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Cabozantinib Versus Mitoxantrone-prednisone in Symptomatic Metastatic Castration-resistant Prostate Cancer: A Randomized Phase 3 Trial with a Primary Pain Endpoint

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.033.

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Abstract

Background: Bone metastases in patients with metastatic castration-resistant prostate cancer (mCRPC) are associated with debilitating pain and functional compromise.

Objective: To compare pain palliation as the primary endpoint for cabozantinib versus mitoxantrone-prednisone in men with mCRPC and symptomatic bone metastases using patient-reported outcome measures.

Design, setting, and participants: A randomized, double-blind phase 3 trial (COMET-2; NCT01522443) in men with mCRPC and narcotic-dependent pain from bone metastases who had progressed after treatment with docetaxel and either abiraterone or enzalutamide.

Intervention: Cabozantinib 60 mg once daily orally versus mitoxantrone 12 mg/m^2 every 3 wk plus prednisone 5 mg twice daily orally.

Outcome measurements and statistical analysis: The primary endpoint was pain response at week 6 confirmed at week 12 (≥30% decrease from baseline in patient-reported average daily worst pain score via the Brief Pain Inventory without increased narcotic use). The planned sample size was 246 to achieve ≥90% power.

Results and limitations: Enrollment was terminated early because cabozantinib did not demonstrate any survival benefit in the companion COMET-1 trial. At study closure, 119 participants were randomized (cabozantinib: N=61; mitoxantrone-prednisone: N = 58). Complete pain and narcotic use data were available at baseline, week 6, and week 12 for 73/106 (69%) patients. There was no significant difference in the pain response with cabozantinib versus mitoxantrone-prednisone: the proportions of responders were 15%versus 17%,a −2%difference(95%confidenceinterval:−16%to11%, p = 0.8). Barriers to accrual included pretreatment requirements for a washout period of prior anticancer therapy and a narcotic optimization period to maximize analgesic dosing.

Conclusions: Cabozantinib treatment did not demonstrate better pain palliation than mitoxantrone-prednisone in heavily pretreated patients with mCRPC and symptomatic bone

metastases. Future pain-palliation trials should incorporate briefer timelines from enrollment to treatment initiation.

Patient summary: Cabozantinib was not better than mitoxantrone-prednisone for pain relief in patients with castration-resistant prostate cancer and debilitating pain from bone metastases.

Keywords

Pain assessment; Cabozantinib; Clinical trial; Prostate cancer

1. Introduction

Most prostate cancer-specific deaths occur in patients with metastatic castration-resistant prostate cancer (mCRPC), frequently preceded by debilitating pain and functional compromise [1]. Pain related to osseous disease is often poorly controlled, even with narcotic analgesics [1,2]. Durable control and pain relief remain critical unmet needs that are rarely studied as the primary objective of clinical trials in mCRPC.

Among approved agents, only mitoxantrone and samarium-153 have formal indications for pain palliation; however, these approvals were based on trial designs that do not meet contemporary methodological standards [3–6]. Pain relief has been shown for docetaxel, abiraterone, enzalutamide, and radium-223 as secondary efficacy measures in survival-based trials, but none have been studied in dedicated prospective pain studies [7–11]. Given the importance of pain control in men with symptomatic osseous metastases, we used rigorously validated patient- reported outcomes (PROs) in a registration trial in which pain relief was the primary objective, adhering to standards described by the US Food and Drug Administration (FDA) and the Prostate Cancer Working Group [12,13].

Cabozantinib inhibits tyrosine kinases, including vascular endothelial growth factor receptors, MET, and AXL [14]. In preclinical models, cabozantinib inhibits the growth of prostate tumor xenografts in soft tissue and bone, and alters bone remodeling [15–18]. In a nonrandomized expansion cohort of a phase 2 randomized discontinuation trial, cabozantinib demonstrated significant pain reduction in men with mCRPC who had progressed on one life- prolonging therapy [19–21]. Specifically, 68% of cabozantinib-treated patients experienced pain reduction (≥30% reduction in mean worst daily pain scores from baseline at one or more 7-d intervals spaced 3 or 6 wk apart), 57% experienced pain relief at two consecutive intervals, and >50% had decreased narcotic use [19]. Moreover, improved progression-free survival (PFS) and bone scan response were observed for cabozantinib relative to placebo [20,21].

Based on these results, two phase 3 trials were initiated to assess cabozantinib in mCRPC. COMET-1 compared cabozantinib with prednisone in men with mCRPC but without significant pain, with overall survival (OS) as the primary endpoint [22]. COMET-2 compared cabozantinib with mitoxantrone-prednisone in men with progressing mCRPC after two or more lines of life-prolonging therapy (docetaxel and either abiraterone or enzalutamide). The study design was based on consultation with prostate cancer researchers and FDA guidance on the use of PROs and pain measurements [13]. The objective was to

use validated measures to quantify pain and use of analgesics with a primary endpoint of pain improvement. Here, we provide results from the primary analysis of COMET-2.

2. Patients and methods

2.1. Patients

Eligible patients ≥18 yr of age had a pathological diagnosis of mCRPC, serum testosterone levels <50 ng/dl, prostate cancer-related bone metastases evidenced on bone scans, and documented pain from bone metastases that required opioid narcotic intervention (including both sustained-release and rescue drugs). Patients must have received three or more cycles of docetaxel or progressed after docetaxel-containing therapy and discontinued abiraterone or enzalutamide due to disease progression [23]. The average daily worst pain intensity during a 7-d run-in stage (≥4 d of reporting) had to be 4–8, as measured on the Brief Pain Inventory (BPI) Short Form (Item 3) [24]. The BPI uses an 11-point numerical rating system for pain assessment (ranging from 0 to 10, with 0 representing “no pain” and 10 representing “pain as bad as you can imagine”). The narcotic analgesic regimen of each patient was required to be optimized at baseline following National Comprehensive Cancer Network Practice Guidelines [25] to provide maximal pain relief without intolerable side effects. Patients could not have had prior treatment with cabozantinib or mitoxantrone. Patients were also excluded if they had received systemic anticancer therapy within 2 wk or radiation therapy within 4 wk of randomization (Supplementary material).

All patients provided informed consent. The study was approved by the institutional review board or ethics committee at each center and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. An independent data monitoring committee monitored patient safety.

2.2. Study design

This was a phase 3, randomized, double-blind controlled trial (NCT01522443). Patients were assigned 1:1 to receive cabozantinib or mitoxantrone-prednisone. Randomization was stratified by Eastern Cooperative Oncology Group performance status (0–1 vs ≥2) and prior receipt of cabazitaxel.

Cabozantinib was administered orally at 60 mg once daily (QD) with mitoxantrone-matched placebo infusion every 3 wk (≤10 infusions), plus oral prednisone-matched placebo twice daily (BID). Mitoxantrone was administered at 12 mg/m^2 every 3 wk(≤10 infusions) plus oral 5 mg BID prednisone and oral cabozantinib-matched placebo QD (Supplementary material). Patients continued study treatment as long as they experienced clinical benefit, as determined by the investigator, and did not experience unacceptable toxicity. Dose reductions were allowed to manage adverse events (AEs; Supplementary material).

2.3. Endpoints

The primary endpoint was the rate of pain response at week 6 confirmed at week 12, defined as a ≥30% decrease from baseline in average daily worst pain score using a minimum of four BPI reports during a 7-d period without an increase in daily opiate use, use of a new

opiate analgesic type, or clinical pain progression. Secondary endpoints were OS and bone scan response at week 12, defined as a ≥30% decrease in bone scan lesion area from baseline per independent radiology committee (IRC). Exploratory endpoints included IRC-assessed PFS, defined as the earlier progression in soft tissue per Response Evaluation Criteria in Solid Tumors version 1.1 or progression on bone scan [26], and the rate of skeletal-related events (Supplementary material).

2.4. Study assessments

Patient-reported worst daily pain scores were collected by an automated telephone interactive voice response system over 7-d reporting periods at run-in (baseline) and at weeks 3, 6, and 12, and every 6 wk thereafter until disease progression. Participants tracked the use of all analgesic drugs in a daily diary. On the final day of each assessment period, patients were asked about the frequency, severity, and interference of common adverse symptom events using 21 items from the National Cancer Institute PRO version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE) [27]. Tumor assessments were performed at baseline and every 12 wk thereafter (Supplementary material).

Safety assessments were conducted at screening, on day 1 of each cycle, and at a follow-up visit scheduled within 30 d of treatment discontinuation. AE severities were evaluated by the investigator using the CTCAE version 4.0 (Supplementary material).

2.5. Statistical analysis

A planned sample size of 246 randomized patients was selected to achieve ≥90% power for the primary endpoint of pain reduction and 80% power for OS using a two-sided $\alpha = 0.05$ chi-squared test. For the primary endpoint, it was estimated that 8% of patients receiving mitoxantrone-prednisone would experience a confirmed pain response [28], versus 25% in the cabozantinib arm (Supplementary material).

3. Results

3.1. Patients

Between March 2012 and July 2014, 216 patients were screened, of whom 119 were randomized—61 to cabozantinib and 58 to mitoxantrone-prednisone (intent-to-treat [ITT] population). Although the planned sample size was 246 randomized patients, enrollment was terminated early because no significant OS benefit was observed in the companion COMET-1 trial [22]. Baseline characteristics were generally balanced between treatment groups (Table 1). Fig. 1 summarizes patient disposition. One hundred and seventeen patients received study treatment: 60 received cabozantinib and 57 received mitoxantrone-prednisone, of whom 87% and 95%, respectively, had discontinued treatment as of the cutoff date (October 6, 2014).

3.2. Efficacy

3.2.1. Pain response—The primary analysis of the ITT population did not demonstrate a significant difference in confirmed pain response for cabozantinib versus mitoxantrone-

prednisone; the rates of confirmed pain response were, respectively, 15% and 17%, a −2% difference (95% confidence interval [CI]: −16% to 11%, $p = 0.8$; Table 2). As the primary endpoint was not met, all other efficacy analyses are considered descriptive. Pain score and narcotic use on a perpatient basis are summarized in Supplementary Figures 1 and 2, and the change in pain score versus time is summarized in Supplementary Figure 3. An analysis of the percent change from baseline for pain scores at week 6 as continuous endpoints did not affect our principal findings; the difference between the means was 4.6% (95% CI: −7.8% to 17%).

Compliance was excellent, as 100% of patients at baseline, 92% at week 6, and 82% at week 12 completed the requisite four out of seven daily pain assessments (Table 2). The proportion of patients with complete pain assessments at all three time points was 82%, with complete narcotic use data being 70% and complete pain plus narcotic use data 69%. Only 11% of patients in the cabozantinib arm and 8.6% in the mitoxantrone-prednisone arm had missing data that could have resulted in classification as responders (Supplementary Table 1).

3.2.2. Additional endpoints—Analysis of bone scan response at week 12 per IRC showed a higher rate for cabozantinib versus mitoxantrone-prednisone (31% vs 5.2%, a 26% difference, 95% CI: 13–39%; Supplementary Table 2), median OS was 9.0 versus 7.9 mo (stratified hazard ratio [HR]: 0.70; 95% CI: 0.44–1.10; Supplementary Figure 4), median PFS per IRC was 2.9 versus 2.8 mo (stratified HR: 0.74; 95% CI: 0.41–1.34), and the rate of skeletal events was 0.93 versus 1.47 events/person-year.

3.3. Safety

Median duration of exposure was 14.6 wk (interquartile range [IQR]: 9.1–27.1) for cabozantinib versus 12.1 wk (IQR: 9.1–19.7) for mitoxantrone-prednisone. The median dose intensity was 80% (IQR:66–99%) for cabozantinib versus 97% (IQR: 87–100%) for mitoxantrone-prednisone.

All patients experienced at least one AE (Table 3). Grade 3/4 AEs were reported for 70% of cabozantinib-treated patients and 67% of mitoxantrone-prednisone-treated patients. Compared with mitoxantrone-prednisone, cabozantinib-treated patients experienced a higher incidence of grade 3/4 hypertension (22% vs 0%), fatigue (18% vs 8.8%), increased aspartate aminotransferase (10% vs 1.8%), diarrhea (8.3% vs 1.8%), and decreased weight (5.0% vs 0%), but a lower incidence of vomiting (1.7% vs 7.0%) and dyspnea (0% vs 5.3%). Serious AEs were reported in 72% of patients receiving cabozantinib and 61% receiving mitoxantrone-prednisone.

Table 4 summarizes patient responses to 21 items from the NCI PRO-CTCAE. The most common symptoms with a score of ≥3 were pain, fatigue, decreased appetite, nausea, and diarrhea in the cabozantinib arm, and pain and fatigue in the mitoxantrone-prednisone arm.

Study drug discontinuation due to AEs occurred in 17% of patients in the cabozantinib arm and 30% of patients in the mitoxantrone-prednisone arm (Supplementary Table 3), and AEs

leading to dose reduction/interruptions occurred in 87% and 60% of patients, respectively (Supplementary Table 4).

Grade 5 AEs occurring within 30 d of the last study drug dose were reported for 11 (18%) patients receiving cabozantinib and five (8.8%) patients receiving mitoxantrone-prednisone, and were commonly considered related to disease progression and not to study treatment (Supplementary material).

4. Discussion

This randomized, controlled trial prospectively compared pain relief as the primary endpoint for cabozantinib relative to mitoxantrone-prednisone in mCRPC patients with bone metastases and moderate to severe pain despite narcotic optimization who had progressed after treatment with docetaxel and either abiraterone or enzalutamide. The trial was stopped early, after 119 of the planned 246 patients had been randomized, due to the failure of cabozantinib to demonstrate a survival benefit in the companion COMET-1 trial [22]. The study did not meet the primary endpoint; the rate of pain response at week 6 that was confirmed at week 12 was 15% for cabozantinib and 17% for mitoxantrone-prednisone. Although results are not directly comparable due to differences in response definitions, the 15% pain response rate for cabozantinib was lower than the clinically meaningful 57% rate of pain relief at two consecutive intervals observed for cabozantinib in a phase 2 cohort of patients with mCRPC [19], while the 17% response rate for mitoxantrone-prednisone was higher than the 8% rate observed in a previous trial [28].

One reason for these discrepancies is the difference in study populations with respect to the number of life-prolonging therapies previously administered: one in the phase 2 trial, which accrued before the approvals of abiraterone and enzalutamide, and two or more, including docetaxel, in the present study. This limitation rendered a highly symptomatic patient population with more heterogeneous and advanced disease that would be less likely to benefit from a targeted agent, such as cabozantinib compared with cytotoxic therapy [29]. Other reasons include the more rigid enrollment criteria in COMET-2, which required an average pain intensity level of ≥4 despite narcotic analgesic use. In addition, the more rigid approach to narcotic adjustments in this trial may have better controlled for pain reduction related to narcotic use.

Cabozantinib treatment did not significantly improve OS; median OS was 9.0 mo for cabozantinib and 7.9 mo for mitoxantrone-prednisone (HR: 0.70; 95% CI: 0.44–1.10). Notably, no significant OS benefit was observed in COMET-1, where median OS was 11.0 mo for cabozantinib and 9.8 mo for prednisone (HR: 0.90; 95% CI: 0.76–1.06; $p = 0.2$) [22].

The safety profile of cabozantinib was similar to that reported for earlier studies in mCRPC [20–22]. Inclusion of the NCI PRO-CTCAE provided insights about the comparative tolerability of study treatments from the patient perspective.

Although this trial did not meet the primary endpoint, it provides valuable insights about the design and conduct of oncology trials assessing symptom control with PROs. Despite enrolling 119 patients, 45% of potential participants failed screening. The requirement for

patients to be heavily pretreated and to have advanced disease, along with a requirement for washout and narcotic optimization periods, limited the pool of patients, particularly those with rapidly progressing disease who required immediate treatment. Notwithstanding these challenges, patient compliance with self-reporting was relatively high due to rigorous operational support and patient willingness to participate.

Pain palliation remains a critical unmet need of patients with mCRPC. To address this objective successfully in future trials, we recommend the following: (1) patients with any level of pain should be eligible with a composite endpoint evaluating pain progression, palliation, and elimination; (2) washout and narcotic optimization periods should be shortened, particularly for highly symptomatic or heavily pretreated populations in whom progression is rapid; (3) multiple lines of prior therapy should not be required because later-stage disease is more heterogeneous and less likely to respond to treatment; and (4) pain and narcotic use should be assessed independently as well as together in an exploratory composite endpoint.

Several elements of FDA guidance [12,13] remain essential to assure meaningful pain assessment in future pain trials and survival-based trials with secondary pain endpoints. First, valid, reliable, and responsive metrics should be selected. The BPI used in this study has robust psychometric properties and an established meaningful change score [12,13,24]. Second, metrics should be administered at time points that allow patients to respond between visits, such as the automated telephone interactive voice response system. Third, pain response should be confirmed at a subsequent time point or at progression/disenrollment. Fourth, the level of each patient's narcotic usage should be quantified at baseline. Pain response could then be assessed without narcotic optimization or inclusion of narcotic use in the responder definition.

5. Conclusions

Although COMET-2 did not demonstrate better pain palliation for cabozantinib compared with mitoxantrone-prednisone in patients with mCRPC, this study provides insights about the design and conduct of oncology trials using symptom control as the primary objective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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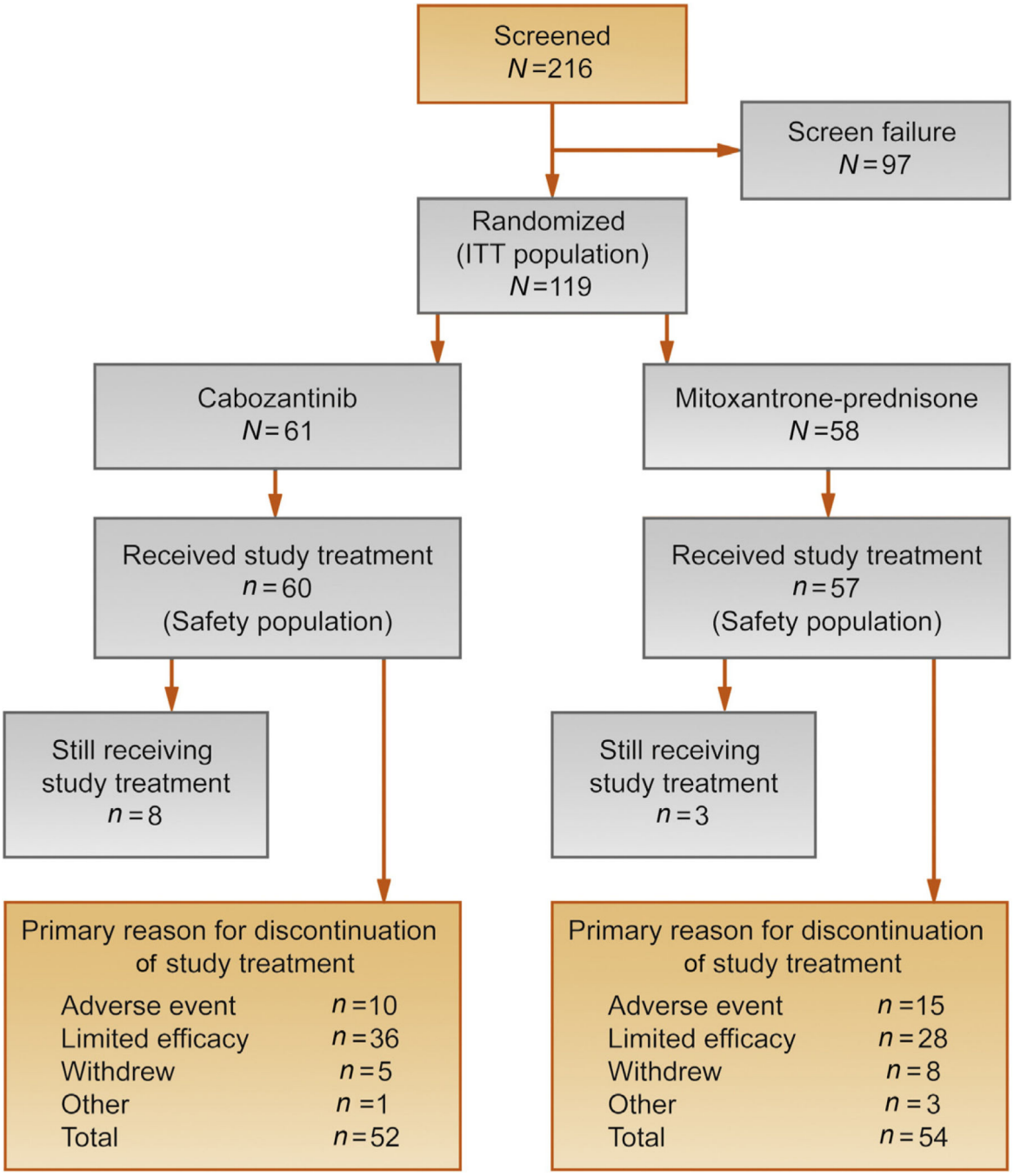

Fig. 1 -
CONSORT diagram. Patient disposition shown at the time of study closure. ITT = intent to treat.

Table 1 -

Baseline demographics and clinical characteristics

Characteristics	Cabozantinib (*N* =61)	Mitoxantrone-prednisone (*N* = 58)
Age (yr), median (IQR)	65.0 (61–69)	66.0 (63–71)
Race, *n* (%)		
White	49 (80)	51 (88)
Black/African American	8 (13)	3 (5.2)
Asian	1 (1.6)	3 (5.2)
American Indian/Alaska native	1 (1.6)	0
Multiple	1 (1.6)	0
Other	1 (1.6)	0
Not reported	0	1 (1.7)
Country of enrollment, *n* (%)		
USA	40 (66)	30 (52)
Canada	4 (6.6)	6 (10)
UK	8 (13)	12 (21)
Ireland	0	1 (1.7)
Australia	9 (15)	9 (16)
Time from diagnosis to randomization (yr), median (IQR)	4.7 (3.6–8.5)	5.3 (3.8–9.7)
ECOGPS, *n* (%)		
0 or 1	53 (87)	52 (90)
≥2	8 (13)	6 (10)
Gleason score >7 at diagnosis, *n* (%)	40 (66)	28 (48)
Prostate Specific Antigen (μg/ml), median (IQR)	191.8 (60.1–482.1)	251.6 (78.2–833.1)
Bone scan lesion area (mm^2), median (IQR)	72 865 (26 900–125166)	72 703 (35 848–135 289)
Sites of metastasis, *n* (%)		
Bone	61 (100)	58 (100)
Soft tissue		
Lymph node	29 (48)	18 (31)
Visceral	10 (16)	12 (21)
Liver	8 (13)	8 (14)

Characteristics	Cabozantinib (*N* =61)	Mitoxantrone-prednisone (*N* = 58)
Lung	2 (3.3)	5 (8.6)
Other soft tissue	7 (11)	3 (5.2)
BPI pain score (item 3) during run-in stage, median (range)	6.0 (4.0–8.0)	6.1 (4.0–8.0)
4–5, *n* (%)	10 (16)	15 (26)
>5–6, *n* (%)	22 (36)	13 (22)
>6–7, *n* (%)	18 (30)	15 (26)
>7–8, *n* (%)	11 (18)	15 (26)
Number of prior anticancer agents (excluding agents to maintain castrate status and steroids), *n* (%)		
2	0	3 (5.2)
3	6 (10)	4 (6.9)
4	20 (33)	14 (24)
≥5	35 (57)	37 (64)
Time from end of most recent prior systemic anticancer therapy to randomization (excluding corticosteroids and agents to maintain castrate status; wk), median (IQR)	5.4 (3.7–9.4)	5.1 (3–8)
Received prior docetaxel, *n* (%)	61 (100)	58 (100)
Total cumulative dose (mg/m^2), median (IQR)	571.5 (375–883.5)	667.5 (446–960)
Duration of treatment (mo), median (IQR)	5.0 (3.4–6.2)	5.0 (3.8–6.6)
Received prior abiraterone, *n* (%)	55 (90)	53 (91)
Duration of treatment (mo), median (IQR)	6.9 (3.9–10.4)	5.6 (4.2–10.1)
Received prior enzalutamide, *n* (%)	28 (46)	23 (40)
Duration of treatment (mo), median (IQR)	3.4 (2.0–6.0)	3.7 (2.8–4.9)
Received prior docetaxel and abiraterone and enzalutamide, *n* (%)	22 (36)	18 (31)
Received prior cabazitaxel, *n* (%)	25 (41)	24 (41)
Prior radiation therapy for CRPC, *n* (%)[a]	49 (80)	47 (81)
Bone-targeted therapy within 28 d of randomization, *n* (%)[b]	48 (79)	45 (78)
Bisphosphonates	16 (26)	19 (33)
Denosumab	31 (51)	20 (34)

BPI = Brief Pain Inventory; CRPC = castration-resistant prostate cancer; ECOGPS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range.

[a]Excludes radionuclides.

[b]Includes any treatment with these agents ≤28 d before randomization and/or on the randomization date.

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Table 2 -

Pain response and compliance (ITT population)

Primary endpoint	**Cabozantinib (*N* =61)**	**Mitoxantrone-prednisone (*N* = 58)**	***p* value (stratified)[a]**
Week 6 pain response, primary endpoint[b] confirmed at week 12, *n* (%)	9 (15)	10 (17)	0.8
≥30% reduction in week 6, pain confirmed at week 12, regardless of narcotic use, *n* (%)	17 (28)	19 (33)	0.6
Adequate pain data[c]			
Baseline, *n* (%)	61 (100)	58 (100)	NA
Week 6, *n/N* (%)[d]	52/57 (91)	54/58 (93)	NA
Week 12, *n/N* (%)[d]	42/51 (82)	45/55 (82)	NA
Baseline, week 6, and week 12, *n/N* (%)[d]	42/51 (82)	45/55 (82)	NA
Adequate narcotics data[c]			
Baseline, *n* (%)	60 (98)	58 (100)	NA
Week 6, *n/N* (%)[d]	47/57 (82)	50/58 (86)	NA
Week 12, *n/N* (%)[d]	41/51 (80)	36/55 (65)	NA
Baseline, week 6, and week 12, *n/N* (%)	39/51 (76)	35/55 (64)	NA
Adequate pain plus narcotics data[c]			
Baseline, *n* (%)	60 (98)	58 (100)	NA
Week 6, *n/N* (%)[d]	47/57 (82)	50/58 (86)	NA
Week 12, *n/N* (%)[d]	40/51 (78)	36/55 (65)	NA
Baseline, week 6, and week 12, *n/N* (%)[d]	38/51 (75)	35/55 (64)	NA
Missing pain and narcotic data through week 12 of patients who could be potential responders, *n* (%)[e]	7 (11)	5 (8.6)	NA

ITT = intent-to-treat; NA = not applicable.

[a] A *p* value was obtained using the Cochran-Mantel-Haenszel test adjusted for stratification factors.

[b] Pain response was defined as a ≥30% decrease from baseline in patient-reported average daily worst pain score (assessed by the Brief Pain Inventory) during a 7-d reporting period without an increase in average daily opiate use, use of a new opiate analgesic type, or occurrence of any other clinical pain progression event.

[c] Adequate data were defined as ≥4/7 daily assessments per week.

[d] Cell denominators exclude patients who died before the end of the reporting interval.

[e] Patients with missing data and those alive through week 12 without clinical deterioration or pain progression by pain score, by narcotic increase or change, or by clinical criteria.

Table 3 -

Summary of investigator-reported adverse events occurring in ≥20% of patients in either treatment arm[a]

Preferred Terms	Cabozantinib (*N* =60)		Mitoxantrone-prednisone (*N* =57)	
	Grade		Grade	
	All	3/4	All	3/4
Patients with ≥1 AE, *n* (%)	60 (100)	42 (70)	57 (100)	38 (67)
Nausea	39 (65)	4 (6.7)	26 (46)	4 (7.0)
Fatigue	34 (57)	11 (18)	27 (47)	5 (8.8)
Decreased appetite	28 (47)	1 (1.7)	23 (40)	3 (5.3)
Diarrhea	28 (47)	5 (8.3)	17 (30)	1 (1.8)
Constipation	25 (42)	2 (3.3)	19 (33)	1 (1.8)
Weight decreased	25 (42)	3 (5.0)	8 (14)	0
Anemia	24 (40)	13 (22)	29 (51)	15 (26)
Vomiting	24 (40)	1 (1.7)	19 (33)	4 (7.0)
Hypertension	18 (30)	13 (22)	0	0
Asthenia	16 (27)	3 (5.0)	4 (7.0)	1 (1.8)
Back pain	15 (25)	5 (8.3)	16 (28)	6 (11)
Depression	14 (23)	1 (1.7)	8 (14)	1 (1.8)
Dyspnea	14 (23)	0	22 (39)	3 (5.3)
Increased aspartate aminotransferase	13 (22)	6 (10)	2 (3.5)	1 (1.8)
Dysgeusia	13 (22)	0	10 (18)	0
Hypokalemia	13 (22)	4 (6.7)	4 (7.0)	1 (1.8)
Pain in extremity	12 (20)	4 (6.7)	12 (21)	2 (3.5)
Pyrexia	10 (17)	2 (3.3)	12 (21)	1 (1.8)
Arthralgia	9 (15)	1 (1.7)	16 (28)	1 (1.8)

AE = adverse event.

[a]A patient was counted once for the most severe event if the patient experienced one or more events. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Table 4 -

Maximum postscreening score for symptoms from NCI PRO-CTCAE

NCI PRO-CTCAE item	Cabozantinib, *n*	Mitoxantrone-prednisone, *n*	Maximum postscreening score Score 1+			Maximum postscreening score Score 3+		
			Cabozantinib, *n* (%)	Mitoxantrone-prednisone, *n* (%)	Fisher *p* value	Cabozantinib, *n* (%)	Mitoxantrone-prednisone, *n* (%)	Fisher *p* value
Constipation (S)	53	54	50 (94)	47 (87)	0.3	19 (36)	11 (20)	0.09
Decreased appetite (S)	52	54	50 (96)	48 (89)	0.3	27 (52)	10 (19)	<0.001
Decreased appetite (I)	52	54	48 (92)	39 (72)	0.01	23 (44)	11 (20)	0.01
Diarrhea (F)	52	54	48 (92)	34 (63)	<0.001	23 (44)	6 (11)	<0.001
Fatigue (S)	53	54	53 (100)	54 (100)	–	39 (74)	32 (59)	0.2
Fatigue (I)	53	54	53 (100)	54 (100)	–	40 (75)	35 (65)	0.3
Insomnia (S)	53	54	44 (83)	47 (87)	0.6	10 (19)	8 (15)	0.6
Insomnia (I)	53	54	36 (68)	41 (76)	0.4	10 (19)	10 (19)	1
Mouth or throat sores (S)	52	54	34 (65)	25 (46)	0.05	6 (12)	1 (1.9)	0.06
Nausea (F)	52	54	49 (94)	38 (70)	0.002	25 (48)	11 (20)	0.004
Nausea (S)	52	54	49 (94)	36 (67)	<0.001	21 (40)	9 (17)	0.009
Numbness/tingling in hands/feet (S)	52	54	44 (85)	40 (74)	0.2	16 (31)	7 (13)	0.03
Numbness/tingling in hands/feet (I)	52	54	34 (65)	26 (48)	0.08	11 (21)	5 (9.3)	0.1
Pain (F)	53	54	53 (100)	54 (100)	–	44 (83)	44 (81)	1
Pain (S)	53	54	53 (100)	54 (100)	–	32 (60)	36 (67)	0.6
Pain (I)	53	54	53 (100)	54 (100)	–	26 (49)	33 (61)	0.3
Rash (P)	52	54	16 (31)	11 (20)	0.3	–	–	–
Shortness of breath (S)	50	54	40 (80)	43 (80)	1	8 (16)	9 (17)	1
Shortness of breath (I)	50	54	36 (72)	37 (69)	0.8	12 (24)	12 (22)	1
Vomiting (F)	52	54	40 (77)	26 (48)	0.003	6 (12)	4 (7.4)	0.5
Vomiting (S)	52	54	37 (71)	20 (37)	<0.001	11 (21)	4 (7.4)	0.05

F = frequency; I = interference; NCI PRO-CTCAE = National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; P = presence; S = severity.