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Cabozantinib for Progressive Metastatic Castration-resistant Prostate Cancer Following Docetaxel: Combined Analysis of Two Phase 3 Trials

Guru P. Sonpavde[a,†,*], **Gregory R. Pond**[b,†], **Karim Fizazi**[c], **Johann S. de Bono**[d], **Ethan M. Basch**[e], **Howard I. Scher**[f], **Matthew R. Smith**[g]

[a]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

[b]McMaster University, Hamilton, ON, Canada

[c]Gustave Roussy Institute of Oncology, University of Paris-Sud, Villejuif, France

[d]Institute of Cancer Research and The Royal Marsden Hospital, London, UK

[e]University of North Carolina, Chapel Hill, NC, USA

[f]Memorial Sloan Kettering Cancer Center, New York, NY, USA

[g]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

Abstract

Two phase 3 trials, COMET-1 and COMET-2, have reported that cabozantinib did not significantly extend overall survival (OS) compared to prednisone and prednisone plus mitoxantrone, respectively, in post-docetaxel patients with metastatic castration-resistant prostate cancer (mCRPC). We conducted a retrospective analysis of a combined data set from these trials to identify a benefit in subsets of patients according to prognostic risk factors. The prognostic ability of factors to predict survival was evaluated using Cox proportional hazards regression models. Evaluation of potential beneficial subsets was performed using interaction terms between factors and cabozantinib. All tests were two-sided and $p \leq 0.05$ was considered statistically significant. A total of 1147 post-docetaxel patients with mCRPC were available (1028 from COMET-1 and

[*]Corresponding author. Dana Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA. Tel. +1 617 6322429; Fax: +1 617 6322165. gurup_sonpavde@dfci.harvard.edu (G. Sonpavde).

[†]These authors contributed equally to this work.

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Study concept and design: Sonpavde, Pond, Smith.

Acquisition of data: Sonpavde, Pond, Fizazi, de Bono, Basch, Scher, Smith.

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119 from COMET-2). The following factors were prognostic for OS: age, disease-free interval, hemoglobin, prostate-specific antigen, alkaline phosphatase, albumin, bone scan lesion area, lactate dehydrogenase, Eastern Cooperative Oncology Group performance status, and pain (all $p < 0.05$). There was no interaction effect on survival between cabozantinib versus comparator arms and any prognostic group. After adjusting for prognostic factors, cabozantinib was associated with better OS (hazard ratio 0.80, 95% confidence interval 0.67–0.95; $p = 0.012$). Further investigation of cabozantinib in a better-powered trial or a rational patient population based on a molecular biomarker may be warranted.

Patient summary:

Two phase 3 trials have reported no survival benefit for cabozantinib, a multitarget oral drug, in metastatic castration-resistant prostate cancer. This analysis pooled 1147 patients from these trials to identify a survival benefit for cabozantinib. This study suggests that further rational development may be justified.

Keywords

Cabozantinib; Metastatic; Post-docetaxel; Castration-resistant; Prostate cancer; Survival; Prognosis

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Cabozantinib is an orally administered tyrosine kinase inhibitor of MET and VEGF receptors that has been approved by the US Food and Drug Administration for metastatic renal cell carcinoma and medullary thyroid cancer. Two phase 3 trials, COMET-1 and COMET-2, have reported that cabozantinib did not extend overall survival (OS) among post-docetaxel patients with metastatic castration-resistant prostate cancer (mCRPC) compared to prednisone and prednisone plus mitoxantrone, respectively [1,2]. However, there were multiple signals of activity and benefit when examining secondary endpoints. In the COMET-1 trial ($n = 1028$), cabozantinib significantly improved radiographic progression-free survival (median 5.6 vs 2.8 mo; $p < 0.001$) but not OS (median 11.0 vs 9.8 mo; hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.77–1.07; $p = 0.213$), which was the primary endpoint.

Cabozantinib was also associated with improvements in circulating tumor cell conversion, bone biomarkers, and the incidence of symptomatic skeletal events.

After 119 patients were randomized, the COMET-2 trial was discontinued after COMET-1 reported a lack of survival extension, and although the primary endpoint of pain response was not significantly different (15% vs 17%; $p = 0.773$), there was a trend for better OS (9 vs 7.9 mo; HR 0.71, 95% CI 0.45–1.12; $p = 0.121$) and a significantly better bone scan response with cabozantinib (31% vs 5.2%; $p < 0.001$). Previous phase 2 trials in mCRPC also demonstrated robust bone-targeted activity in terms of bone scan improvements [3,4].

Notably, analysis of the phase 3 METEOR trial comparing cabozantinib and everolimus in metastatic renal cell carcinoma demonstrated greater relative benefit among those with bone disease [5]. We conducted a retrospective analysis of a combined data set from

the COMET-1 and COMET-2 phase 3 trials with the hypothesis that a benefit would be observed in subsets of high-risk groups and those with a higher burden of bone metastasis.

Deidentified patient-level data were obtained from the COMET-1 and COMET-2 trials. Cox proportional hazards regression models were constructed to explore the OS prognostic ability of clinical and laboratory factors [6–8]. The trial (COMET-1 or COMET-2) was included as a stratification factor for all models. Subsets were identified by testing for an interaction term between treatment and selected factors. Patients were grouped into risk quartiles according to the previously described post-docetaxel nomogram [6–8]. Analyses were performed in SAS v.9.0 (SAS Institute, Cary, NC, USA) or R v.3.2.2 (R Foundation for Statistical Computing, Vienne, Austria).

Patient characteristics have been described previously and are summarized in Supplementary Table 1 [1,2]. The following factors were significantly predictive for OS on univariable analyses: age, disease-free interval (post-docetaxel and post-androgen deprivation therapy initiation), hemoglobin, prostate-specific antigen, albumin, bone scan lesion area (BSLA), lactate dehydrogenase, Eastern Cooperative Oncology Group performance status, and pain (all $p < 0.05$; Table 1). No interaction was statistically significant, indicating no differential impact of cabozantinib on OS for any prognostic factor evaluated or risk group based on quartiles (Fig. 1). After adjusting for all potential prognostic factors in a multivariable model (Table 1), treatment with cabozantinib versus the comparator was associated with better OS (HR 0.80, 95% CI 0.67–0.95; $p = 0.012$).

These data suggest that cabozantinib may confer benefits in a rationally selected mCRPC patient population. Our hypothesis that those with higher prognostic risk and greater bone tumor burden (measured as BSLA in the COMET-1 and −2 trials) or higher risk groups might experience greater benefits was not demonstrated by the analysis. Surprisingly, a modest survival benefit was observed in the overall population. These data suggest that an undefined subgroup of patients, potentially selected on the basis of molecular factors, may derive clinically relevant benefits from cabozantinib. In this context, studies in other malignancies suggest that MET alterations or expression levels may be a potential predictive biomarker for benefit [9,10]. Given the trend for better OS in COMET-2, which enrolled only symptomatic patients, a larger trial targeting this subgroup could also be considered. Indeed, given the elderly mCRPC population and the potential toxicities of cabozantinib, better patient selection might improve the therapeutic index.

Systemic therapy for mCRPC has witnessed several advances with the emergence of second-generation androgen inhibitors (enzalutamide, apalutamide, abiraterone acetate) and a potential role for PARP inhibitors and T-cell checkpoint inhibitors in appropriately selected patients. However, most of these agents are expected to provide incremental advances and are not expected to be curative. Evaluation of cabozantinib in a better-powered trial or optimal patient population guided by the discovery of a potential predictive molecular biomarker of activity (eg, *MET* expression) could resurrect a role for this drug in patients with mCRPC and should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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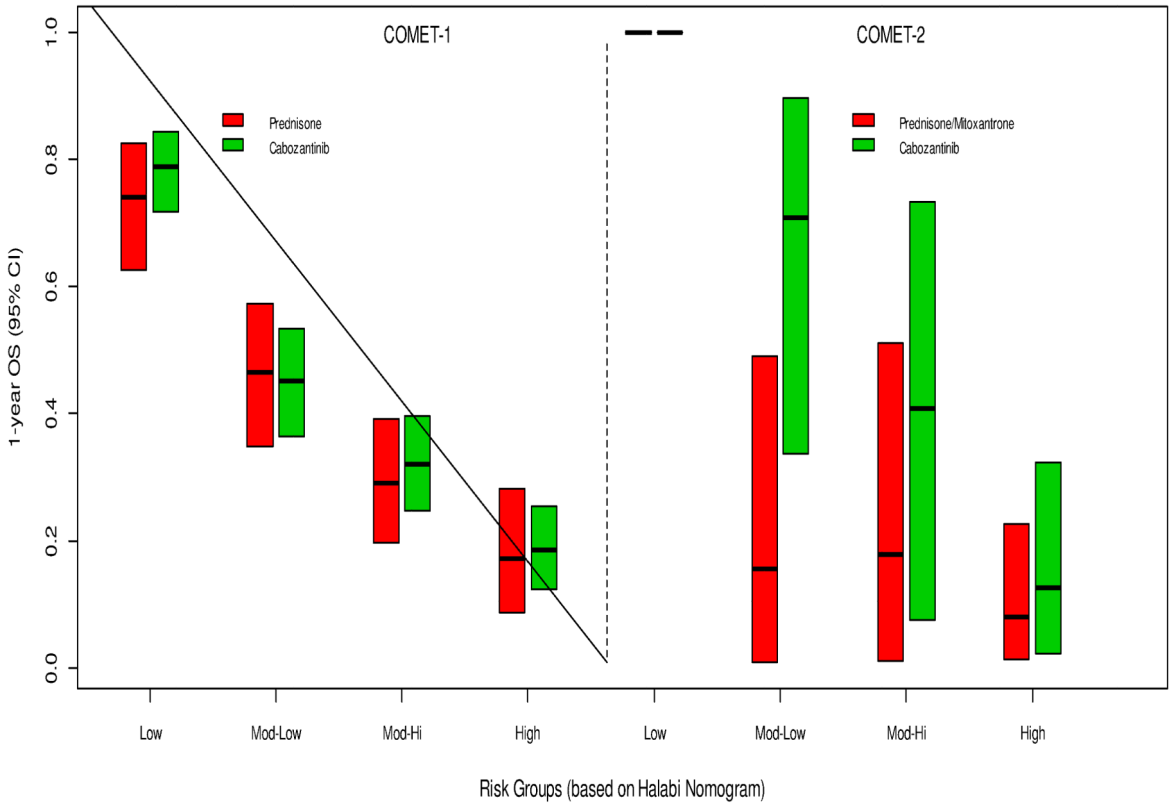

Fig. 1 –.

Survival according to risk group quartile. There was no significant difference in survival between the cabozantinib and control arms stratified by prognostic risk group quartile.

Table 1 –

Univariable and multivariable Cox regression analyses for association of factors with overall survival

Parameter	HR (95% CI)	*p* value	Interaction *p* value
Univariable			
Age per decade	1.12 (1.02–1.23)	0.019	0.59
DFI post-docetaxel per year	0.88 (0.82–0.94)	<0.001	0.20
DFI post-ADT per year	0.95 (0.93–0.97)	<0.001	0.20
Hemoglobin per 10 U	0.73 (0.69–0.77)	<0.001	0.72
PSA log-transform	1.25 (1.20–1.31)	<0.001	0.14
BSLA log-transform	1.31 (1.23 –1.40)	<0.001	0.23
LDH log-transform	2.54 (2.26–2.86)	<0.001	0.61
LDH ≥ ULN (280 U/l)	3.10 (2.67–3.59)	<0.001	0.47
ECOG performance status			
0	0.28 (0.22–0.35)	<0.001	0.59
1	0.52 (0.43–0.64)		
≥2	Reference		
Lymph node metastases	1.27 (1.10–1.46)	0.001	0.79
Liver metastases	3.03 (2.50–3.68)	<0.001	0.20
Lung metastases	1.34 (1.07–1.69)	0.012	0.95
BPI score ≥4	1.79 (1.54–2.09)	<0.001	0.93
Prior abiraterone	1.09 (0.83–1.43)	0.54	0.48
Prior enzalutamide	1.17 (1.00–1.38)	0.055	0.43
Site of disease Visceral	2.32 (1.93–2.79)	<0.001	0.30
Lymph node ± bone	1.24 (1.05–1.46)		
Bone only	Reference		
Cabozantinib treatment	0.87 (0.75–1.01)	0.062	
Multivariable			
Age per decade	1.39 (1.23–1.56)	<0.001	
DFI post-docetaxel per year	0.84 (0.77–0.91)	<0.001	
DFI post-ADT per year	0.99 (0.97–1.02)	0.53	
Hemoglobin per 10 U	0.90 (0.94–0.96)	0.002	
PSA log-transform	1.10 (1.03–1.17)	0.002	
LDH log-transform	1.63 (1.38–1.91)	<0.001	
ECOG performance status			
0	0.50 (0.37–0.68)		
1	0.68 (0.54–0.86)		
≥2	Reference		
Lymph node metastases	1.18 (0.99–1.40)	0.069	
Liver metastases	1.89 (1.48–2.42)	<0.001	
Lung metastases	1.03 (0.77–1.37)	0.84	
BPI score ≥4	1.32 (1.10–1.58)	0.003	
Prior abiraterone	0.67 (0.48–0.94)	0.019	

Parameter	HR (95% CI)	*p* value	Interaction *p* value
Prior enzalutamide	1.09 (0.89–1.34)	0.41	
Prior cabazitaxel	1.66 (1.37–2.00)	<0.001	
BSLA log-transform	1.14 (1.05–1.24)	0.003	
Cabozantinib treatment	0.80 (0.67–0.95)	0.012	

HR = hazard ratio; CI = confidence interval; DFI = disease-free interval; ADT = androgen deprivation therapy; PSA = prostate-specific antigen; BSLA= bone scan lesion area; LDH = lactate dehydrogenase; ULN = upper limit of normal; ECOG = Eastern Cooperative Oncology Group; BPI = Brief Pain Inventory.