

## ORIGINAL ARTICLE

# Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

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## ABSTRACT

**BACKGROUND**

The efficacy and safety of cabazitaxel, as compared with an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide), in patients with metastatic castration-resistant prostate cancer who were previously treated with docetaxel and had progression within 12 months while receiving the alternative inhibitor (abiraterone or enzalutamide) are unclear.

**METHODS**

We randomly assigned, in a 1:1 ratio, patients who had previously received docetaxel and an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide) to receive cabazitaxel (at a dose of 25 mg per square meter of body-surface area intravenously every 3 weeks, plus prednisone daily and granulocyte colony-stimulating factor) or the other androgen-signaling–targeted inhibitor (either 1000 mg of abiraterone plus prednisone daily or 160 mg of enzalutamide daily). The primary end point was imaging-based progression-free survival. Secondary end points of survival, response, and safety were assessed.

**RESULTS**

A total of 255 patients underwent randomization. After a median follow-up of 9.2 months, imaging-based progression or death was reported in 95 of 129 patients (73.6%) in the cabazitaxel group, as compared with 101 of 126 patients (80.2%) in the group that received an androgen-signaling–targeted inhibitor (hazard ratio, 0.54; 95% confidence interval [CI], 0.40 to 0.73;  $P<0.001$ ). The median imaging-based progression-free survival was 8.0 months with cabazitaxel and 3.7 months with the androgen-signaling–targeted inhibitor. The median overall survival was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling–targeted inhibitor (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.89;  $P=0.008$ ). The median progression-free survival was 4.4 months with cabazitaxel and 2.7 months with an androgen-signaling–targeted inhibitor (hazard ratio for progression or death, 0.52; 95% CI, 0.40 to 0.68;  $P<0.001$ ), a prostate-specific antigen response occurred in 35.7% and 13.5% of the patients, respectively ( $P<0.001$ ), and tumor response was noted in 36.5% and 11.5% ( $P=0.004$ ). Adverse events of grade 3 or higher occurred in 56.3% of patients receiving cabazitaxel and in 52.4% of those receiving an androgen-signaling–targeted inhibitor. No new safety signals were observed.

**CONCLUSIONS**

Cabazitaxel significantly improved a number of clinical outcomes, as compared with the androgen-signaling–targeted inhibitor (abiraterone or enzalutamide), in patients with metastatic castration-resistant prostate cancer who had been previously treated with docetaxel and the alternative androgen-signaling–targeted agent (abiraterone or enzalutamide). (Funded by Sanofi; CARD ClinicalTrials.gov number, NCT02485691.)

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\*A list of investigators in the CARD trial is provided in the Supplementary Appendix, available at NEJM.org.

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PROSTATE CANCER IS THE SECOND LEADING cause of cancer-related death among men in the United States and the third leading cause of cancer-related death in Europe.<sup>1,2</sup> Four different classes of medical treatments have prolonged survival among patients with metastatic castration-resistant prostate cancer, including taxanes (docetaxel and cabazitaxel), androgen-signaling–targeted inhibitors (abiraterone and enzalutamide), immunotherapy (sipuleucel-T), and a bone-targeted radiopharmaceutical agent (radium-223 dichloride).<sup>3–8</sup> The therapeutic landscape has shifted toward treatment with life-extending therapies during earlier stages of disease. Docetaxel, abiraterone, enzalutamide, and apalutamide, in combination with androgen-deprivation therapy, prolonged survival among patients with metastatic hormone-sensitive prostate cancer.<sup>9–14</sup> Androgen-signaling–targeted inhibitors have also prolonged metastasis-free survival, as compared with placebo, among patients with nonmetastatic castration-resistant prostate cancer.<sup>15–17</sup>

Cabazitaxel is a next-generation taxane that has been approved for the treatment of metastatic castration-resistant prostate cancer in patients who have previously been treated with a docetaxel-containing regimen.<sup>4</sup> Studies suggest that cabazitaxel retains activity in patients whose disease progressed while they were receiving docetaxel or androgen-signaling–targeted inhibitors.<sup>4,18,19</sup> Furthermore, cabazitaxel has a different safety profile from docetaxel, including a lower incidence of alopecia, peripheral neuropathy, peripheral edema, and nail disorders.<sup>20,21</sup>

Although patients with metastatic castration-resistant prostate cancer have several treatment options, few data inform the treatment sequence. Evidence suggests that patients may not have a response to abiraterone or enzalutamide after their disease progresses while they are receiving an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide).<sup>22–25</sup> A previous study has also suggested that partial cross-resistance may develop between androgen-signaling–targeted inhibitors and docetaxel.<sup>26</sup>

Androgen-signaling–targeted inhibitors and docetaxel are frequently used in earlier stages of the disease, and it is likely that most patients who are considered to be candidates for chemotherapy will have received both, in either order. The CARD trial investigated whether cabazitaxel would be superior to an androgen-signaling–targeted inhibitor in patients who had previously

been treated with docetaxel and the alternative androgen-signaling–targeted agent (abiraterone or enzalutamide).

## METHODS

### TRIAL OVERSIGHT

We conducted this multicenter, randomized, open-label, clinical trial at 62 sites across 13 European countries. The trial was designed to compare cabazitaxel with either abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel and who had disease progression within 12 months while they had been receiving an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide). The trial was approved by the institutional review board at each center and was conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

The trial was sponsored by Sanofi. The sponsor and the members of the steering committee contributed to the trial design, data analysis and interpretation, and critical review of the manuscript. All authors had full access to the trial data, were responsible for the content of the manuscript, and made the decision to submit the manuscript for publication. The authors developed the first draft of the manuscript with editorial assistance funded by Sanofi. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org.

### PATIENTS

Eligible patients had histologically confirmed prostate cancer, had castrate levels of serum testosterone (<0.5 ng per milliliter [1.73 nmol per liter]), had previously been treated with three or more cycles of docetaxel, had disease progression (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or had the appearance of at least two new bone lesions or a rising prostate-specific antigen (PSA) level (according to Prostate Cancer Working Group 2 criteria), and had previously had disease progression during 12 months of treatment with an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide, before or after docetaxel therapy).<sup>27</sup> The use of abiraterone or docetaxel in the context of metastatic hormone-sensitive

disease was allowed. The type of progression at enrollment was classified as the following: PSA progression only, imaging-based progression (defined as objective tumor progression according to RECIST, version 1.1, or progression of bone lesions according to Prostate Cancer Working Group 2 criteria — with or without PSA progression and without pain), or pain progression (defined as a Brief Pain Inventory-Short Form score  $>1$  [on an 11-point scale, with higher numbers indicating greater pain] or a World Health Organization cancer pain analgesic level of 2 to 3 [on a 3-point scale, with higher numbers indicating use of stronger analgesic agents] — with or without PSA or imaging-based progression).<sup>28</sup> The complete inclusion and exclusion criteria are provided in the protocol and the Supplementary Methods–Patients section in the Supplementary Appendix, available at NEJM.org.

#### RANDOMIZATION AND TREATMENT

Eligible patients were randomly assigned in a 1:1 ratio to receive either cabazitaxel or an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide, with the choice being dependent on the use of a previous androgen-signaling–targeted inhibitor; see below). Stratification criteria were the Eastern Cooperative Oncology Group performance-status score (0 or 1 vs. 2; scores are on a 5-point scale, with higher numbers indicating greater disability), time to disease progression ( $\leq 6$  months vs.  $>6$  to 12 months), and timing of the previous alternative androgen-signaling–targeted inhibitor (before vs. after docetaxel).

Cabazitaxel at a dose of 25 mg per square meter of body-surface area, according to the European label, was administered intravenously over a period of 1 hour every 3 weeks. Patients in the cabazitaxel group also received oral prednisone at a dose of 10 mg daily. Premedication included an antihistamine, glucocorticoid (dexamethasone at a dose of 8 mg or equivalent), and histamine<sub>2</sub>-receptor antagonist. Antiemetic prophylaxis was administered at the physician's discretion. Primary prophylactic granulocyte-colony stimulating factor was a requirement of this trial during each cycle of cabazitaxel. Patients who had been assigned to receive an androgen-signaling–targeted inhibitor received either abiraterone (1000 mg orally once daily and oral prednisone 5 mg twice daily) or enzalutamide (160 mg orally once daily) continuously. A treatment cycle was 3 weeks in both trial

groups. Abiraterone was given to patients who had previously received enzalutamide before trial entry, and enzalutamide was given to patients who had previously received abiraterone.

The trial was open label. Each patient was treated until the occurrence of imaging-based disease progression, the occurrence of unacceptable toxic effects, the start of a subsequent treatment, or a request by the patient to discontinue trial therapy. Details regarding dose delays and modifications are provided in the protocol and in the Supplementary Methods–Assessment Schedule section.

#### END POINTS

The primary end point for the trial was imaging-based progression-free survival (this is often termed “radiographic” progression-free survival, but the assessment includes nonradiographic measures), which was defined as the time from randomization until objective tumor progression (according to RECIST, version 1.1), progression of bone lesions (according to the Prostate Cancer Working Group 2 criteria), or death.<sup>27</sup> No blinded central review of imaging was conducted.

Secondary end points included overall survival, progression-free survival, PSA response, tumor and pain responses, the first occurrence of a symptomatic skeletal event in a time-to-event analysis, and safety. Health-related quality of life, biomarker analyses, and additional efficacy outcomes were assessed but are not reported here. The complete list of end points reported, with definitions, is provided in the Supplementary Methods–End Points section.

#### STATISTICAL ANALYSIS

The trial was designed to have 80% power to detect a hazard ratio of 0.67 (cabazitaxel vs. androgen-signaling–targeted inhibitor) in the analysis of imaging-based progression-free survival, with the use of a stratified log-rank test at a two-sided alpha level of 5%. We calculated that approximately 234 patients would need to undergo randomization in order for data on 196 events to be assessed (achieved on March 27, 2019). All the efficacy analyses used data that were obtained at this cutoff date, as specified in the protocol. If an imaging-based progression event or death did not occur during the trial, then the data on imaging-based progression-free survival were censored at the last tumor assessment or at the cutoff date, whichever occurred first. If no valid tumor as-

assessment was available, data were censored at the date of randomization. No interim analysis was performed. A descriptive final analysis was planned to occur after all the patients reached the end of the trial.

The efficacy analysis included all the patients who had undergone randomization. Stratified log-rank tests were used to analyze time-to-event data. The primary analysis compared imaging-based progression-free survival between the two treatment groups with the use of a stratified log-rank test. Survival curves were generated with the use of Kaplan–Meier estimates. Hazard ratios and associated 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Stratified Cochran–Mantel–Haenszel chi-square tests were used to analyze categorical data. Descriptive statistics were used to summarize the characteristics of the patients. The safety population, which included all the patients who had undergone randomization and had received at least one dose of trial treatment, was used for all safety analyses.

To control for type I error due to multiple comparisons, a hierarchical testing procedure was applied for the primary and key secondary end points. Only if imaging-based progression-free survival differed significantly between two treatment groups would key secondary end points be tested in the following order: overall survival, progression-free survival, PSA response, and tumor response. Further tests were stopped once a comparison was found not to be significant at a two-sided alpha level of 0.05.

## RESULTS

### **BASELINE AND TREATMENT CHARACTERISTICS**

From November 2015 through November 2018, a total of 255 patients were randomly assigned to receive cabazitaxel (129 patients) or an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide; 126 patients), which represented the intention-to-treat population (Fig. S1 in the Supplementary Appendix). Of these patients, 250 were treated (126 with cabazitaxel and 124 with an androgen-signaling–targeted inhibitor). Of the 124 patients who received an androgen-signaling–targeted inhibitor, 58 received abiraterone and 66 received enzalutamide. Two patients in the cabazitaxel group were lost to follow-up. The median follow-up (from randomization to the end of the trial) was 9.2 months.

The baseline characteristics of the patients are described in Table 1 and in Tables S1 and S2. The median age of the patients was 70 years, with 31.0% of the patients being 75 years of age or older. At randomization, 21 patients (8.2%) had PSA progression only, 39 patients (15.3%) had imaging-based progression, and 176 (69.0%) had pain progression. Metastases were present at diagnosis in 42.7% of the patients, and 44.3% of the patients had a duration of response to first androgen-deprivation therapy of less than 1 year.

The median duration of treatment was longer in patients receiving cabazitaxel than in those receiving an androgen-signaling–targeted inhibitor (22.0 weeks vs. 12.5 weeks), and the median number of treatment cycles received was higher in patients receiving cabazitaxel than in those receiving an androgen-signaling–targeted inhibitor (7 vs. 4) (Table S3). The principal reasons for the discontinuation of treatment with cabazitaxel or the androgen-signaling–targeted inhibitor were disease progression (in 43.7% and 71.0% of the patients, respectively) or an adverse event (in 19.8% and 8.9%) (Tables S3 and S4).

### **PRIMARY END POINT**

At the cutoff date, imaging-based disease progression or death from any cause was reported in 196 patients, of whom 95 (73.6%) had been assigned to receive cabazitaxel and 101 (80.2%) had been assigned to receive an androgen-signaling–targeted inhibitor. The median imaging-based progression-free survival was 8.0 months in the cabazitaxel group, as compared with 3.7 months in the androgen-signaling–targeted inhibitor group (hazard ratio for imaging-based progression or death, 0.54; 95% confidence interval [CI], 0.40 to 0.73;  $P < 0.001$ ) (Fig. 1A and Table S5 and Fig. S2). The treatment effect with regard to imaging-based progression-free survival was consistent across all the prespecified subgroups (Fig. 1B).

### **KEY SECONDARY END POINTS**

At the cutoff date, 153 deaths were noted, with 70 deaths (54.3% of the patients) occurring in the cabazitaxel group and 83 (65.9%) in the androgen-signaling–targeted inhibitor group. The median overall survival was 13.6 months in the cabazitaxel group, as compared with 11.0 months in the androgen-signaling–targeted inhibitor group (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.89;  $P = 0.008$ ) (Fig. 2A and Table S5).

Progression was noted in 111 patients (86.0%)

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	Cabazitaxel (N = 129)	Androgen-Signaling- Targeted Inhibitor (N = 126)
<b>Age</b>		
Median (range) — yr	70.0 (46–85)	71.0 (45–88)
≥75 yr — no. (%)	45 (34.9)	34 (27.0)
<b>ECOG performance-status score — no. (%)†</b>		
0 or 1	123 (95.3)	119 (94.4)
2	6 (4.7)	7 (5.6)
<b>Liver or lung metastases — no. (%)</b>		
	21 (16.3)	25 (19.8)
<b>PSA — ng/ml</b>		
Mean	264.4±1352.5	232.9±453.8
Median (range)	62.0 (1.1–15,000.0)	60.5 (1.5–2868.0)
<b>Neutrophil count per mm<sup>3</sup></b>		
Mean	5000±2000	4700±1700
Median (range)	4500 (2000–11,000)	4500 (2000–9000)
<b>Hemoglobin — g/liter</b>		
Mean	122.0±14.1	121.2±14.1
Median (range)	121.0 (91–170)	122.0 (82–162)
<b>Alkaline phosphatase — IU/liter</b>		
Mean	226.6±322.2	235.3±306.8
Median (range)	132.5 (41–2275)	122.0 (35–1980)
<b>Lactate dehydrogenase — IU/liter</b>		
Mean	331.0±276.3	348.5±348.3
Median (range)	248.0 (135–2753)	251.0 (50–3374)
<b>Type of progression at trial entry — no. (%)</b>		
PSA only	11 (8.5)	10 (7.9)
Imaging-based, with or without PSA progression	23 (17.8)	16 (12.7)
Pain, with or without PSA or imaging-based progression	86 (66.7)	90 (71.4)
Missing data	9 (7.0)	10 (7.9)
<b>Disease history</b>		
M1 disease at diagnosis — no. (%)‡	49 (38.0)	60 (47.6)
Gleason score 8–10 at diagnosis — no. (%)§	73 (56.6)	81 (64.3)
<b>First androgen-deprivation therapy</b>		
Median duration (range) — mo	13.7 (2–114)	12.6 (3–179)
Duration <12 mo — no. (%)	56 (43.4)	57 (45.2)
<b>Previous androgen-signaling-targeted inhibitor — no. (%)</b>		
Abiraterone	56 (43.4)	67 (53.2)
Enzalutamide	72 (55.8)	59 (46.8)
Missing data	1 (0.8)	0
<b>Timing of previous androgen-signaling-targeted inhibitor — no. (%)</b>		
Before docetaxel	50 (38.8)	49 (38.9)
After docetaxel	79 (61.2)	77 (61.1)
Time from initiation of previous androgen-signaling-targeted inhibitor to progression ≤6 mo — no. (%)	65 (50.4)	62 (49.2)

\* Plus-minus values are means ±SD. Patients in the androgen-signaling-targeted inhibitor group received either abiraterone or enzalutamide. PSA denotes prostate-specific antigen.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a 5-point scale, with higher numbers indicating greater disability.

‡ M1 disease was defined as metastatic disease (distant metastases).

§ Gleason scores range from 2 to 10, with scores of 8 to 10 indicating a high-grade cancer.

in the cabazitaxel group and in 115 (91.3%) in the androgen-signaling–targeted inhibitor group. The median progression-free survival was 4.4 months in the cabazitaxel group, as compared with 2.7 months in the androgen-signaling–targeted inhibitor group (hazard ratio for progression or death, 0.52; 95% CI, 0.40 to 0.68;  $P < 0.001$ ) (Fig. 2B and Table S5).

PSA response was evaluated in 115 patients in the cabazitaxel group and in 111 patients in the androgen-signaling–targeted inhibitor group. A reduction in the PSA level of at least 50% from baseline, confirmed by a second value obtained at least 3 weeks later, was observed in 35.7% of the patients in the cabazitaxel group and in 13.5% of those in the androgen-signaling–targeted inhibitor group ( $P < 0.001$ ) (Table S5). The waterfall plot of the best change in PSA level during treatment is provided in Figure S3.

Tumor response was evaluated in 63 patients in the cabazitaxel group and in 52 patients in the androgen-signaling–targeted inhibitor group. Among patients with measurable disease at baseline, the percentage of patients with a tumor response was 37% with cabazitaxel and 12% with an androgen-signaling–targeted inhibitor ( $P = 0.004$ ) (Table S5).

#### OTHER EFFICACY OUTCOMES

Pain response could be evaluated in 111 patients in the cabazitaxel group and in 109 patients in the androgen-signaling–targeted inhibitor group. Confirmed pain response was observed in 45.0% of the patients in the cabazitaxel group, as compared with 19.3% of those in the androgen-signaling–targeted inhibitor group (Table S5).

Skeletal events occurred in 24 patients (18.6%) in the cabazitaxel group and in 35 patients (27.8%) in the androgen-signaling–targeted inhibitor group. The median time to a symptomatic skeletal event was not reached in the cabazitaxel group and was 16.7 months in the androgen-signaling–targeted inhibitor group (hazard ratio, 0.59; 95% CI, 0.35 to 1.01) (Fig. 3 and Table S5). A total of 28.8% of the patients in the cabazitaxel group and 51.4% of those in the androgen-signaling–targeted inhibitor group were estimated to have had a symptomatic skeletal event at 18 months.

#### ADDITIONAL POST HOC ANALYSES

Cabazitaxel remained superior regardless of the androgen-signaling–targeted inhibitor received

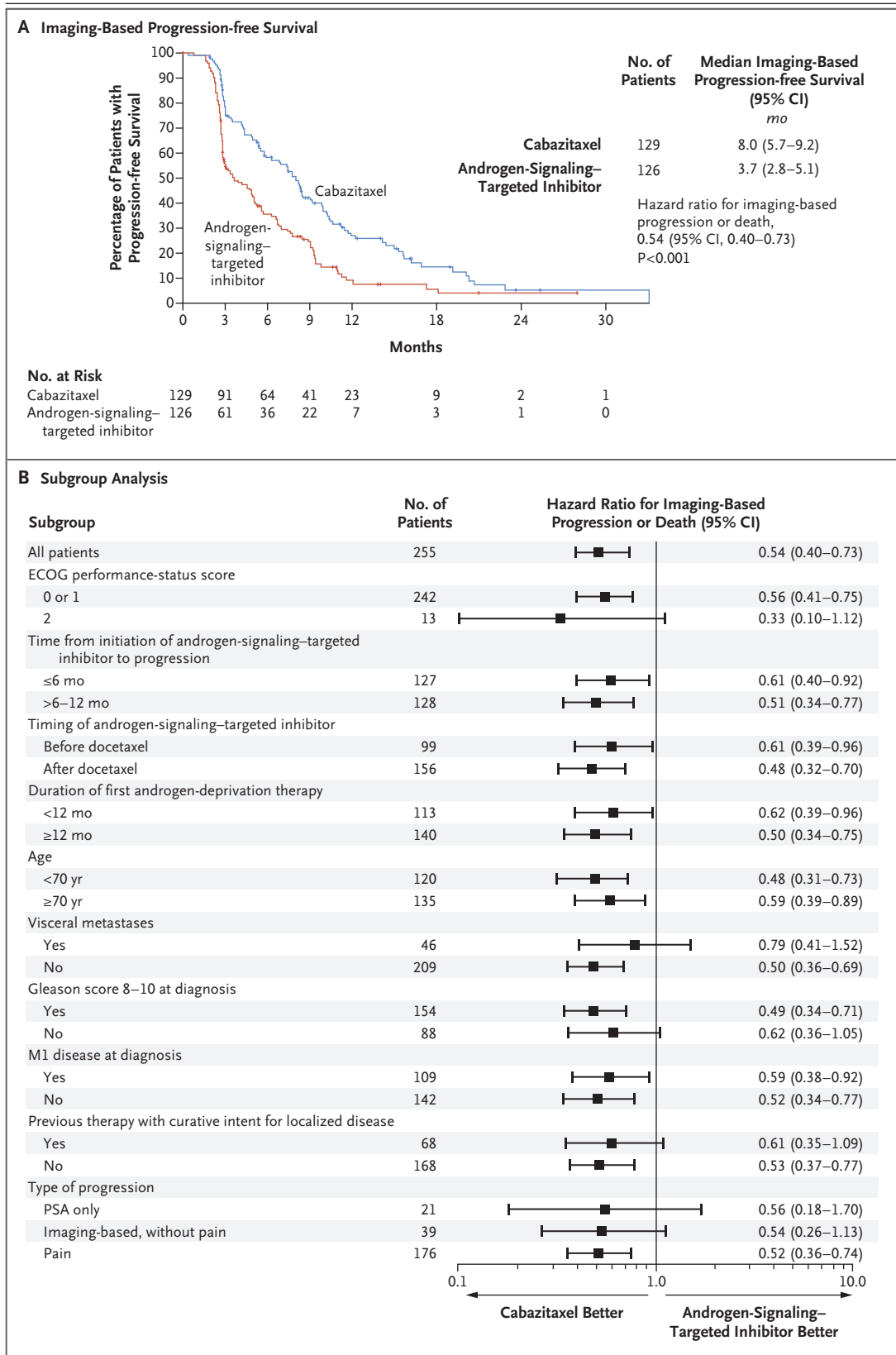
(hazard ratio for imaging-based progression or death with cabazitaxel vs. enzalutamide, 0.57 [95% CI, 0.36 to 0.90]; hazard ratio with cabazitaxel vs. abiraterone, 0.44 [95% CI 0.29 to 0.67]) (Fig. S4). Post hoc multivariate analyses confirmed the robustness of the treatment effect seen in the primary analysis (Table S6).

#### SAFETY

Almost all the patients in both treatment groups had an adverse event of any grade (98.4% in the cabazitaxel group vs. 94.4% in the androgen-signaling–targeted inhibitor group) (Table 2). The incidence of serious adverse events of any grade was similar in the cabazitaxel group (38.9%) and the androgen-signaling–targeted inhibitor group (38.7%). Adverse events leading to treatment discontinuation occurred more frequently with cabazitaxel (19.8%) than with an androgen-signaling–targeted inhibitor (8.9%). However, adverse events leading to death during the assessment period from randomization to 30 days after the last treatment administration occurred less frequently with cabazitaxel (7 patients [5.6%]) than with an androgen-signaling–targeted inhibitor (14 patients [11.3%]) (Table S7).

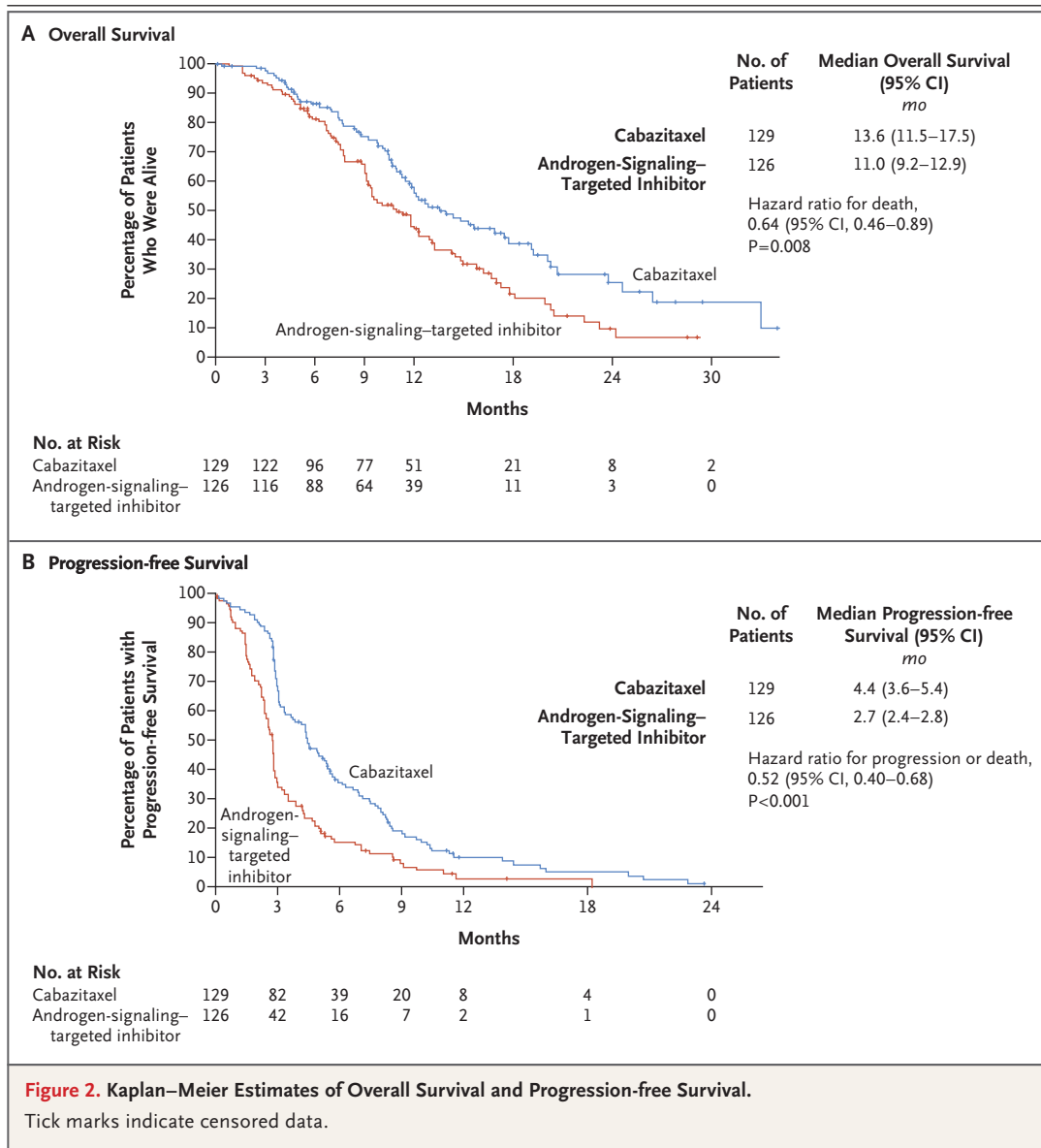
The grade 5 adverse events that were reported in the cabazitaxel group were related to infection (two patients), bronchial aspiration (one patient), general health deterioration due to progressive disease (two patients), spinal cord compression (one patient), and head injury (one patient). The grade 5 adverse events that were reported in the androgen-signaling–targeted inhibitor group were related to infection (two patients), pulmonary thromboembolism (one patient), cardiac disorder (two patients), cerebral bleeding associated with hyperfibrinolysis (one patient), renal failure (two patients), and general health deterioration due to progressive disease (six patients), which in one patient was associated with upper gastrointestinal bleeding, hypertensive crisis, and cardiac failure.

Adverse events of grade 3 or higher that occurred more frequently with cabazitaxel than with an androgen-signaling–targeted inhibitor were asthenia or fatigue (in 4.0% vs. 2.4% of the patients), diarrhea (3.2% vs. no patients), peripheral neuropathy (3.2% vs. no patients), and febrile neutropenia (3.2% vs. no patients). Adverse events of grade 3 or higher that occurred less frequently with cabazitaxel than with an androgen-sig-

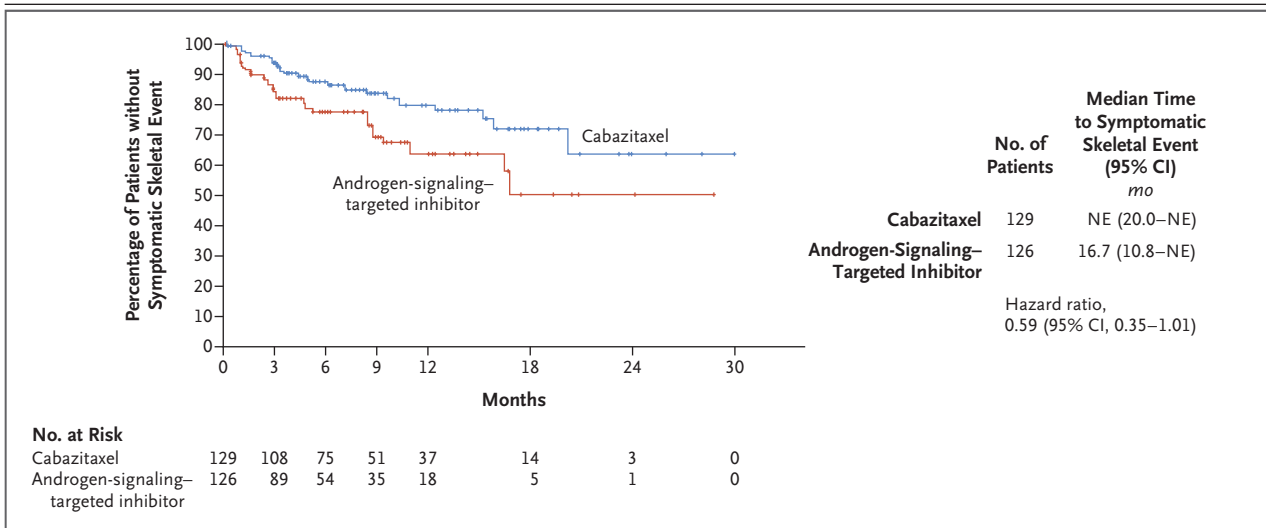


**Figure 1 (facing page).** Kaplan–Meier Estimates of Imaging-Based Progression-free Survival and Corresponding Subgroup Analyses.

The primary end point for the trial was imaging-based progression-free survival, which was defined as the time from randomization until objective tumor progression, progression of bone lesions, or death. Patients who received an androgen-signaling–targeted inhibitor received either abiraterone or enzalutamide. Tick marks indicate censored data. Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a 5-point scale, with higher numbers indicating greater disability. Gleason scores range from 2 to 10, with scores of 8 to 10 indicating a high-grade cancer. M1 disease was defined as metastatic disease (distant metastases). PSA denotes prostate-specific antigen.







**Figure 3.** Kaplan–Meier Estimates of Time to First Symptomatic Skeletal Event.

The median time to the first symptomatic skeletal event could not be evaluated (NE) in the cabazitaxel group. Tick marks indicate censored data.

**Table 2.** Adverse Events (Safety Population).

Event	Cabazitaxel (N=126)		Androgen-Signaling-Targeted Inhibitor (N=124)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	124 (98.4)	—	117 (94.4)	—
Any grade ≥3 adverse event — no. (%)	—	71 (56.3)	—	65 (52.4)
Any serious adverse event — no. (%)	49 (38.9)	—	48 (38.7)	—
Any adverse event leading to permanent discontinuation of treatment — no. (%)	25 (19.8)	—	11 (8.9)	—
Any adverse event leading to death — no. (%)*	7 (5.6)	—	14 (11.3)	—
Common adverse events — no. (%)†				
Asthenia or fatigue	67 (53.2)	5 (4.0)	45 (36.3)	3 (2.4)
Diarrhea	50 (39.7)	4 (3.2)	8 (6.5)	0
Infection	40 (31.7)	10 (7.9)	25 (20.2)	9 (7.3)
Musculoskeletal pain or discomfort‡	34 (27.0)	2 (1.6)	49 (39.5)	7 (5.6)
Nausea or vomiting	33 (26.2)	0	29 (23.4)	2 (1.6)
Peripheral neuropathy	25 (19.8)	4 (3.2)	4 (3.2)	0
Constipation	19 (15.1)	0	13 (10.5)	0
Hematuria	19 (15.1)	1 (0.8)	7 (5.6)	2 (1.6)
Decreased appetite	17 (13.5)	1 (0.8)	19 (15.3)	3 (2.4)
Dysgeusia	14 (11.1)	0	5 (4.0)	0
Bladder or urethral symptom§	12 (9.5)	0	10 (8.1)	0
Abdominal pain	10 (7.9)	1 (0.8)	3 (2.4)	1 (0.8)
Stomatitis	10 (7.9)	0	2 (1.6)	0
Peripheral edema	10 (7.9)	0	11 (8.9)	1 (0.8)

Table 2. (Continued.)

Event	Cabazitaxel (N=126)		Androgen-Signaling–Targeted Inhibitor (N=124)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Renal disorder¶	8 (6.3)	4 (3.2)	14 (11.3)	10 (8.1)
Cardiac disorder	8 (6.3)	1 (0.8)	10 (8.1)	6 (4.8)
Arthralgia	8 (6.3)	0	16 (12.9)	1 (0.8)
Dyspnea	7 (5.6)	0	3 (2.4)	0
Alopecia	7 (5.6)	0	0	0
Spinal cord or nerve-root disorder	6 (4.8)	3 (2.4)	9 (7.3)	5 (4.0)
Psychiatric disorder**	5 (4.0)	0	15 (12.1)	0
Hypertensive disorder	5 (4.0)	3 (2.4)	10 (8.1)	3 (2.4)
Weight decreased	5 (4.0)	0	7 (5.6)	0
Febrile neutropenia	4 (3.2)	4 (3.2)	0	0
Bone fracture	3 (2.4)	1 (0.8)	7 (5.6)	2 (1.6)
Laboratory abnormalities — no./total no. (%)††				
Anemia	124/125 (99.2)	10/125 (8.0)	118/124 (95.2)	6/124 (4.8)
Leukopenia	93/125 (74.4)	40/125 (32.0)	39/124 (31.5)	2/124 (1.6)
Neutropenia	81/123 (65.9)	55/123 (44.7)	8/124 (6.5)	4/124 (3.2)
Thrombocytopenia	51/125 (40.8)	4/125 (3.2)	20/124 (16.1)	2/124 (1.6)
Aspartate aminotransferase increased	27/124 (21.8)	4/124 (3.2)	35/124 (28.2)	0/124
Alanine aminotransferase increased	24/124 (19.4)	1/124 (0.8)	11/124 (8.9)	0/124
Hypokalemia	15/125 (12.0)	1/125 (0.8)	19/124 (15.3)	1/124 (0.8)

- \* Adverse events leading to death were assessed during the period from randomization to 30 days after the last treatment administration.
- † Common adverse events were events of any grade that were reported in at least 5% of the patients in either treatment group or events of grade 3 or higher that were reported in at least 3% of the patients in either treatment group.
- ‡ Musculoskeletal pain or discomfort included back pain, flank pain, musculoskeletal discomfort and pain, neck pain, or pain in extremities.
- § Bladder or urethral symptom included dysuria, pollakiuria, lower urinary tract symptoms, micturition urgency, urinary incontinence, or urinary retention.
- ¶ Renal disorder included, acute kidney injury, renal failure and impairment, hydronephrosis, or pyelocaliectasis.
- || Spinal cord or nerve-root disorder included sciatalgia, radiculopathy, or spinal cord compression.
- \*\* Psychiatric disorder included anxiety, depression, confusion, disorientation, or sleep disorder.
- †† Laboratory abnormalities were based on systematic analysis of blood samples obtained at each cycle and may not have been reported as an adverse event.

naling–targeted inhibitor were renal disorders (3.2% vs. 8.1%), musculoskeletal pain or discomfort (1.6% vs. 5.6%), cardiac disorders (0.8% vs. 4.8%), and spinal cord or nerve-root disorders (2.4% vs. 4.0%) (Table 2). Neutropenia of grade 3 or higher, measured at nadir by blood testing, was observed in 55 of 123 patients (44.7%) who received cabazitaxel. In the cabazitaxel group, hematuria of any grade was reported in 19 patients (15.1%), and mild alopecia was reported in 7 (5.6%); no nail disorders were reported in the cabazitaxel group. No new safety signals were reported.

At least one dose reduction occurred in 27 pa-

tients (21.4%) receiving cabazitaxel and in 47 patients (37.9%) receiving an androgen-signaling–targeted inhibitor. A dose reduction occurred in 17 of 58 patients (29%) receiving abiraterone and in 30 of 66 (45%) receiving enzalutamide (Table S3).

#### FIRST SUBSEQUENT ANTICANCER TREATMENT

Of 126 patients in the androgen-signaling–targeted inhibitor group, 42 (33.3%) crossed over to receive cabazitaxel. Of 129 patients in the cabazitaxel group, 30 (23.3%) crossed over to receive abiraterone or enzalutamide. Anticancer therapies that were received as the first subsequent treatment after the trial treatments are listed in Table S8.

## DISCUSSION

Our trial results prospectively confirm that patients with metastatic castration-resistant prostate cancer who had previously been treated with docetaxel and had disease progression within 12 months while receiving an androgen-signaling–targeted inhibitor (abiraterone or enzalutamide) had longer imaging-based progression-free survival and overall survival when treated with cabazitaxel than when treated with the other androgen-signaling–targeted inhibitor (abiraterone in patients who had previously received enzalutamide, or enzalutamide in those who had previously received abiraterone). Cabazitaxel more than doubled the imaging-based progression-free survival (median, 8.0 months vs. 3.7 months with an androgen-signaling–targeted inhibitor), and this benefit was observed across all the prespecified subgroups, regardless of the timing of the previous alternative androgen-signaling–targeted inhibitor therapy (before or after docetaxel). Cabazitaxel resulted in a risk of death from any cause that was 36% lower than that with abiraterone or enzalutamide, despite 33% of the patients in the androgen-signaling–targeted inhibitor group crossing over to receive cabazitaxel at the time of progression. All key secondary end points (overall survival, progression-free survival, PSA response, and tumor response) also favored cabazitaxel.

The results of the CARD trial are in agreement with those of previous studies that have shown poor outcomes with a second androgen-signaling–targeted inhibitor.<sup>22-25</sup> This is probably due to the fact that these agents target the same pathway and thus share common mechanisms of resistance. Conversely, taxanes, owing to their different mechanism of action, are able to overcome several mechanisms of resistance to androgen-signaling–targeted inhibitors, such as increased androgen-receptor signaling and PTEN (phosphatase and tensin homologue) loss.<sup>29-33</sup> In addition, although some studies suggest that docetaxel loses some activity in tumors that are resistant to androgen-signaling–targeted inhibitors, prospective and retrospective data show that cabazitaxel retains its activity in this context.<sup>18,19,26,34,35</sup> This may be attributed to greater intratumoral penetration with cabazitaxel than with docetaxel, especially in treatment-resistant tumors.<sup>36,37</sup>

The incidence of adverse events of grade 3 or

higher was similar in the two treatment groups (56.3% with cabazitaxel and 52.4% with an androgen-signaling–targeted inhibitor). The incidence of adverse events leading to death during the trial was twice as high with an androgen-signaling–targeted inhibitor as with cabazitaxel; this finding was mainly related to disease progression. Neutropenic complications with cabazitaxel usually occur at cycle 1, especially when the baseline neutrophil count is below 4000 per cubic millimeter.<sup>38</sup> Therefore, all patients in the cabazitaxel group received prophylactic granulocyte colony-stimulating factor during every cycle in the trial. With granulocyte colony-stimulating factor, the incidence of febrile neutropenia of grade 3 or higher that was observed in this trial (3.2%) was similar to that observed in the AFFINITY phase 3 trial (3%), which also allowed the use of prophylactic granulocyte colony-stimulating factor from cycle 1, with 59% of the patients having received both docetaxel and an androgen-signaling–targeted inhibitor.<sup>39</sup>

This was an open-label trial with no central review of the standard imaging, although a previous study has suggested little variance between local and central imaging review in this population.<sup>40</sup> Moreover, results regarding multiple secondary end points, including overall survival, in this trial were significant in favor of cabazitaxel. Second, the cabazitaxel starting dose of 20 mg per square meter was not tested. In the prospective, noninferiority, phase 3 trial PROSELICA, a dose of 20 mg per square meter maintained at least 50% of the survival benefit of a dose of 25 mg per square meter (which had been compared with mitoxantrone in the TROPIC trial) and was associated with a lower incidence of adverse events of grade 3 or higher.<sup>4,20</sup> For the CARD trial, we used a dose of 25 mg per square meter because the trial was conducted in Europe and the European label was used as a reference. The incidence of febrile neutropenia with the cabazitaxel dose of 25 mg per square meter was lower in the CARD trial (3.2%) than in TROPIC (8%) and PROSELICA (9.2%), probably owing to the use of prophylactic granulocyte colony-stimulating factor from cycle 1.<sup>4,20</sup>

No preplanned analysis of the influence of the sequence of abiraterone–enzalutamide (or vice versa) was undertaken. However, since retrospective studies suggest that the sequence of androgen-signaling–targeted inhibitors may influence progression-free survival, post hoc analyses were performed, which confirmed the superiority of

cabazitaxel over the androgen-signaling–targeted inhibitor regardless of whether abiraterone or enzalutamide was received during the trial.<sup>41–44</sup>

In conclusion, cabazitaxel led to longer imaging-based progression-free survival than abiraterone or enzalutamide among patients with metastatic castration-resistant prostate cancer who had previously received docetaxel and the alternative androgen-signaling–targeted inhibitor (abiraterone or enzalutamide). Cabazitaxel also significantly improved overall survival and other secondary end points.

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#### APPENDIX

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