues. After liver, kidney, or heart injury, plasma levels of hepatocyte growth factor rise, and increased expression is observed in other organs too, indicating this might be a general physiological response to tissue damage. It is also noted that release of cytokines such as interleukin-1 and interleukin-6 activate transcription of hepatocyte growth factor.⁹ Germline mutation in the tyrosine kinase domain of the c-*MET* proto-oncogene on chromosome 7q31 results in derangement of processes like angiogenesis,

Table I Clinical activity of cabozantinib in prostate cancer

Author/ref	Study design	Response rate	PFS	Predominant toxicities (Grade 3 or 4)
Smith et al ⁶	Phase II randomized discontinuation trial Starting dose 100 mg daily	ORR-7.6% SD-75% Bone scan CR-12% Bone pain relief-67%	Median 23.9 weeks with cabozantinib vs 5.9 weeks with placebo	Fatigue 16% Hypertension 12% Hand foot syndrome 8%
Lee et al ³⁰	Dose ranging study: adaptive scheme Doses of 40 and 20 mg daily. Dose escalation to 60 mg was planned is necessary	40 mg daily dose: 15/24 PR 1/11 CR 8/24 SD 0/24 PD 20 mg daily dose: 1/10 PR 0/10 CR 5/10 SD 5/10 PD	Overall bone scan response: 68% Pain response: 67% Median treatment duration 25.9 weeks on the 40 mg dose cohort	Anorexia, fatigue, weight loss were the most likely Grade 1 or 2 adverse events 1 Grade 3 thromboembolism noted.

Abbreviations: vs, versus; ref, reference; SD, stable disease; CR, complete response; PR, partial response; PD, progressive disease; ORR, overall response rate; PFS, progression free survival.

cell motility, proliferation, and morphogenic differentiation.^{10–12} This ultimately contributes to carcinogenesis and progression of malignancy. The *MET* tyrosine kinase receptor for hepatocyte growth factor has been implicated as a mediator in many important aspects of tumor pathobiology, including tumor survival, growth, angiogenesis, invasion, and dissemination,^{9,10} and several *MET* tyrosine kinase receptors have been reported to show activity in cell lines and animal models. *Met* and VEGFR2 play synergistic roles in promoting tumor angiogenesis and subsequent dissemination.^{13–15} In summary, *MET* protects cancer cells against apoptosis, increases their invasive ability, motility, and epithelial-mesenchymal transition, and promotes resistance to VEGF inhibitor therapy.

Dysregulation of the *MET*/VEGF axis has been reported in human malignancies, and this effect is likely to be seminal in a tumor such as prostate cancer, for which the most common site of metastasis is bone. VEGF results in phosphorylation of *MET* and activates the hepatocyte growth factor/*MET* pathway. VEGF alone without *MET* inhibition promotes rapid progression of tumors, as demonstrated in animal models.^{10,11} Cabozantinib is a novel, orally bioavailable inhibitor of multiple receptor tyrosine kinases with growth-promoting and angiogenic properties.⁷ Data from pharmacodynamic experiments show that cabozantinib inhibits *MET* and VEGFR2 (vascular endothelial growth factor receptor 2) in vivo. Cabozantinib also demonstrates an inhibitory effect against *KIT* and *RET*, thus making it clinically effective against medullary thyroid cancer.⁸ Oral administration of cabozantinib resulted in blockade of *MET* phosphorylation in human lung tumor xenografts grown in nude mice, blockade of *MET* phosphorylation in the mouse

liver, and blockade of VEGFR2 phosphorylation in mouse lung tissue. Treatment with cabozantinib results in antiangiogenic effects in xenograft tumors, with disruption of the vasculature starting within 24 hours of administration and proapoptotic effects. These effects translate into significant inhibition of tumor growth or tumor regression after treatment with cabozantinib in multiple tumor models, including medullary thyroid cancer, prostate cancer, breast cancer, carcinoma of the lung, and glioblastoma.⁷

Treatment with cabozantinib for 3 weeks inhibited the development of liver metastasis in the RIP-Tag2 model.^{16,17} This was in contrast with the increased number of metastases noted in the same model with anti-VEGF treatment alone. The number of liver metastases observed was five-fold greater in anti-VEGF antibody-treated animals compared with vehicle-treated animals and, interestingly, no liver metastases were detected in cabozantinib-treated animals. In addition, improved overall survival was noted in the cabozantinib-treated animals. Median survival was 14.7 weeks for vehicle-treated animals (n=12) and 16.4 weeks for anti-VEGF antibody-treated animals (n=7; $P<0.05$ versus vehicle). Animals treated with *MET* inhibitors demonstrated improved survival of >20 weeks.

Cabozantinib activity in a preclinical bone metastasis model

The *MET* and VEGF signaling pathways appear to play important roles in the function of osteoblasts and osteoclasts. The *MET* receptor for hepatocyte growth factor has been implicated as a mediator in many important aspects of tumor pathobiology, including tumor survival, growth, angiogenesis, invasion, and dissemination, and several *MET* tyrosine kinase

receptors have been reported to show activity in cell lines and animal studies.^{18–21} *MET* expression has been observed by immunohistochemistry in both bone cell types in developing bone.¹⁰ Hepatocyte growth factor and *MET* are expressed by osteoblasts and osteoclasts in vitro and mediate cellular responses such as proliferation and migration. Osteoblasts and osteoclasts express VEGF and its receptors, and VEGF signaling in these cells is involved in potential autocrine and/or paracrine feedback mechanisms regulating cell migration, differentiation, and survival.¹⁸ Secretion of hepatocyte growth factor by osteoblasts has been proposed as a key factor in osteoblast/osteoclast coupling and in the development of bone metastases by tumor cells that express *MET*.¹⁹ Bone metastases in prostate cancer are more likely to express *MET* than other soft tissue metastases.¹⁰ Preclinical studies in prostate cancer xenografts reported responses to cabozantinib therapy in nude mouse tibia (minimal bone lesions seen) as compared with development of multiple osteoblastic and osteolytic lesions in vehicle-treated controls.²⁰ It is hypothesized that the osteoclast differentiation induced by cabozantinib may be responsible for the bone scan responses seen; however, the exact mechanism via which this occurs is unknown at present.²⁰ Treatment with cabozantinib appeared to decelerate both osteoblastic and osteolytic progression of prostate xenograft tumors in bone.

Cabozantinib activity in prostate cancer

A recently reported study²² evaluated the preclinical in vivo activity of cabozantinib in numerous prostate cancer cell lines, including Ace-1, C4-2B, and PC-3. In the tibial model of each of these cell lines, apoptosis of cancer cells in bone and improvement in bone mineral content were noted in the osteoblastic metastasis model (Ace-1) and in the mixed osteolytic and osteoblastic model (C4-2B). In the osteolytic model of PC-3 cells, no growth inhibition was noted in bone, but a response was noted in soft tissue metastases. Inhibition of angiogenesis was noted in subcutaneous PC-3 metastases but not in bone metastases. This suggests that close correlation of VEGF and *MET* inhibition is required for cabozantinib activity. In the androgen-responsive (LuCaP 35) model, administration of cabozantinib prevented or delayed tumor progression, as compared with in vehicle-treated control mice. The above observations would create a rationale for future evaluation of cabozantinib in earlier stages of prostate cancer, such as in the adjuvant setting for high-risk disease or hormone-sensitive disease.

VEGF inhibition, either by a single agent or coupled with chemotherapy, has not demonstrated clinical benefit in

advanced prostate cancer. The presence of hypoxia results in increased generation of proangiogenic factors via activation of the met proto-oncogene and subsequent tumor growth and proliferation.^{23,24} This was demonstrated clinically in the randomized Phase III trials of docetaxel ± bevacizumab²⁵ and docetaxel ± aflibercept,²⁶ with a lack of incremental benefit in comparison with docetaxel alone. It may be hypothesized that the critical role of *MET* in progression and proliferation of metastases is emphasized by the fact that dual Met and VEGF inhibition is essential to produce an anticancer effect in prostate cancer. Compounds that simultaneously inhibit VEGF and *MET* tyrosine kinase receptors are hence likely to be more effective anticancer agents than agents that target each of these receptors individually.^{27,28} In addition, cabozantinib has activity against other tyrosine kinase receptors that have been implicated in tumor pathobiology, including *RET*, *KIT*, *FMS*-like tyrosine kinase 3, and *Tie-2*.²⁷

Clinical activity of cabozantinib in prostate cancer

Cabozantinib has demonstrated broad clinical activity in multiple tumor types, including medullary thyroid cancer, papillary thyroid cancer, breast, ovarian, prostate, and lung cancers, melanoma, glioblastoma, hepatocellular carcinoma, and renal cell carcinoma.^{6,26,27} Randomized registration trials in metastatic CRPC are currently ongoing (Figures 1 and 2). Promising responses have been noted in soft tissue tumor lesions and in visceral metastases, in addition to those seen in bone metastases (partial or complete resolution on bone scan). Reduction in markers of bone resorption and formation, reduction in circulating tumor cells (in subjects with prostate cancer), increased hemoglobin, improvement of bone pain, and less narcotic use in subjects with bone metastases are other indications of a response to cabozantinib.

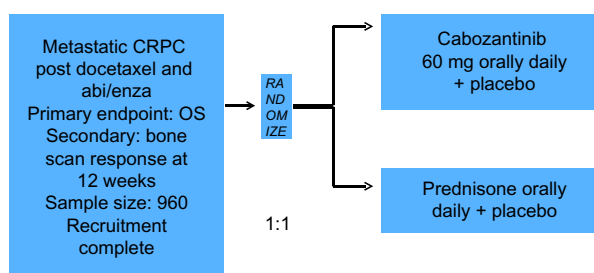


Figure 1 COMET-I[NCT01605227]: Phase III double blind randomized trial of cabozantinib vs prednisone in metastatic CRPC post docetaxel and abiraterone/enzalutamide.

Notes: Multicenter trial completed accrual, results awaited. Target sample size 960 patients.

Abbreviations: CRPC, castrate-resistant prostate cancer; OS, overall survival; abi, abiraterone; enza, enzalutamide.

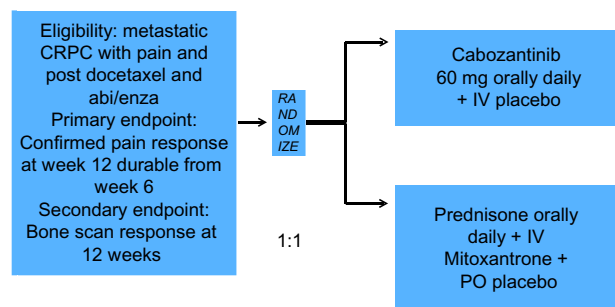


Figure 2 COMET-2(NCT01522443): Phase III placebo controlled double blind randomized trial of cabozantinib vs mitoxantrone + prednisone in metastatic CRPC patients with pain, post docetaxel and abiraterone/enzalutamide.

Notes: Multicenter trial. Target accrual: 246, recruitment ongoing 100 patients.

Abbreviations: CRPC, castrate-resistant prostate cancer; IV, intravenous; PO, per os (by mouth); vs, versus.

Clinical efficacy has been demonstrated to date in medullary thyroid cancer. In a randomized, placebo-controlled study⁸ of 330 subjects with medullary thyroid cancer, a significant increase in median progression-free survival was demonstrated in the cabozantinib arm compared with the placebo arm (11.2 months versus 4.0 months, respectively; hazard ratio 0.28, 95 confidence interval 0.19–0.40). Twenty-eight percent of cabozantinib-treated subjects demonstrated objective partial responses as compared with none in the placebo arm. Responses were durable, with a median response duration of 14.6 months. The only clinical trial completed in prostate cancer to date is a randomized Phase II discontinuation study. However, the results broadly revealed clinical activity in men with CRPC. An increase in median progression-free survival was observed in the cabozantinib arm compared with the placebo arm (23.9 weeks versus 5.9 weeks, respectively).⁶ The objective response rate at 12 weeks was only 5% and the stable disease rate was 75% (Table 1). In addition, effects on bone scan were assessed by an independent reader, and pain and narcotic use were prospectively assessed using an interactive voice recording system and a diary. Figure 3

shows examples of the different bone scan effects seen with cabozantinib therapy in CRPC bone metastases. Sixty-seven percent of subjects achieved a bone scan response, of which 4 subjects demonstrated a complete response. A bone scan response was noted even in the absence of a prostate-specific antigen (PSA) response, with discordance noted between PSA and bone scan responses in about 54% of patients. Among subjects with baseline pain of at least 4 on a 0–10 scale, 64% had a minimum 30% decrease in average daily worst pain as compared with baseline. A third of the subjects were able to discontinue use of narcotic pain medication. As expected in a typical metastatic CRPC population, the majority of patients in the trial had bone metastases. These patients showed a marked reduction in total alkaline phosphatase from the elevated levels seen at baseline. This effect continued during the nonrandomized expansion phase of the study, and the majority of CRPC subjects on the assigned dose of 100 mg showed a reduction in circulating bone-specific alkaline phosphatase. These effects were independent of prior or concomitant treatment with bisphosphonates. Reductions in bone biomarkers were also evident in the 40 mg dose cohort. Subjects achieved a bone scan response in both the 100 mg and 40 mg assigned nonrandomized expansion dose cohorts (67% and 49%, respectively). Sixty-four percent of subjects treated with the 100 mg daily dose and 69% of those treated with the 40 mg daily dose had a decrease of at least 30% in average daily worst pain score compared with baseline. In addition, more than half of the subjects decreased their use of narcotic pain medication.

Pharmacokinetics, dose selection, and toxicities

Cabozantinib is administered as a daily oral dose and has a half-life of about 91.3 ± 33.3 hours. Steady-state plasma

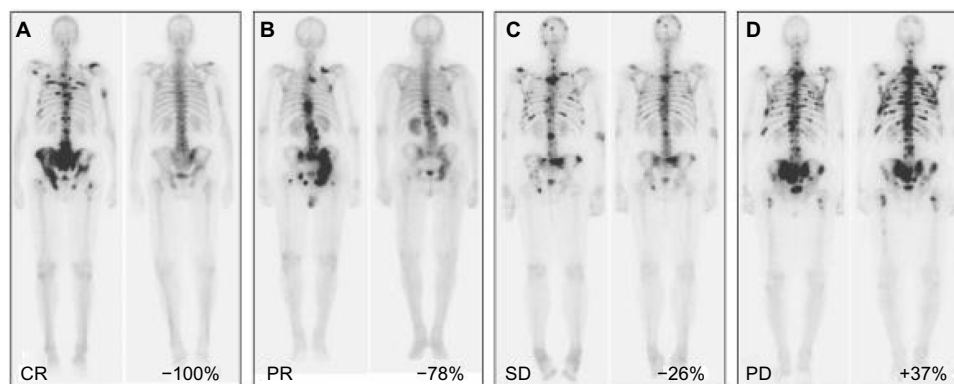


Figure 3 Cabozantinib effects on prostate cancer bone metastases. (A) Complete response: complete resolution of bone scan abnormalities; (B) partial response: $\geq 30\%$ decrease in total bone scan lesion area (BSLA); (C) stable disease: $< 30\%$ increase or decrease in BSLA; (D) progressive disease: $> 30\%$ increase in BSLA.

Abbreviations: SD, stable disease; CR, complete response; PR, partial response; PD, progressive disease.

concentrations are reached within 15 days,²⁹ and are about 4–5-fold higher at this time than plasma levels on day 1. The dose-escalation trial²⁹ identified the Phase II dose to be 175 mg daily; however, the increased incidence of toxicities (90% of patients in the Phase I trial had at least one adverse event) warranted dose reduction in the Phase II and III trials. The dose used in the medullary thyroid cancer clinical trial was 140 mg daily, and a number of toxicities were found to be dose-dependent. In the initial randomized discontinuation trial, the frequency of drug discontinuation due to toxicities was 16%. In a subsequent study in advanced prostate cancer, dose de-escalation was done with continued assessment of efficacy to determine the optimal dose for CRPC trials.³⁰ Dose levels of 60 mg and 40 mg were found to have equivalent efficacy and remarkably lower toxicity, thereby justifying the choice of a lower starting dose of 60 mg daily in the ongoing Phase III prostate cancer trials.³⁰

Discussion

The response rate and progression-free survival on cabozantinib in the Phase I/II untreated or pretreated CRPC patient populations are comparable with other therapies that have already established overall survival benefit in advanced CRPC. These include therapies such as sipuleucel T, abiraterone, cabazitaxel, enzalutamide, and alpharadin/RAD-223. Cabozantinib demonstrated palliative efficacy against bone lesions, and the potential to alleviate the morbidities of bone metastases, such as pain and other skeletal-related events. Biomarkers that would help guide selection of therapy are not available at present. The decreases in pain, t-alkaline phosphatase, PSA, bone-specific alkaline phosphatase, and circulating tumor cell levels can be used collectively for assessment of response. The governing indicator of response remains patient-reported pain scores and symptom relief achieved. However, in the current environment of prostate cancer therapeutics, a palliative benefit or a time to progression advantage will not be adequate to justify clinical use of an agent. An overall survival benefit would be required. Crossover of placebo-treated patients to other effective regimens could make achievement of that target challenging. Eligibility for the randomized, placebo-controlled trial³¹ requires patients to have disease progression following at least docetaxel and either abiraterone or enzalutamide. If cabozantinib does not demonstrate an overall survival benefit in this pretreated patient population, justification of additional studies in earlier stages of prostate cancer will be very difficult.

Cabozantinib is well tolerated and has the potential to demonstrate antitumor responses even in heavily pretreated

advanced prostate cancer. Remarkable responses in bone metastases as well as in measurable disease have been reported to date.^{6,30} Clinicians using this agent will face the dilemma of response assessment. PSA changes are discordant with benefit and progression-free survival at least 50% of the time, and the changes seen on bone scans have not been validated as determinants of response. It has not been clear whether the bone scan changes seen are related to bone modulation alone or indicate a specific anticancer effect on metastases. Pain assessment is a very cumbersome and subjective endpoint to characterize. Bone markers such as total and bone-specific alkaline phosphatase may need to be used as surrogates for response to cabozantinib; however, these are nonspecific and could be affected by other bone-targeted therapies such as zoledronate or denosumab. Preclinical and metastatic tissue imaging and biopsy studies are in progress at our institution (Karmanos Cancer Institute) and will enhance our understanding of the mechanism of response to this intriguing agent.³² In addition, the above-mentioned study may help to establish better surrogates of response that can guide duration and extent of therapy.

Cabozantinib has a rational clinical development plan starting with the indication in an orphan status disease, ie, medullary thyroid cancer. After preliminary evidence of anticancer effects in advanced prostate cancer, a randomized clinical trial³¹ has completed accrual in patients with metastatic CRPC pretreated with docetaxel, and abiraterone or enzalutamide. The future of cabozantinib in prostate cancer hinges on the overall survival results of this registration trial. Combination studies with agents such as abiraterone, enzalutamide, and docetaxel can be considered in the future. Studies of cabozantinib are also ongoing in other disease entities with limited therapeutic options, such as hepatocellular and non-small cell lung cancer.

Conclusion

Cabozantinib is a promising agent that could be incorporated into the therapeutic armamentarium for advanced prostate cancer. The registration clinical trial³¹ is evaluating the overall survival benefit in metastatic CRPC with progression after docetaxel, abiraterone, and/or enzalutamide. Cabozantinib-based combination therapies are likely to be evaluated in the future. A better understanding of the mechanism of action could help in the development of biomarkers that would enable patient selection and response assessments when using this dual *MET* and VEGF inhibitor.

Disclosure

The author is the Principal Investigator of a study that has received drug only support from Exelixis Inc. The author reports no other conflicts in this work.

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