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Prostate Cancer

Efficacy and Safety of Cabazitaxel Versus Abiraterone or Enzalutamide in Older Patients with Metastatic Castration-resistant Prostate Cancer in the CARD Study

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Abstract

Background: In the CARD study (NCT02485691), cabazitaxel significantly improved median radiographic progression-free survival (rPFS) and overall survival (OS) versus abiraterone/enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) who had previously received docetaxel and progressed ≤12 mo on the alternative agent (abiraterone/enzalutamide).
Objective: To assess cabazitaxel versus abiraterone/enzalutamide in older (≥70 yr) and younger (<70 yr) patients in CARD.
Design, setting, and participants: Patients with mCRPC were randomized 1:1 to cabazitaxel (25 mg/m^2 plus prednisone and granulocyte colony-stimulating factor) versus abiraterone (1000 mg plus prednisone) or enzalutamide (160 mg).
Outcome measurements and statistical analysis: Analyses of rPFS (primary endpoint) and safety by age were prespecified; others were post hoc. Treatment groups were compared using stratified log-rank or Cochran–Mantel-Haenszel tests.
Results and limitations: Of the 255 patients randomized, 135 were aged ≥70 yr (median 76 yr). Cabazitaxel, compared with abiraterone/enzalutamide, significantly improved median rPFS in older (8.2 vs 4.5 mo; hazard ratio [HR] = 0.58; 95% confidence interval [CI] = 0.38–0.89; p = 0.012) and younger (7.4 vs 3.2 mo; HR = 0.47; 95% CI = 0.30–0.74; p < 0.001) patients. The median OS of cabazitaxel versus abiraterone/enzalutamide was 13.9 versus 9.4 mo in older patients (HR = 0.66; 95% CI = 0.41–1.06; p = 0.084), and it

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was 13.6 versus 11.8 mo in younger patients (HR = 0.66; 95% CI = 0.41–1.08; p = 0.093). Progression-free survival, prostate-specific antigen, and tumor and pain responses favored cabazitaxel, regardless of age. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 58% versus 49% of older patients receiving cabazitaxel versus abiraterone/enzalutamide and 48% versus 42% of younger patients. In older patients, cardiac adverse events were more frequent with abiraterone/enzalutamide; asthenia and diarrhea were more frequent with cabazitaxel.
Conclusions: Cabazitaxel improved efficacy outcomes versus abiraterone/enzalutamide in patients with mCRPC after prior docetaxel and abiraterone/enzalutamide, regardless of age. TEAEs were more frequent among older patients. The cabazitaxel safety profile was manageable across age groups.
Patient summary: Clinical trial data showed that cabazitaxel improved survival versus abiraterone/enzalutamide with manageable side effects in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel and the alternative agent (abiraterone/enzalutamide), irrespective of age.

1. Introduction

Like most other neoplasms, prostate cancer is an age-related disorder. It is the most frequently diagnosed cancer in men, and represents the third and fourth leading cause of male cancer death in Europe and the USA, respectively, with the majority of deaths occurring in patients ≥75 yr of age [1–3]. With an aging population and increasing life expectancy worldwide, a substantial increase in the burden of prostate cancer is anticipated in the next 10 yr [4]. Consequently, there is a need to better manage patients with prostate cancer and adequately balance the benefits and risks of therapies according to a patient's health status, rather than age alone.

Although there are currently multiple treatments available for patients with metastatic castration-resistant prostate cancer (mCRPC), there are little data informing the optimal treatment choice with respect to improved patient survival, treatment sequence, and safety profile [5]. Treatment-associated adverse events (AEs) are a particular challenge in older patients due to associated comorbidities and/or age-related decline in organ function, polypharmacy, and risk of potentially serious drug-drug interactions [6,7].

To better understand treatment sequencing in mCRPC, the CARD study (NCT02485691) was designed to compare cabazitaxel with abiraterone or enzalutamide in patients with mCRPC who had received prior docetaxel and had previously progressed within 12 mo while receiving an alternative androgen receptor (AR)-targeted agent (abiraterone or enzalutamide) [8]. In CARD, cabazitaxel improved radiographic progression-free survival (rPFS) and overall survival (OS) compared with abiraterone or enzalutamide [8]. This preplanned analysis of CARD investigated the impact of cabazitaxel versus abiraterone/enzalutamide on the primary endpoint (rPFS) in older (≥70 yr of age) and younger (<70 yr of age) patient subgroups. Post hoc analyses of other secondary endpoints were also assessed in these patient subgroups. The cutoffs of ≥70 and <70 yr of age were selected based on the International Society of Geriatric Oncology guidelines on prostate cancer [9].

2. Patients and methods

2.1. Study design and population

CARD (NCT02485691) is a multicenter, randomized (1:1), open-label clinical trial involving 79 sites in 13 European countries; the study design has been described previously [8]. The study was designed to compare cabazitaxel with abiraterone or enzalutamide in patients with mCRPC who had previously been treated with three or more cycles of docetaxel and who had progressed within 12 mo of treatment with the alternative AR-targeted agent, received before or after docetaxel. Eligible patients received intravenous cabazitaxel 25 mg/m^2 every 3 wk, oral prednisone 10 mg daily and granulocyte colony-stimulating factor (G-CSF) or oral abiraterone 1000 mg daily and oral prednisone 5 mg twice daily or oral enzalutamide 160 mg daily. G-CSF was mandatory during each cycle of cabazitaxel. The duration of one cycle was 3 wk in each arm; treatment continued until radiographic progression, unacceptable toxicity, or change in treatment.

2.2. Endpoints

The primary endpoint was rPFS, defined as the time from randomization until objective tumor progression (according to Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1), progression of bone lesions (according to the Prostate Cancer Working Group 2 criteria), or death [10]. If radiological progression or death was not observed during the study, data on rPFS were censored at the last valid tumor assessment or at the cutoff date, whichever came first. Secondary endpoints included OS, progression-free survival (PFS), prostate-specific antigen (PSA), tumor and pain responses, and safety. A PSA response was defined as a decline of serum PSA from baseline of ≥50% confirmed with an additional measurement ≥3 wk apart. A tumor response was defined as a partial or complete response according to RECIST version 1.1, in patients with measurable disease. A pain response was assessed using the Brief Pain Inventory-Short Form (BPI-SF) pain intensity score and defined as a >30% decrease from baseline in the BPI-SF pain intensity score observed at two consecutive evaluations ≥3 wk apart without an increase in analgesic usage score [11]. Treatment-emergent AEs (TEAEs), regardless of causality, were defined by the first occurrence or worsening of an AE after the first dose and up to 30 d after the last study drug administration. TEAEs were assessed using the National Cancer Institute Common Terminology Criteria for AEs version 4.0.

2.3. Statistical analysis

For this analysis, patients were classified into two age subgroups: ≥70 yr (older) and <70 yr of age (younger). This age cutoff was selected based

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upon the International Society of Geriatric Oncology guidelines on prostate cancer [9]. An rPFS analysis by age subgroup (≥70 vs <70 yr of age) was prespecified; analyses of secondary endpoints (OS, PFS, PSA, and tumor and pain responses) by these age subgroups were post hoc. Analyses conducted in patients aged ≥75 yr were post hoc. The comparison of rPFS, OS, and PFS between treatment groups was performed using a stratified log-rank test. Survival curves were generated using Kaplan-Meier estimates. Stratified Cox proportional-hazard models were used to estimate hazard ratios (HRs) and associated 95% confidence intervals (CIs). Sensitivity analyses used the stratified Cox proportional-hazard model adjusted for Gleason score 8–10 and M1 disease at diagnosis as covariates due to the imbalance of these characteristics between age subgroups. For PSA, and tumor and pain response comparisons between treatment groups, a stratified Cochran–Mantel-Haenszel test was used. The log-rank tests, Cox proportional-hazard models, and Cochran–Mantel-Haenszel tests were stratified by Eastern Cooperative Oncology Group performance status (0/1 vs 2), time from AR-targeted agent initiation to progression (0–6 vs 6–12 mo), and timing of the AR-targeted agent as specified at the time of randomization (before vs after docetaxel).

3. Results

3.1. Patient baseline and disease characteristics

CARD enrolled 255 patients with mCRPC who were randomly assigned to receive cabazitaxel (n = 129) or abiraterone or enzalutamide (n = 126; Fig. 1). Of them, 135 patients were aged ≥70 yr (cabazitaxel arm, n = 66; abiraterone or enzalutamide arm, n = 69), with a median age of 76 yr. Compared with patients aged ≥70 yr, younger patients had higher rates of Gleason score 8–10 (72% vs 50%) and metastatic disease (49% vs 37%) at diagnosis, and were more likely to have received docetaxel as first life-extending therapy (70% vs 53%); other variables were well balanced between age subgroups (Table 1). Among patients aged ≥70 yr, those receiving abiraterone or enzalutamide versus cabazitaxel had higher rates of Gleason score 8–10 (58% vs 42%) and metastatic disease

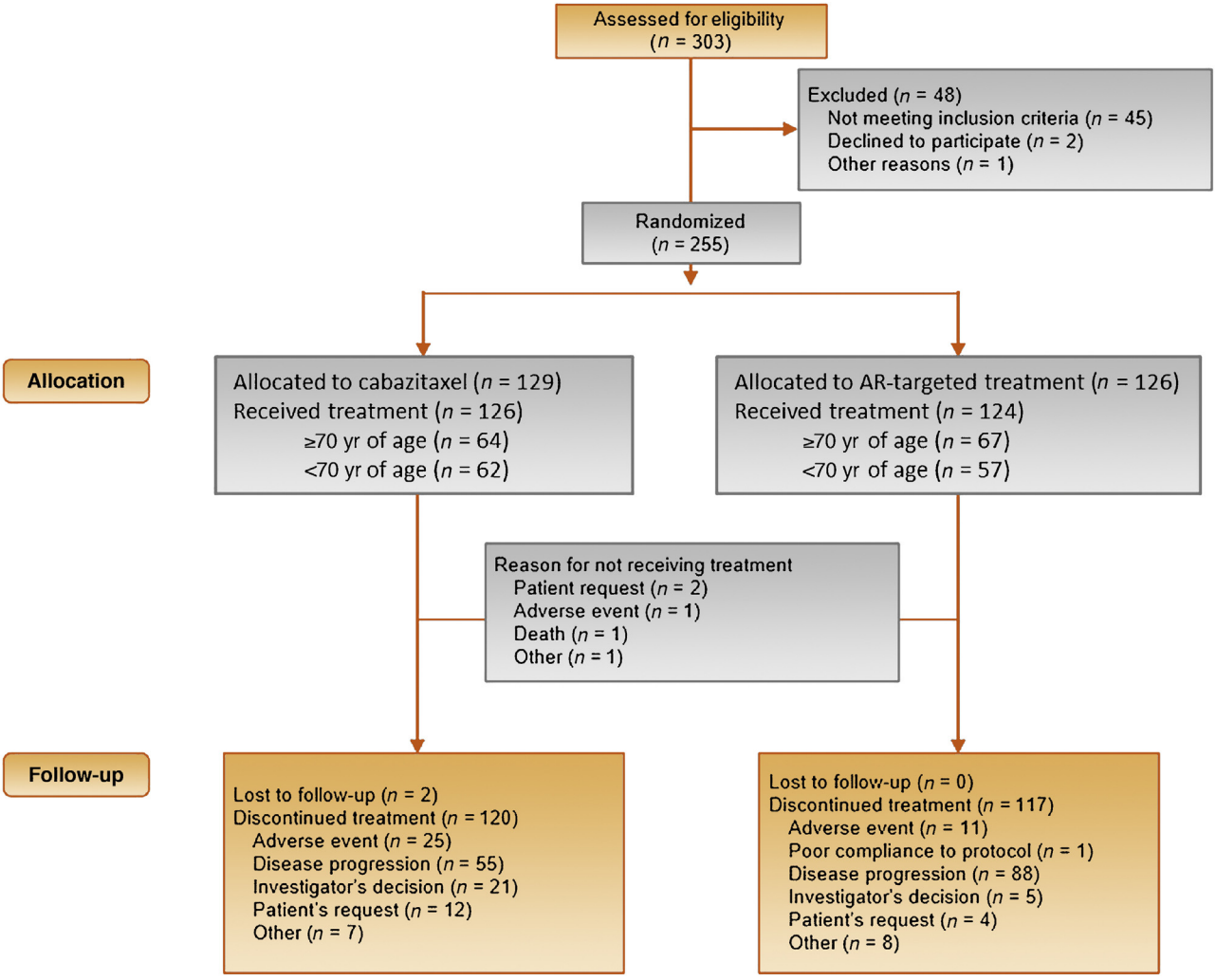

Fig. 1 – CONSORT diagram.
AR = androgen receptor.

Table 1 – Patient baseline and disease characteristics

	≥70 yr of age		<70 yr of age	
	Cabazitaxel (*n* = 66)	Abiraterone or enzalutamide (*n* = 69)	Cabazitaxel (*n* = 63)	Abiraterone or enzalutamide (*n* = 57)
Age at screening (yr), median (range)	76 (70–85)	74 (70–88)	65 (46–69)	63 (45–69)
ECOG PS at randomization, *n* (%)				
0 or 1	65 (99)	68 (99)	60 (95)	54 (95)
2	1 (1.5)	1 (1.4)	3 (4.8)	3 (5.3)
Metastatic sites at randomization, *n* (%)				
Bone	40 (61)	40 (58)	34 (54)	36 (63)
Lymph nodes	5 (7.6)	4 (5.8)	3 (4.8)	2 (3.5)
Liver or lung	8 (12)	15 (22)	13 (21)	10 (18)
Other	13 (20)	10 (15)	13 (21)	9 (16)
Type of progression at randomization, *n* (%)				
Pain	43 (65)	49 (71)	43 (68)	41 (72)
Imaging-based progression (±PSA) and no pain	12 (18)	8 (12)	11 (18)	7 (12)
PSA only	5 (7.6)	5 (7.2)	6 (9.5)	5 (8.8)
Missing data	6 (9.1)	7 (10)	3 (4.8)	4 (7.0)
M1 disease at diagnosis, *n* (%)	19 (29)	31 (45)	30 (48)	29 (51)
Gleason score 8–10 at diagnosis, *n* (%)	28 (42.4)	40 (58)	45 (71.4)	41 (71.9)
Previous AR-targeted agent, *n* (%)				
Abiraterone	29 (44)	40 (58)	27 (43)	27 (47)
Enzalutamide	36 (55)	29 (42)	36 (57)	30 (53)
Missing data	1 (1.5)	0	0	0
Timing of AR-targeted agent, *n* (%)				
Before docetaxel	29 (44)	34 (49)	21 (33)	15 (26)
After docetaxel	37 (56)	35 (51)	42 (67)	42 (74)

AR = androgen receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

(45% vs 29%) at diagnosis, and higher rates of pain (71% vs 65%) and visceral metastases (22% vs 12%) at randomization, but performance status was similar between treatment arms (Table 1). Clinical variables were well balanced between treatment arms in younger patients. The median follow-up for CARD was 9.2 mo and the median event-free times for rPFS, OS, and PFS were 5.4, 10.6, and 5.2 mo, respectively. The median duration of treatment was longer for patients receiving cabazitaxel than for patients receiving abiraterone or enzalutamide, regardless of age (patients aged ≥70 yr: 5.1 vs 3.0 mo; younger patients: 5.5 vs 2.8 mo). The proportion of patients discontinuing treatment was similar among patients receiving cabazitaxel versus abiraterone or enzalutamide both in patients aged ≥70 yr (96% vs 93%) and younger patients (91% vs 93%). The main reasons for treatment discontinuation in both treatment arms were disease progression and AEs (Supplementary Table 1).

3.2. *Efficacy*

As previously reported, the median rPFS for the overall population was 8.0 mo with cabazitaxel versus 3.7 mo with abiraterone or enzalutamide (HR [95% CI] = 0.54 [0.40–0.73]; $p < 0.001$) [8]. In patients aged ≥70 yr, the median rPFS was 8.2 mo with cabazitaxel versus 4.5 mo with abiraterone or enzalutamide (HR [95% CI] = 0.58 [0.38–0.89]; $p = 0.012$; Fig. 2A); the sensitivity analysis (adjusted for Gleason score 8–10 and M1 disease at diagnosis) HR (95% CI) was 0.61 (0.39–0.97). Among patients aged <70 yr, the median rPFS was also significantly improved with cabazitaxel versus abiraterone or enzalutamide (7.4 vs 3.2 mo; HR [95% CI] = 0.47 [0.30–0.74]; $p < 0.001$; Fig. 2A).

The median OS (main secondary endpoint) was numerically longer for cabazitaxel than for abiraterone or enzalutamide in patients aged ≥70 yr (13.9 vs 9.4 mo; HR [95% CI] = 0.66 [0.41–1.06]; $p = 0.084$) and younger patients (13.6 vs 11.8 mo; HR [95% CI] = 0.66 [0.41–1.08]; $p = 0.093$), but differences did not reach statistical significance (Fig. 2B); the sensitivity analysis HR (95% CI) was 0.69 (0.42–1.15). In patients aged ≥70 yr, the median PFS was 4.5 mo with cabazitaxel versus 2.8 mo with abiraterone or enzalutamide (HR [95% CI] = 0.57 [0.39–0.84]; $p = 0.003$; Fig. 2C); the sensitivity analysis HR (95% CI) was 0.55 (0.36–0.83). Among patients aged <70 yr, a significant improvement in median PFS was also observed with cabazitaxel versus abiraterone or enzalutamide (4.4 vs 2.5 mo; HR [95% CI] = 0.45 [0.30–0.68]; $p < 0.001$; Fig. 2C). Interaction *p* values between treatment and age group for rPFS, OS, and PFS were 0.5, 0.9, and 0.5, respectively. Lastly, an exploratory analysis was performed in the subgroup of patients aged ≥75 yr (Supplementary Table 2). rPFS, OS, and PFS numerically favored cabazitaxel versus abiraterone or enzalutamide, but as a consequence of the low number of patients aged ≥75 yr, a meaningful statistical comparison could not be performed. Overall and by age subgroup patient event and censoring data can be found in Supplementary Table 3.

PSA and pain responses were significantly improved with cabazitaxel versus abiraterone or enzalutamide,

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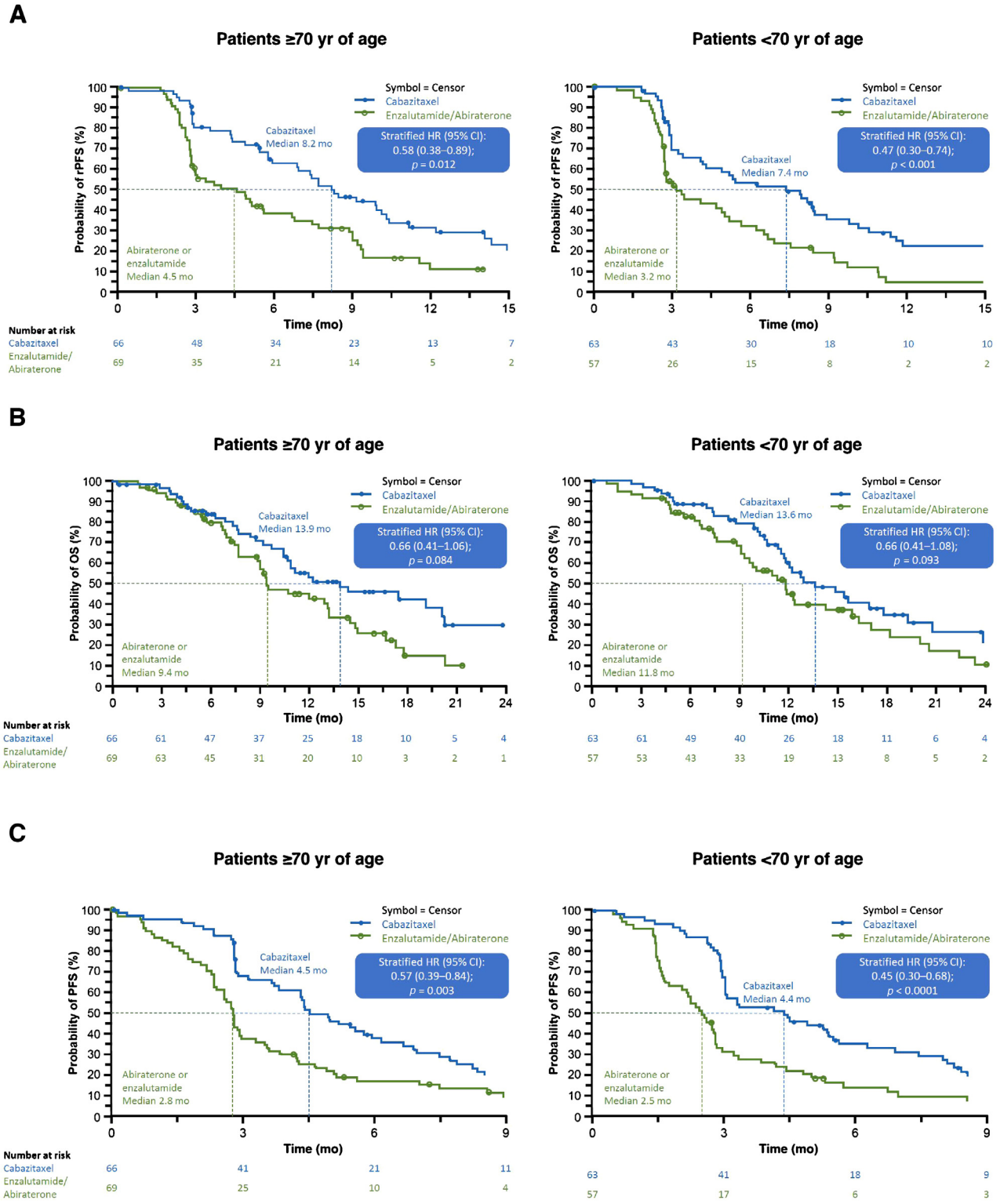

Fig. 2 – Kaplan-Meier estimates: (A) radiographic progression-free survival according to age, (B) overall survival according to age, and (C) progression-free survival according to age. Kaplan-Meier estimates at later time points should be interpreted with caution due to small samples sizes.
CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; rPFS = radiographic progression-free survival.

regardless of age (Fig. 3). Tumor response in patients aged ≥70 yr numerically favored cabazitaxel versus abiraterone or enzalutamide, but this difference did not reach statistical significance.

3.3. *Safety*

Almost all patients had a TEAE of any grade, irrespective of age and treatment (Table 2 and Supplementary Table 4).

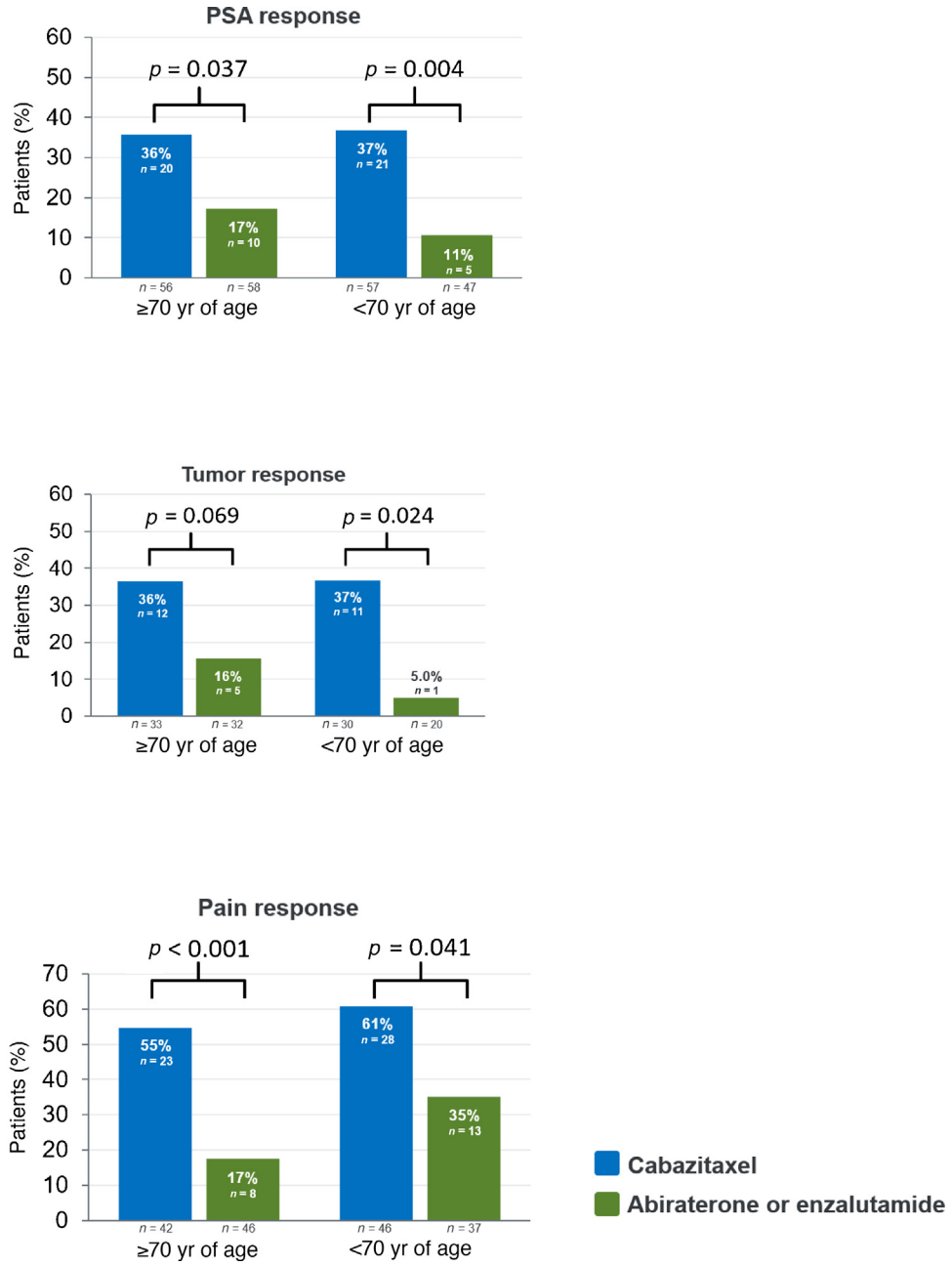

Fig. 3 – Prostate-specific antigen, and tumor and pain responses according to age. PSA = prostate-specific antigen.

Serious TEAEs of any grade were more frequent in patients aged ≥70 yr than in younger patients, both in the cabazitaxel (45% vs 32%) and in the abiraterone or enzalutamide (45% vs 33%) arm. Any grade ≥3 TEAEs were also more frequent in patients aged ≥70 yr than in younger patients, both in the cabazitaxel (58% vs 48%) and in the abiraterone or enzalutamide (49% vs 42%) arm. Grade ≥3 TEAEs that occurred more frequently in patients aged ≥70 yr receiving cabazitaxel than in patients receiving abiraterone or enzalutamide included asthenia/fatigue (6.3% vs 1.5%), diarrhea (6.3% vs 1.5%), and febrile neutropenia (3.1% vs 0%). Grade ≥3 TEAEs that occurred more frequently in patients aged ≥70 yr receiving abiraterone or enzalutamide than in patients receiving cabazitaxel included infection (9.0% vs 4.7%), renal disorders (7.5% vs 3.1%), and cardiac disorders (9.0% vs 0%). TEAEs leading to permanent treatment discontinuation were more frequent in patients receiving cabazitaxel than in patients receiving abiraterone or enzalutamide among patients aged ≥70 yr (25% vs 12%) and younger patients (15% vs 5.3%). TEAEs leading to death were less frequent in patients receiving cabazitaxel than in patients receiving abiraterone or enzalutamide among patients aged ≥70 yr (9.4% vs 15%) and younger patients (1.6% vs 7.0%). In patients aged ≥70 yr, grade 5 TEAEs occurred in six patients receiving cabazitaxel (disease progression [*n* = 2], urinary tract infection [*n* = 1],

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Table 2 – Treatment-emergent adverse events according to age

Patients, *n* (%)	≥70 yr of age				<70 yr of age			
	Cabazitaxel (*n* = 64)		Abiraterone or enzalutamide (*n* = 67)		Cabazitaxel (*n* = 62)		Abiraterone or enzalutamide (*n* = 57)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	64 (100)	37 (58)	63 (94)	33 (49)	60 (97)	30 (48)	54 (95)	24 (42)
Any serious TEAE	29 (45)	24 (38)	30 (45)	30 (45)	20 (32)	16 (26)	19 (33)	17 (30)
Any TEAE leading to permanent treatment discontinuation	16 (25)	–	8 (12)	–	9 (15)	–	3 (5.3)	–
Any TEAE leading to death	6 (9.4)	–	10 (15)	–	1 (1.6)	–	4 (7.0)	–
Frequent TEAEs (grade ≥3 TEAEs reported in ≥3% in any subgroup) [a]								
Asthenia or fatigue	38 (59)	4 (6.3)	29 (43)	1 (1.5)	29 (47)	1 (1.6)	16 (28)	2 (3.5)
Diarrhea	27 (42)	4 (6.3)	3 (4.5)	1 (1.5)	23 (37)	0	6 (11)	0
Infection	19 (30)	3 (4.7)	17 (25)	6 (9.0)	21 (34)	6 (9.7)	9 (16)	3 (5.3)
Nausea or vomiting	15 (23)	0	21 (31)	1 (1.5)	18 (29)	0	8 (14)	1 (1.8)
Decreased appetite	12 (19)	1 (1.6)	13 (19)	1 (1.5)	5 (8.1)	0	6 (11)	2 (3.5)
Musculoskeletal pain or discomfort [b]	18 (28)	1 (1.6)	26 (39)	3 (4.5)	16 (26)	1 (1.6)	23 (40)	4 (7.0)
Peripheral neuropathy [c]	11 (17)	3 (4.7)	2 (3.0)	0	14 (23)	1 (1.6)	2 (3.5)	0
Hematuria	7 (11)	0	4 (6.0)	2 (3.0)	12 (19)	1 (1.6)	3 (5.3)	0
Renal disorder [d]	5 (7.8)	2 (3.1)	9 (13)	5 (7.5)	3 (4.8)	2 (3.2)	5 (8.8)	5 (8.8)
Cardiac disorder	4 (6.3)	0	8 (12)	6 (9.0)	4 (6.5)	1 (1.6)	2 (3.5)	0
Hypertensive disorder [e]	2 (3.1)	1 (1.6)	7 (10)	2 (3.0)	3 (4.8)	2 (3.2)	3 (5.3)	1 (1.8)
Febrile neutropenia	2 (3.1)	2 (3.1)	0	0	2 (3.2)	2 (3.2)	0	0
Disease progression	3 (4.7)	3 (4.7)	8 (12)	7 (10)	0	0	0	0
Spinal cord or nerve-root disorder [f]	2 (3.1)	2 (3.1)	4 (6.0)	3 (4.5)	4 (6.5)	1 (1.6)	5 (8.8)	2 (3.5)
Urinary tract obstruction	0	0	3 (4.5)	3 (4.5)	0	0	0	0
Pulmonary embolism	0	0	0	0	2 (3.2)	2 (3.2)	1 (1.8)	1 (1.8)

TEAE = treatment-emergent adverse event.
[a] The cutoff selected was grade ≥3 TEAEs reported in ≥3% of patients in any subgroup.
[b] Including back pain, flank pain, musculoskeletal discomfort, musculoskeletal pain, discomfort, neck pain, pain in extremity, growing pains, and musculoskeletal chest pain.
[c] Including neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy.
[d] Including acute kidney injury, renal failure, renal impairment, hydronephrosis, and pyelocaliectasis.
[e] Including hypertension and hypertensive crisis.
[f] Including sciatica, radiculopathy, and spinal cord compression.

head injury [*n* = 1], septic shock [*n* = 1], or aspiration [*n* = 1]) and ten patients receiving abiraterone or enzalutamide (acute coronary syndrome [*n* = 1]; tumor-related symptoms including clinical deterioration, reduced mobility and appetite, and dyspnea on exertion [*n* = 1]; renal failure [*n* = 1]; disease progression [*n* = 4]; sepsis [*n* = 1]; cardiac failure [*n* = 1]; or pneumonia [*n* = 1]). In younger patients, grade 5 TEAEs occurred in one patient receiving cabazitaxel (disease progression [*n* = 1]) and four patients receiving abiraterone or enzalutamide (cerebral hemorrhage [*n* = 1], disease progression [*n* = 1], acute kidney injury [*n* = 1], or a pulmonary embolism [*n* = 1]). The proportion of patients with one or more dose reductions was lower in patients receiving cabazitaxel than in those receiving abiraterone or enzalutamide among patients aged ≥70 yr (20% vs 39%) and younger patients (23% vs 37%). The TEAE profiles of cabazitaxel and abiraterone/enzalutamide were further investigated using three different age cutoffs (≥75, 70–74, and <70 yr; Supplementary Table 5).

4. Discussion

Management of older patients with metastatic prostate cancer is challenging due to multiple comorbidities, the problem of polypharmacy, and the risk of severe drug-drug interactions, with older patients taking approximately ten prescription medications prior to receiving chemotherapy [4,6,12]. There is also the problem of cost, with several studies identifying older patients as some of the highest resource users [13–16]. Since 2010, SIOG guidelines consistently recommend that treatment choices should be based on patient health status, mainly driven by comorbidities and patient preference, and not on chronological age [4,9]. Advanced age is thus not a contraindication to chemotherapy. However, in daily practice, many older patients with mCRPC receive AR-targeted agents sequentially because these are given orally and perceived as less toxic than chemotherapy [17,18].

The CARD study prospectively randomized a high proportion (53%) of patients aged ≥70 yr, enabling an effective assessment of the efficacy and safety of cabazitaxel compared with abiraterone or enzalutamide in older patients with mCRPC previously treated with docetaxel and who had disease progression within 12 mo on the alternative AR-targeted agent. The results demonstrate that cabazitaxel provides a greater benefit than a second AR-targeted agent and shows an acceptable safety profile, regardless of age. In this preplanned analysis of the CARD primary endpoint, cabazitaxel almost doubled rPFS compared with abiraterone or enzalutamide among patients

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aged ≥70 yr (HR = 0.58) and younger patients (HR = 0.47). Cabazitaxel also numerically improved OS (main secondary endpoint) compared with abiraterone or enzalutamide, regardless of age. Other secondary endpoints (PFS, PSA, and tumor and pain responses) consistently favored cabazitaxel compared with abiraterone or enzalutamide, regardless of age [19].

Interestingly, the median rPFS was slightly shorter for patients aged <70 yr (cabazitaxel: 7.4 mo; abiraterone/enzalutamide: 3.2 mo) compared with patients aged ≥70 yr (cabazitaxel: 8.2 mo; abiraterone/enzalutamide: 4.5 mo). This might be a reflection of the more aggressive baseline clinical features of the younger patient population (higher rates of Gleason score 8–10 and metastatic disease at diagnosis). However, this trend was not seen for OS or PFS. Younger patients receiving cabazitaxel also had a higher rate of liver or lung metastases at diagnosis compared with patients aged ≥70 yr receiving cabazitaxel (21% vs 12%). As liver and lung metastases are often associated with more aggressive disease, this may be a contributing factor to the shorter rPFS observed [20].

The percentage of patients who experienced serious TEAEs of any grade was higher among patients aged ≥70 yr versus younger patients in both the cabazitaxel (45% vs 32%) and the abiraterone or enzalutamide (45% vs 33%) treatment arm. Similarly, TEAEs leading to death occurred more often in patients aged ≥70 yr versus younger patients (12% vs 4.2%); however, lower rates of TEAEs leading to death were observed in patients receiving cabazitaxel than in patients receiving abiraterone or enzalutamide across both age subgroups. This would suggest that patients aged ≥70 yr receiving either treatment may need closer monitoring and additional AE mitigation strategies to optimize treatment outcomes.

In this study, the incidence of febrile neutropenia did not exceed 3.2% in patients aged ≥70 yr and younger patients. The rate of febrile neutropenia is lower than in previous phase 3 studies assessing cabazitaxel 25 mg/m^2 (8–12%). This is likely due to the mandatory use of G-CSF during each cycle of cabazitaxel [21–23].

One limitation of this study is that the age subgroup analyses for the secondary endpoints were post hoc and not powered to demonstrate benefit. However, the age subgroup analysis of rPFS was prespecified and was significantly prolonged among patients receiving cabazitaxel compared with abiraterone or enzalutamide. Another limitation of this study is the imbalance in some poor prognostic features between the age subgroups and the treatment arms, which may suggest different underlying mCRPC biology. However, sensitivity analyses adjusted for these imbalances did not alter the findings.

The CARD results are important for several reasons. First, they provide additional confirmation that patients with mCRPC progressing following receipt of an AR-targeted agent respond suboptimally to a second alternative AR-targeted agent, as already shown by several prospective randomized trials [24,25]. Second, the results demonstrate that cabazitaxel is superior to abiraterone or enzalutamide in delaying disease progression, prolonging OS, and relieving pain among patients with mCRPC previously treated with docetaxel and the alternative AR-targeted agent. Finally, the safety profile of cabazitaxel is manageable when prophylactic G-CSF is administered at each cycle. The incidence of febrile neutropenia in patients receiving cabazitaxel in CARD (3.2%) is lower than that reported in previous phase 3 studies assessing cabazitaxel [8,21–23]. In TROPIC, FIRSTANA, and PROSELICA, prophylactic use of G-CSF was not recommended during cycle 1 of cabazitaxel, and the incidence of febrile neutropenia with the 25 mg/m^2 dose was 8–12% [21–23]. A lower incidence of febrile neutropenia (2.1%) has been observed with the 20 mg/m^2 dose of cabazitaxel, which maintained 50% of the OS benefit of the 25 mg/m^2 dose versus mitoxantrone in TROPIC [23]. Although 20 mg/m^2 is a recommended starting dose in the USA, the recommended starting dose in Europe is 25 mg/m^2 [26,27]. In a large European compassionate use program including 746 patients with mCRPC treated with 25 mg/m^2 cabazitaxel (including 225 patients aged ≥70 yr), the rate of febrile neutropenia did not exceed 5.6%, but prophylactic G-CSF was administered at cycle 1 in ~60% of older patients [28]. In the same study, a multivariate analysis demonstrated that patients aged ≥75 yr with a neutrophil count of <4000/mm^3 at baseline who did not receive G-CSF during cycle 1 were independently associated with a risk of neutropenic complications [28]. Conversely, this risk was reduced by 30% when G-CSF was used from cycle 1 [28]. Although patients enrolled in clinical trials need to satisfy stringent inclusion and exclusion criteria, and are, by definition, fitter than those seen in daily clinical practice, the CARD trial results suggest that both patients and physicians can be reassured that cabazitaxel treatment along with prophylactic use of G-CSF from cycle 1 is effective and has a manageable safety profile even in older patients.

5. Conclusions

In this analysis of the CARD study, cabazitaxel significantly improved rPFS (prespecified analysis) compared with abiraterone or enzalutamide among patients aged ≥70 yr and younger patients with mCRPC previously treated with docetaxel and the alternative AR-targeted agent. OS, PSA response, objective tumor response, and pain response also favored cabazitaxel (post hoc analyses), regardless of age. Overall, patients aged ≥70 yr experienced a higher frequency of grade 3 TEAEs than younger patients, but these TEAEs differed between cabazitaxel and the AR-targeted agents. These results support the use of cabazitaxel over abiraterone or enzalutamide as the standard of care, irrespective of age, in patients with mCRPC previously treated with docetaxel and the alternative AR-targeted agent.

***Author contributions*:** Cora N. Sternberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sternberg, Castellano, de Bono, Fizazi, Tombal, Wülfing, Ozatilgan, Geffriaud-Ricouard, de Wit.

Acquisition of data: Sternberg, Castellano, de Bono, Fizazi, Kramer, Eymard, Bamias, Carles, Iacovelli, Melichar, Sverrisdóttir, Theodore, Feyerabend, Helissey, de Wit.
Analysis and interpretation of data: Sternberg, Castellano, de Bono, Fizazi, Tombal, Wülfing, Poole, Ozatilgan, Geffriaud-Ricouard, de Wit.
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Appendix A. Supplementary data

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