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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 previously received docetaxel and progressed ≤12 months on the alternative agent (abiraterone/enzalutamide). Objective: Assess cabazitaxel versus abiraterone/enzalutamide in older (≥70 years) and younger (<70 years) patients in CARD. Design, setting and participants: Patients with mCRPC were randomized 1:1 to cabazitaxel (25mg/m 2 plus prednisone and granulocyte colony-stimulating factor) versus abiraterone (1000mg plus prednisone) or enzalutamide (160mg).

	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: Of 255 patients randomized, 135 were aged ≥70 years (median 76). Cabazitaxel, compared with abiraterone/enzalutamide, significantly improved median rPFS in older (8.2 vs 4.5 months; HR=0.58; 95% CI=0.38–0.89; p=0.01) and younger patients (7.4 vs 3.2 months; HR=0.47; 95% CI=0.30–0.74; p<0.01). Median OS of cabazitaxel versus abiraterone/enzalutamide was 13.9 versus 9.4 months in older patients (HR=0.66; 95% CI=0.41–1.06; p=0.08) and 13.6 versus 11.8 months in younger patients (HR=0.66; 95% CI=0.41–1.08; p=0.09). PFS, prostate-specific antigen, tumor and pain responses favored cabazitaxel, regardless of age. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 57.8% versus 49.3% of older patients receiving cabazitaxel versus abiraterone/enzalutamide and 48.4% versus 42.1% of younger patients. In older patients, cardiac AEs 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: Using clinical trial data, cabazitaxel improved survival versus abiraterone/enzalutamide with manageable side effects in patients with mCRPC who previously received docetaxel and the alternative agent (abiraterone/enzalutamide), irrespective of age.
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Title: Efficacy and safety of cabazitaxel versus abiraterone or enzalutamide in older patients with metastatic castration-resistant prostate cancer in the CARD study

Corresponding author: Professor Cora N. Sternberg

Dear Professor Catto,

We again thank the reviewer for their comments. We have provided individual detailed responses to each of the comments, which are captured in the reply below.

Kind regards,

Professor Cora N. Sternberg

1. Since there are no significant interactions between treatment and age group for rPFS, OS or PFS, there is no justification to present stratified results and the results should only be presented for the overall population.

In the primary CARD publication (de Wit R, et al. N Engl J Med. 2019), cabazitaxel was superior to abiraterone or enzalutamide in patients aged < 70 years and ≥ 70 years. However, management of older patients is challenging and although age should not be considered a barrier to receiving chemotherapy, chemotherapy is often avoided in older patients as AR-targeted agents can be given orally and are perceived as less toxic than chemotherapy (Caffo O, et al. Clin Interv Aging. 2016; Oh WK, et al. Urol Oncol. 2018). There have been important sub-analyses for abiraterone (Mulders PFA, et al. Eur Urol. 2014; Smith MR, et al. J Urol. 2015) and enzalutamide (Sternberg CN, et al. Ann Oncol. 2014) evaluating efficacy in older patients. As a result, although cabazitaxel was superior to abiraterone or enzalutamide regardless of age in the primary analysis, there is a great unmet need to explore the impact of age on the efficacy and safety of chemotherapy. The objective of this manuscript was to further explore whether age influenced efficacy outcomes and safety.

From a statistical perspective, we note that statistical significance is determined by both effect size and sample size. Our studies are often not powered to detect statistical differences among subgroups (i.e. not powered to find significant p-value-for-interactions), so focusing purely on the statistical significance of the interaction has the potential to miss important effect size differences. This approach is supported by the guidelines that state: “Drawing conclusions for research or clinical practice from a clinical research study requires evaluation of the strengths and weakness of study methodology, the results of other

pertinent data published in the literature, biological plausibility, and effect size. Sound and nuanced scientific judgment cannot be replaced by just checking whether one of the many statistics in a paper is or is not P < 0.05."

By reporting stratified analyses in these important subgroups, we are showing consistency in the effect sizes, which is of relevance to the clinical community. Lastly, other studies routinely show stratified results; it is important to see these estimates across studies and useful for potential future meta-analyses.

2. See Guideline 4.16 and truncate the Kaplan-Meier plots when numbers are low.

We have amended the graphs as directed. Please see the updated manuscript and below for convenience.

Figure 2. Kaplan–Meier estimates. (a) Radiographic progression-free survival according to age: Patients ≥ 70 years of age

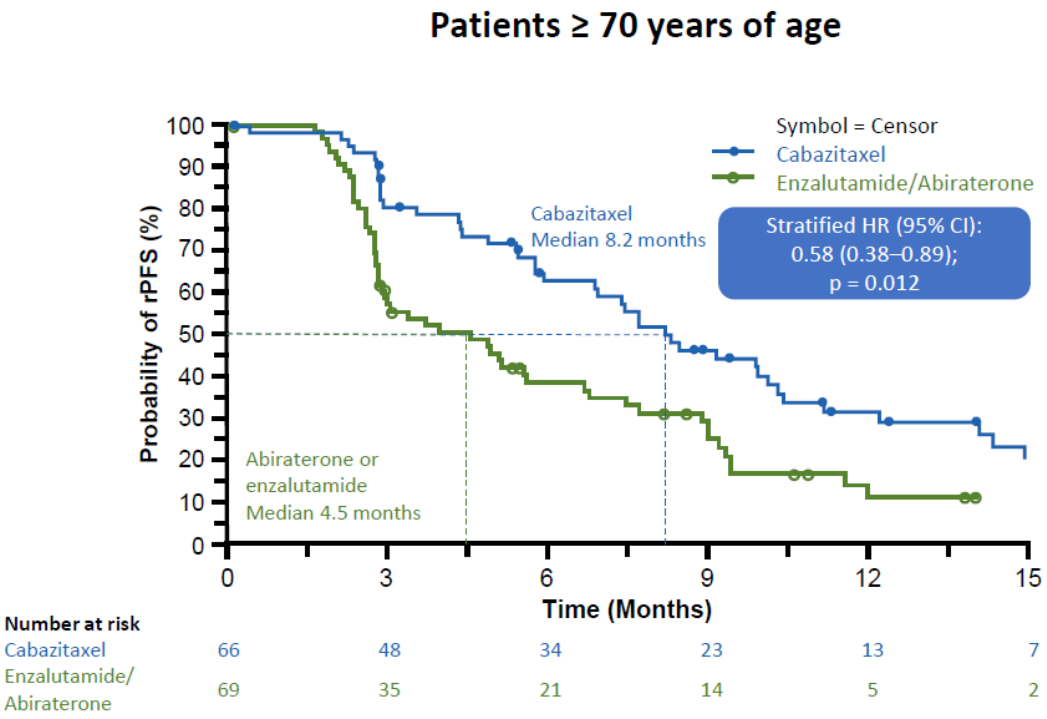


Figure 2. Kaplan–Meier estimates. (a) Radiographic progression-free survival according to age: Patients < 70 years of age

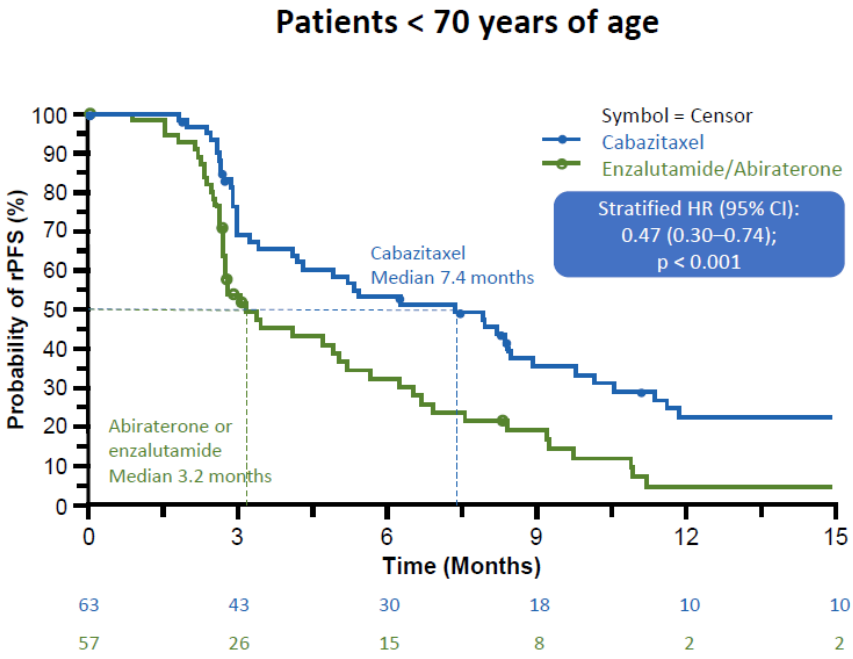


Figure 2. Kaplan–Meier estimates. (b) Overall survival according to age: Patients ≥ 70 years of age

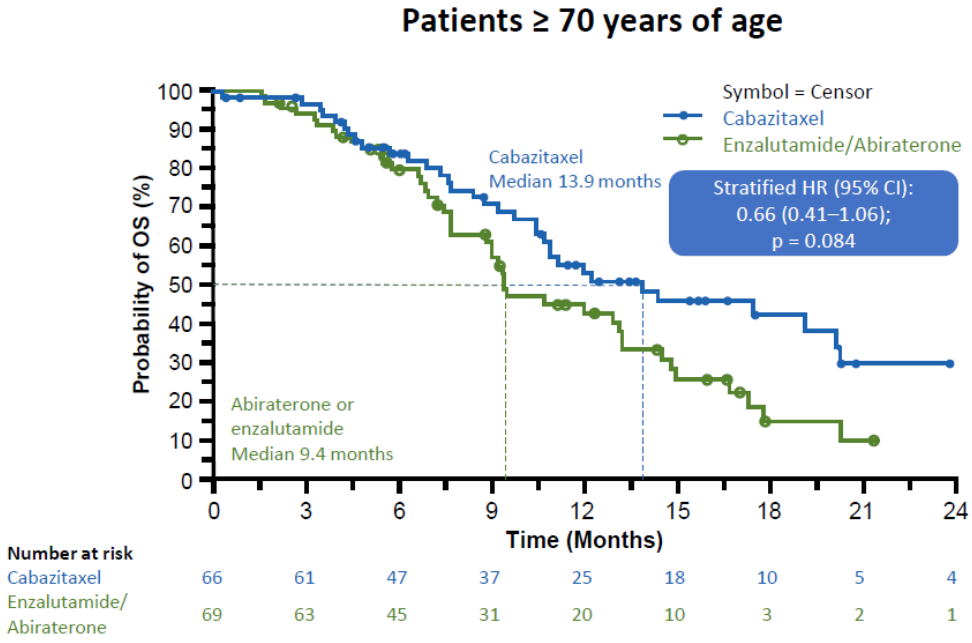


Figure 2. Kaplan–Meier estimates. (b) Overall survival according to age: Patients < 70 years of age

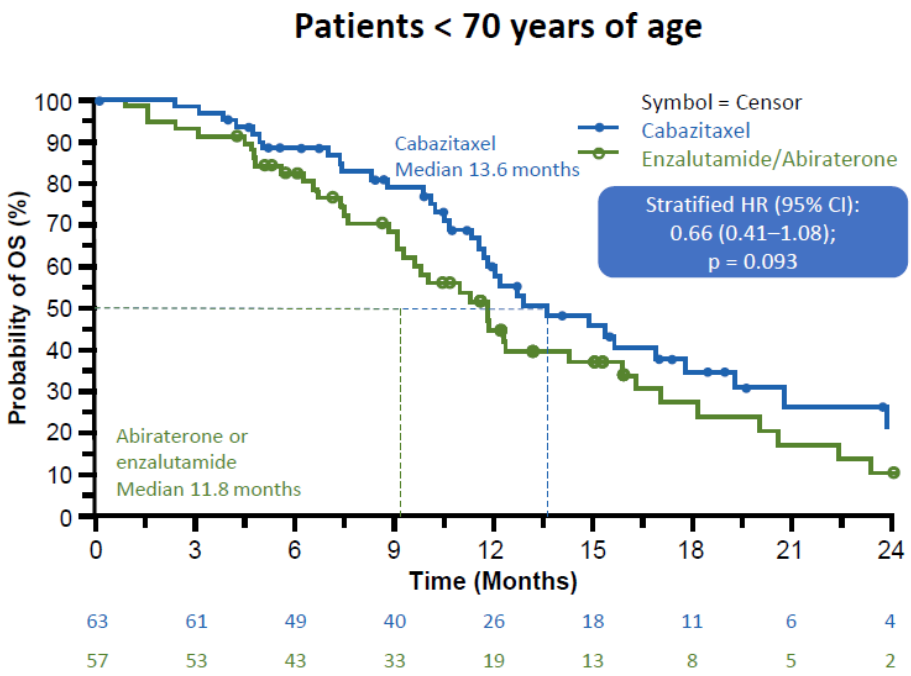


Figure 2. Kaplan–Meier estimates. (c) Progression-free survival according to age: Patients ≥ 70 years of age

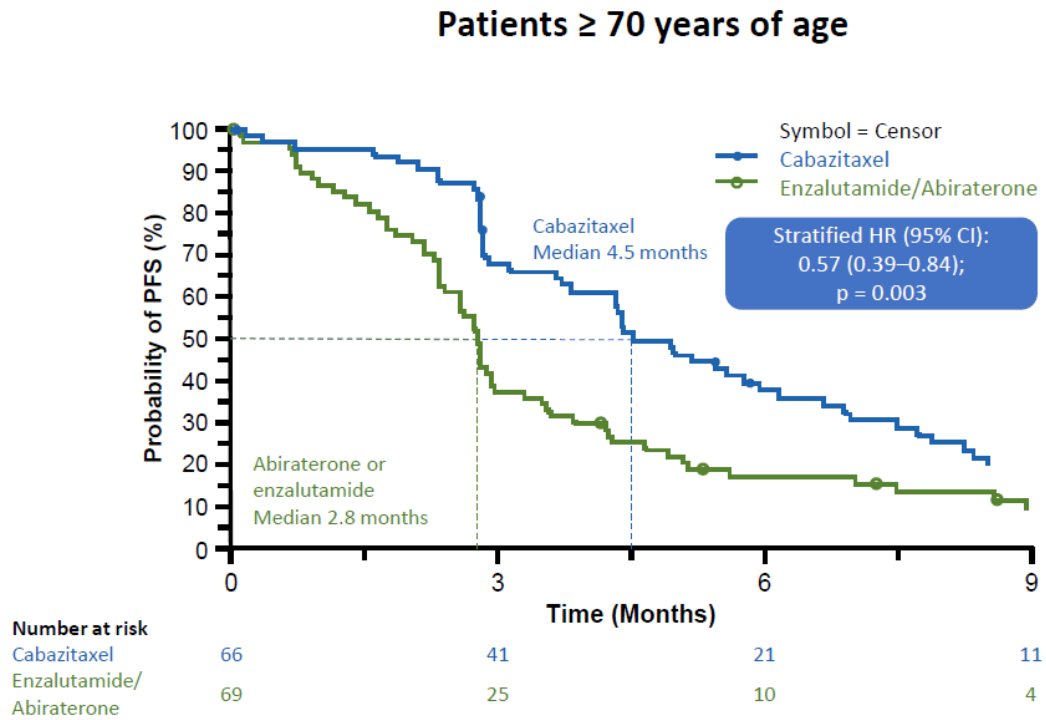
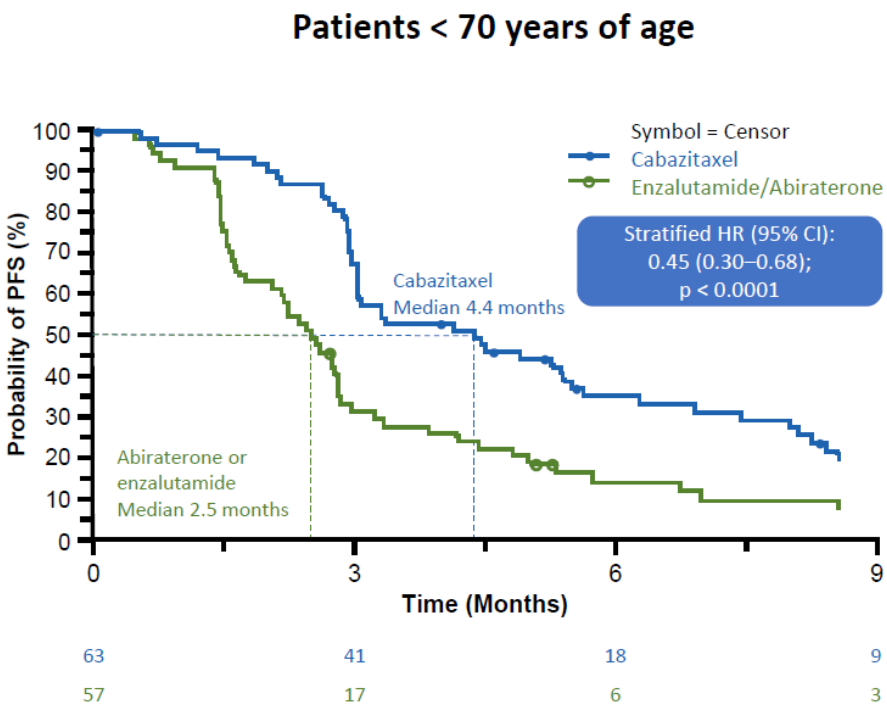


Figure 2. Kaplan–Meier estimates. (c) Progression-free survival according to age: Patients < 70 years of age



Title

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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Key words: Elderly; Cabazitaxel; mCRPC; Prostate cancer

Abstract

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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 previously received docetaxel and progressed ≤12 months on the alternative agent (abiraterone/enzalutamide).

Objective:

Assess cabazitaxel versus abiraterone/enzalutamide in older (≥70 years) and younger (<70 years) patients in CARD.

Design, setting and participants:

Patients with mCRPC were randomized 1:1 to cabazitaxel (25mg/m^2 plus prednisone and granulocyte colony-stimulating factor) versus abiraterone (1000mg plus prednisone) or enzalutamide (160mg).

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:

Of 255 patients randomized, 135 were aged ≥70 years (median 76). Cabazitaxel, compared with abiraterone/enzalutamide, significantly improved median rPFS in older (8.2 vs 4.5

months; HR=0.58; 95% CI=0.38–0.89; p=0.012) and younger patients (7.4 vs 3.2 months; HR=0.47; 95% CI=0.30–0.74; p<0.001). Median OS of cabazitaxel versus abiraterone/enzalutamide was 13.9 versus 9.4 months in older patients (HR=0.66; 95% CI=0.41–1.06; p=0.084) and 13.6 versus 11.8 months in younger patients (HR=0.66; 95% CI=0.41–1.08; p=0.093). PFS, prostate-specific antigen, 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 AEs 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:

Using clinical trial data, cabazitaxel improved survival versus abiraterone/enzalutamide with manageable side effects in patients with mCRPC who previously received docetaxel and the alternative agent (abiraterone/enzalutamide), irrespective of age.

Take home message

Word count: 38 (limit: 40 words)

From the CARD study, we demonstrate that cabazitaxel improves efficacy outcomes versus abiraterone/enzalutamide in patients with metastatic castration-resistant prostate cancer who previously received docetaxel and progressed ≤12 months on the alternative androgen receptor-targeted agent (abiraterone/enzalutamide), irrespective of age.

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 years 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 years [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 is little data informing the optimal treatment choice with respect to both 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 months while receiving the 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 years of age) and younger (<70 years of age) patient subgroups. Post hoc analyses of other secondary endpoints were also assessed in these patient subgroups. The cut-offs of ≥70 and <70 years of age were selected based on the International Society of Geriatric Oncology guidelines on prostate cancer [9].

Materials and Methods

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 previously described [8]. The study was designed to compare cabazitaxel with abiraterone or enzalutamide in patients with mCRPC who had been previously treated with ≥3 cycles of docetaxel and who had progressed within 12 months of treatment with the alternative AR-targeted agent, received before or after docetaxel. Eligible patients received intravenous cabazitaxel 25 mg/m^2 every 3 weeks, 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 weeks in each arm; treatment continued until radiographic progression, unacceptable toxicity or change in treatment.

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 cut-off 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 weeks apart. A tumor response was defined as a partial or complete

response according to RECIST v1.1, 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 weeks apart without an increase in analgesic usage score [11]. Treatment-emergent AEs (TEAEs), regardless of causality, were defined by first occurring or worsening of an AE after the first dose and up to 30 days after the last study drug administration. TEAEs were assessed using the National Cancer Institute Common Terminology Criteria for AEs v4.0.

Statistical analysis

For this analysis, patients were classified into two age subgroups, ≥70 (older) and <70 years of age (younger). This age cut-off was selected based upon the International Society of Geriatric Oncology guidelines on prostate cancer [9]. rPFS analysis by age subgroup (≥70 vs <70 years of age) was pre-specified; analyses of secondary endpoints (OS, PFS, PSA, tumor and pain responses) by these age subgroups were post hoc. Analyses conducted in patients aged ≥75 years 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-hazards 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, tumor and pain response comparisons between treatment groups a stratified Cochran-Mantel Haenszel test was used. The log-rank tests, Cox proportional-hazards 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 months) and timing of AR-targeted agent as specified at the time of randomization (before vs after docetaxel).

Results

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) (**Figure 1**). Of them, 135 patients were aged ≥70 years (cabazitaxel arm, n = 66; abiraterone or enzalutamide arm, n = 69) with a median age of 76 years. Compared with patients aged ≥70 years, younger patients had higher rates of Gleason's 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 years, those receiving abiraterone or enzalutamide versus cabazitaxel had higher rates of Gleason score 8–10 (58% vs 42%) and metastatic disease (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 months and the median event free time for rPFS, OS and PFS was 5.4, 10.6 and 5.2 months, respectively. The median duration of treatment was longer for patients receiving cabazitaxel compared with patients receiving abiraterone or enzalutamide, regardless of age (patients aged ≥70 years: 5.1 vs 3.0 months; younger patients: 5.5 vs 2.8 months). The proportion of patients discontinuing treatment was similar among patients receiving cabazitaxel versus abiraterone or enzalutamide both in patients aged ≥70 years (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**).

Efficacy

As previously reported, the median rPFS for the overall population was 8.0 months with cabazitaxel versus 3.7 months with abiraterone or enzalutamide (HR [95% CI] = 0.54 [0.40–0.73]; p < 0.001) [8]. In patients aged ≥70 years, the median rPFS was 8.2 months with cabazitaxel versus 4.5 months with abiraterone or enzalutamide (HR [95% CI] = 0.58 [0.38–0.89]; p = 0.012; **Figure 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 years, the median rPFS was also significantly improved with cabazitaxel versus abiraterone or enzalutamide (7.4 vs 3.2 months; HR [95% CI] = 0.47 [0.30–0.74]; p < 0.001; **Figure 2a**).

The median OS (main secondary endpoint) was numerically longer for cabazitaxel compared with abiraterone or enzalutamide in patients aged ≥70 years (13.9 vs 9.4 months; HR [95% CI] = 0.66 [0.41–1.06]; p = 0.084) and younger patients (13.6 vs 11.8 months; HR [95% CI] = 0.66 [0.41–1.08]; p = 0.093) but differences did not reach statistical significance (**Figure 2b**); the sensitivity analysis HR (95% CI) was 0.69 (0.42–1.15). In patients aged ≥70 years, the median PFS was 4.5 months with cabazitaxel versus 2.8 months with abiraterone or enzalutamide (HR [95% CI] = 0.57 [0.39–0.84]; p = 0.003; **Figure 2c**); the sensitivity analysis HR (95% CI) was 0.55 (0.36–0.83). Among patients aged <70 years, a significant improvement in median PFS was also observed with cabazitaxel versus abiraterone or enzalutamide (4.4 vs 2.5 months; HR [95% CI] = 0.45 [0.30–0.68]; p < 0.001; **Figure 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 years (**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 years, 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, regardless of age (**Figure 3**). Tumor response in patients aged ≥70 years numerically favored cabazitaxel versus abiraterone or enzalutamide but this difference did not reach statistical significance.

Safety

Almost all patients had a TEAE of any grade, irrespective of age and treatment (**Table 2** and **Supplementary Table 4**). Serious TEAEs of any grade were more frequent in patients aged ≥70 years compared with younger patients, both in the cabazitaxel (45% vs 32%) and abiraterone or enzalutamide arms (45% vs 33%). Any grade ≥3 TEAEs were also more frequent in patients aged ≥70 years compared with younger patients, both in the cabazitaxel (58% vs 48%) and abiraterone or enzalutamide arms (49% vs 42%). Grade ≥3 TEAEs that occurred more frequently in patients aged ≥70 years receiving cabazitaxel compared with 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 years receiving abiraterone or enzalutamide compared with 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 compared with patients receiving abiraterone or enzalutamide among patients aged ≥70 years (25% vs 12%) and younger patients (15% vs

5.3%). TEAEs leading to death were less frequent in patients receiving cabazitaxel compared with abiraterone or enzalutamide among patients aged ≥70 years (9.4% vs 15%) and younger patients (1.6% vs 7.0%). In patients aged ≥70 years, grade 5 TEAEs occurred in six patients receiving cabazitaxel (disease progression [n = 2], urinary tract infection [n = 1], head injury [n = 1], septic shock [n = 1] or aspiration [n = 1]) and 10 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 ≥1 dose reduction was lower among patients receiving cabazitaxel compared with abiraterone or enzalutamide among patients aged ≥70 years (20% vs 39%) and younger patients (23% vs 37%). The TEAE profiles of cabazitaxel and abiraterone/enzalutamide were further investigated using three different age cut-offs (≥75, 70–74 and <70; **Supplementary Table 5**).

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 10 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 they 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 years 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 months on the alternative AR-targeted agent. The results demonstrate that cabazitaxel provides a greater benefit compared with 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 aged ≥70 years (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 and PSA, tumor and pain responses) consistently favored cabazitaxel compared with abiraterone or enzalutamide, regardless of age [19].

Interestingly, median rPFS was slightly shorter for patients aged <70 years (cabazitaxel: 7.4 months; abiraterone/enzalutamide: 3.2 months) compared with patients aged ≥70 years (cabazitaxel: 8.2 months; abiraterone/enzalutamide: 4.5 months). This might be a reflection of the more aggressive baseline clinical features of the younger patient population (higher rates of Gleason's 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 years receiving cabazitaxel (21% vs 12%). As liver and lung metastases are often associated with more aggressive disease, this may be a contributing factor for the shorter rPFS observed [20].

The percentage of patients who experienced serious TEAEs of any grade was higher among patients aged ≥70 years versus younger patients in both the cabazitaxel (45% vs 32%) and abiraterone or enzalutamide (45% vs 33%) treatment arms. Similarly, TEAEs leading to death occurred more often in patients aged ≥70 years versus younger patients (12% vs 4.2%); however, lower rates of TEAEs leading to death were observed in patients receiving cabazitaxel compared with abiraterone or enzalutamide across both age subgroups. This would suggest that patients aged ≥70 years 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 years and younger patients. The rate of febrile neutropenia is lower than in previous Phase III 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 pre-specified 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 a different underlying mCRPC biology. However, sensitivity analyses adjusted for these imbalances did not alter the findings.

The CARD results are important for several reasons. Firstly, they provide additional confirmation that patients with mCRPC progressing following receipt of an AR-targeted agent respond sub-optimally to a second alternative AR-targeted agent, as already shown by several prospective randomized trials [24, 25]. Secondly, 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 in previous Phase III 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 years), 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 years 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.

Conclusions

In this analysis of the CARD study, cabazitaxel significantly improved rPFS (pre-specified analysis) compared with abiraterone or enzalutamide among patients aged ≥70 years 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 years experienced a higher frequency of grade 3 TEAEs compared with 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 standard of care, irrespective of age, in patients with mCRPC previously treated with docetaxel and the alternative AR-targeted agent.

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Tables and figures

Table 1. Patient baseline and disease characteristics

	≥70 years of age		<70 years of age	
	Cabazitaxel n = 66	Abiraterone or enzalutamide n = 69	Cabazitaxel n = 63	Abiraterone or enzalutamide n = 57
Median age at screening, years (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 (58.0)	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.

Table 2. Treatment-emergent adverse events according to age

	≥70 years of age				<70 years of age			
Patients, n (%)	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)

[a] The cut-off 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, musculoskeletal chest pain; [c] Including neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy; [d] Including acute kidney injury, renal failure, renal impairment, hydronephrosis and pyelocaliectasis; [e] Including hypertension, hypertensive crisis; [f] Including sciatica, radiculopathy, spinal cord compression.

TEAE, treatment-emergent adverse event.

Figure 1. CONSORT diagram

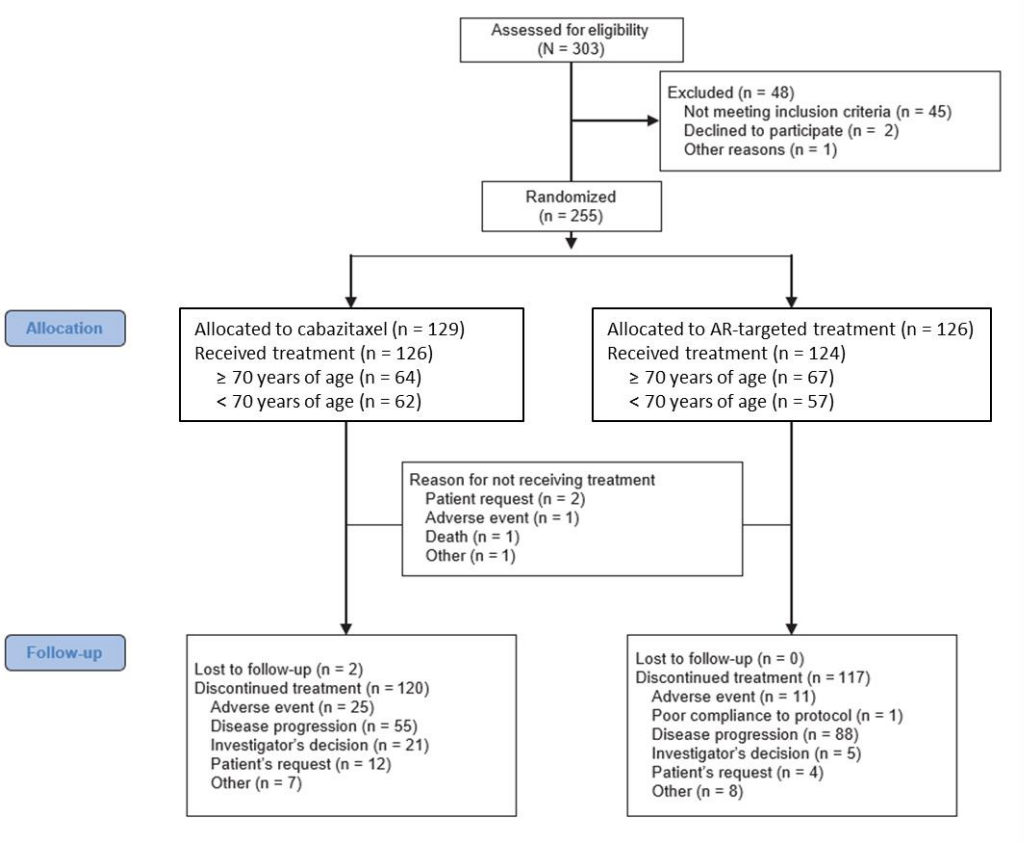
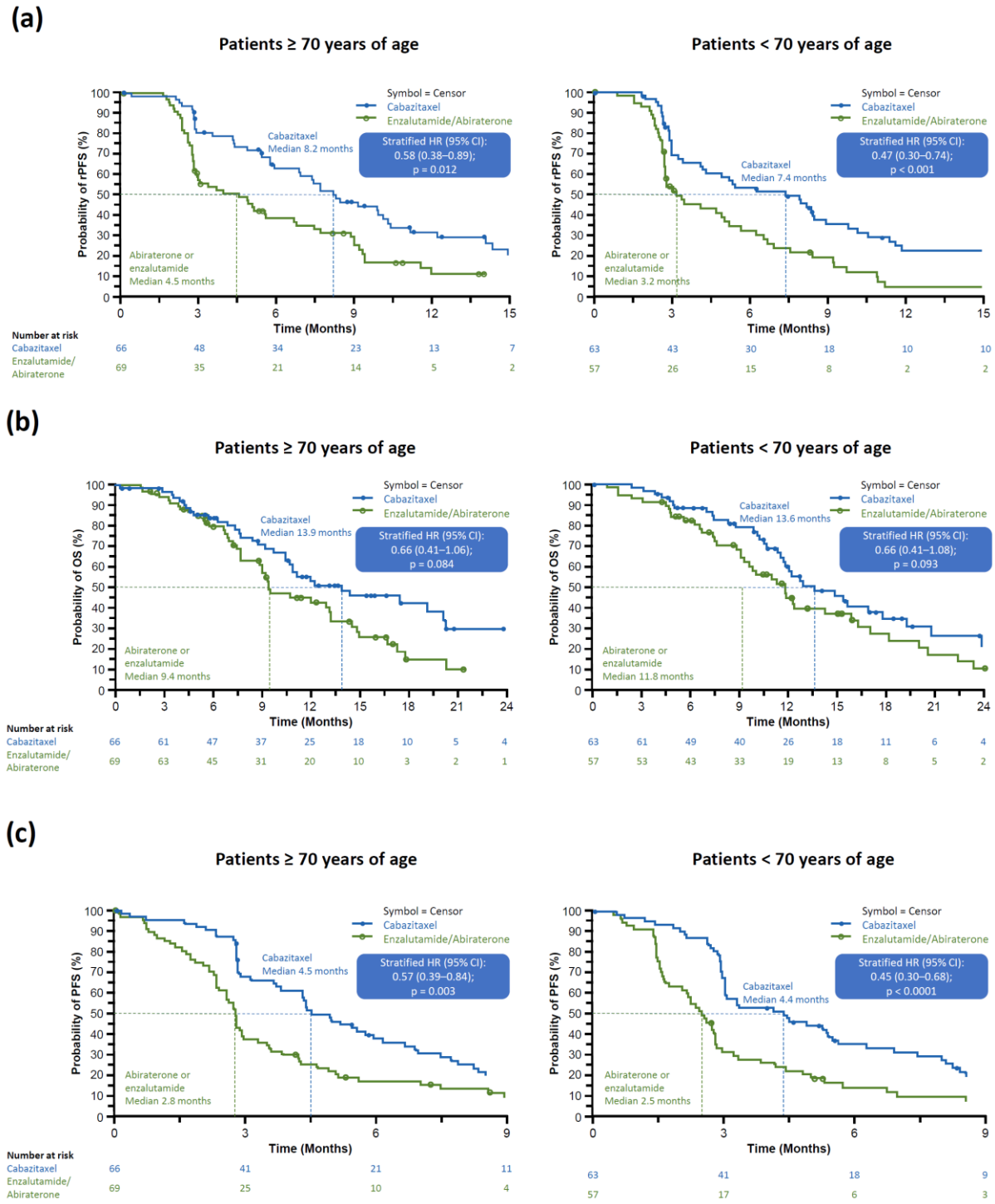
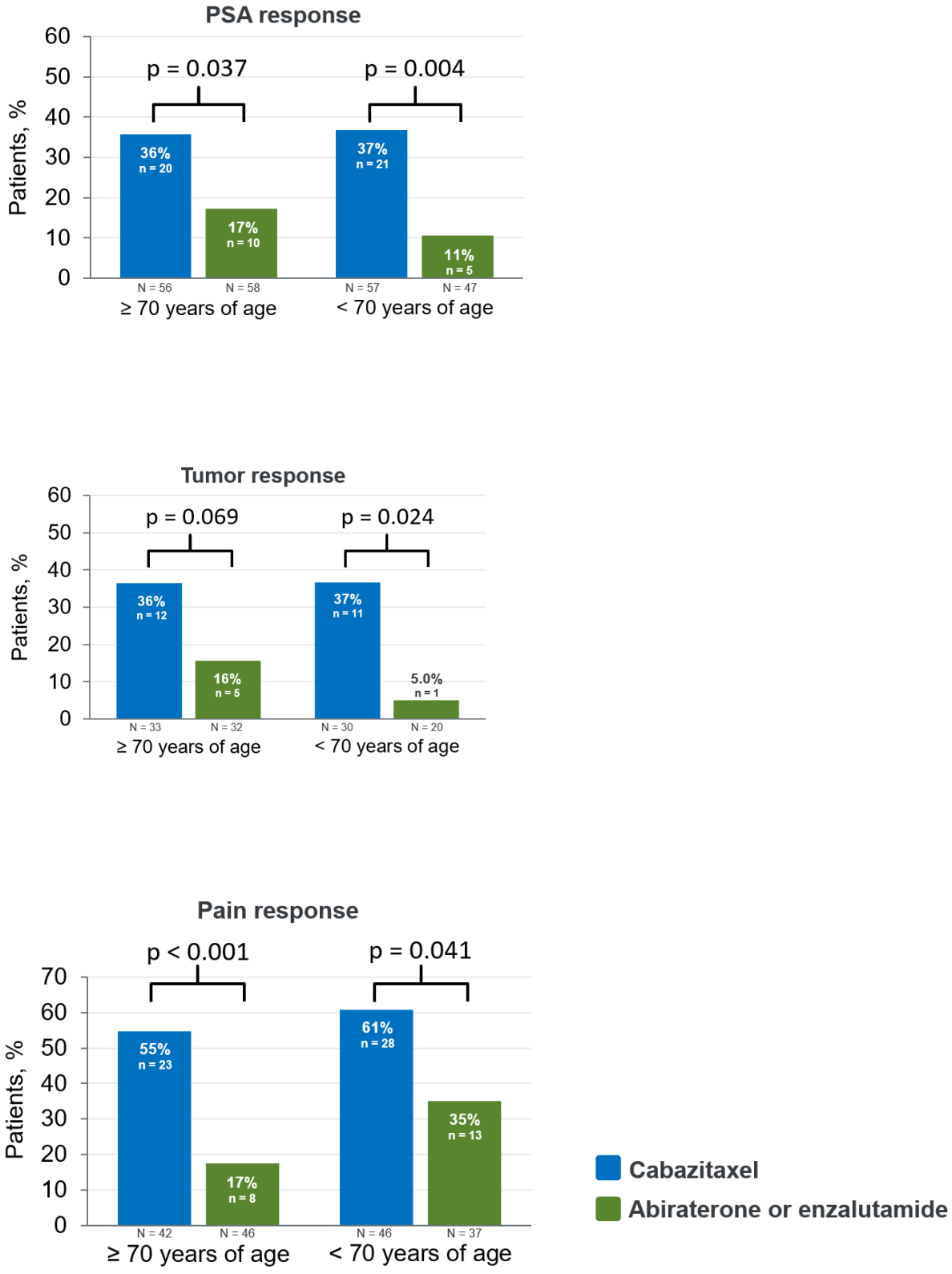


Figure 2. Kaplan–Meier estimates. (a) Radiographic progression-free survival according to age, (b) Overall survival according to age and (c) Progression-free survival according to age.



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.

Figure 3. Prostate-specific antigen, tumor and pain response according to age



PSA, prostate-specific antigen.

Supplementary Table 1. Treatment exposure according to age

	≥70 years of age		<70 years of age	
	Cabazitaxel n = 64[a]	Abiraterone or enzalutamide n = 67[a]	Cabazitaxel n = 62[a]	Abiraterone or enzalutamide n = 57[a]
Treatment duration				
Median duration of treatment exposure, weeks (range)	22.0 (3.0–63.4)	12.9 (3.0–87.3)	24.0 (6.0–87.9)	12.0 (2.0–141.3)
Median number of cycles, n (range)	7.0 (1.0–20.0)	4.0 (1.0–28.0)	7.5 (2.0–29.0)	4.0 (1.0–45.0)
Treatment reduction				
Patients with ≥1 cycle administered at a reduced dose, n (%)	13 (20)	26 (39)	14 (23)	21 (37)
	Cabazitaxel n = 66[b]	Abiraterone or enzalutamide n = 69[b]	Cabazitaxel n = 63[b]	Abiraterone or enzalutamide n = 57[b]
Treatment discontinuation				
Patients with discontinued treatment, n (%)	63 (96)	64 (93)	57 (91)	53 (93)
Reasons for discontinuation, n (%)				
Disease progression	21 (32)	49 (71)	34 (54)	39 (68)
Adverse event	16 (24)	8 (12)	9 (14)	3 (5.3)
Investigator's decision	16 (24)[c]	2 (2.9)	5 (7.9)	3 (5.3)
Patient's request	8 (12)	2 (2.9)	4 (6.3)	2 (3.5)
Other	2 (3.0)	3 (4.3)	5 (7.9)	5 (8.8)
Lost to follow-up	0	0	0	0
Poor compliance to protocol	0	0	0	1 (1.8)

[a] Safety population (randomized and received at least one dose of study treatment); [b] Randomized population; [c] Often following patient receipt of 10 cycles of cabazitaxel.

Supplementary Table 2. Summary of efficacy endpoints in patients ≥75 versus <75 years of age

	≥75 years of age		<75 years of age	
Median, months (95% CI)	Cabazitaxel n = 45	Abiraterone or enzalutamide n = 34	Cabazitaxel n = 84	Abiraterone or enzalutamide n = 92
rPFS	8.3 (6.9–10.4)	4.9 (3.0–9.0)	8.0 (5.0–9.0)	3.2 (2.8–5.1)
OS	14.4 (9.8–26.5)	9.2 (7.5–16.7)	12.9 (11.7–17.7)	11.8 (9.4–13.2)
PFS	5.4 (3.7–6.9)	2.9 (2.4–4.2)	4.4 (3.0–5.3)	2.6 (2.2–2.8)

CI, confidence interval; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Supplementary Table 3. Patient event and censoring data

	Overall		≥70 years of age		<70 years of age	
Patients,[a] n (%)	Cabazitaxel n = 129	Abiraterone or enzalutamide n = 126	Cabazitaxel n = 66	Abiraterone or enzalutamide n = 69	Cabazitaxel n = 63	Abiraterone or enzalutamide n = 57
rPFS						
Events	95 (74)	101 (80)	48 (73)	53 (77)	47 (75)	48 (84)
Censored	34 (26)	25 (20)	18 (27)	16 (23)	16 (25)	9 (16)
OS						
Events	70 (54)	83 (66)	35 (53)	43 (62)	35 (56)	40 (70)
Censored	59 (46)	43 (34)	31 (47)	26 (38)	28 (44)	17 (30)
PFS						
Events	111 (86)	115 (91)	57 (86)	61 (88)	54 (86)	54 (95)
Censored	18 (14)	11 (8.7)	9 (14)	8 (12)	9 (14)	3 (5.3)

[a] *Cut-off date: March 27th, 2019.*

OS, overall survival; PFS, progression-free survival; rPFS, radiological PFS.

Supplementary Table 4. Laboratory abnormalities of clinical interest according to age

	≥70 years of age				<70 years of age			
Patients, n (%)	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
Anemia	62 (98)	2 (3.2)	66 (99)	3 (4.5)	62 (100)	8 (13)	52 (91)	3 (5.3)
Leukopenia	53 (84)	25 (40)	20 (30)	1 (1.5)	40 (65)	16 (26)	21 (37)	1 (1.8)
Neutropenia	49 (79)	30 (48)	6 (9.0)	2 (3.0)	32 (53)	25 (41)	2 (3.5)	2 (3.5)
Thrombocytopenia	26 (41)	2 (3.2)	12 (18)	1 (1.5)	25 (40)	2 (3.2)	8 (14)	1 (1.8)

Supplementary Table 5. Treatment-emergent adverse events according to age

	≥75 years of age				70–74 years of age				<70 years of age			
Patients, n (%)	Cabazitaxel n = 44		Abiraterone or enzalutamide n = 34		Cabazitaxel n = 20		Abiraterone or enzalutamide n = 33		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 grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	44 (100)	29 (66)	33 (97)	18 (53)	20 (100)	8 (40)	30 (91)	15 (46)	60 (97)	30 (48)	54 (95)	24 (42)
Any serious TEAE	26 (59)	21 (48)	18 (53)	18 (53)	3 (15)	3 (15)	12 (36)	12 (36)	20 (32)	16 (26)	19 (33)	17 (30)
Any TEAE leading to treatment discontinuation	14 (32)	-	6 (18)	-	2 (10)	-	2 (6.1)	-	9 (15)	–	3 (5.3)	–
Any TEAE leading to death	5 (11)	-	7 (21)	-	1 (5.0)	-	3 (9.1)	-	1 (1.6)	–	4 (7.0)	–
Frequent TEAEs (grade ≥3 TEAEs reported in ≥3% in any subgroup)[a]												
Asthenia or fatigue	26 (59)	3 (6.8)	16 (47)	1 (2.9)	12 (60)	1 (5.0)	13 (39)	0	29 (47)	1 (1.6)	16 (28)	2 (3.5)
Diarrhea	21 (48)	4 (9.1)	2 (5.9)	1 (2.9)	6 (30)	0	1 (3.0)	0	23 (37)	0	6 (11)	0
Infection	14 (32)	3 (6.8)	9 (27)	4 (12)	5 (25)	0	8 (24)	2 (6.1)	21 (34)	6 (9.7)	9 (16)	3 (5.3)
Nausea or vomiting	11 (25)	0	8 (24)	0	4 (20)	0	13 (39)	1 (3.0)	18 (29)	0	8 (14)	1 (1.8)
Decreased appetite	10 (23)	1 (2.3)	4 (12)	0	2 (10)	0	9 (27)	1 (3.0)	5 (8.1)	0	6 (11)	2 (3.5)
Musculoskeletal pain or discomfort[b]	9 (21)	0	12 (35)	1 (2.9)	9 (45)	1 (5.0)	14 (42)	2 (6.1)	16 (26)	1 (1.6)	23 (40)	4 (7.0)
Peripheral neuropathy[c]	7 (16)	3 (6.8)	1 (2.9)	0	4 (20)	0	1 (3.0)	0	14 (23)	1 (1.6)	2 (3.5)	0
Hematuria	5 (11)	0	3 (8.8)	1 (2.9)	2 (10)	0	1 (3.0)	1 (3.0)	12 (19)	1 (1.6)	3 (5.3)	0
Renal disorder[d]	4 (9.1)	2 (4.5)	6 (18)	2 (5.9)	1 (5.0)	0	3 (9.1)	3 (9.1)	3 (4.8)	2 (3.2)	5 (8.8)	5 (8.8)
Cardiac disorder	4 (9.1)	0	8 (24)	6 (18)	0	0	0	0	4 (6.5)	1 (1.6)	2 (3.5)	0
Hypertensive disorder[e]	2 (4.5)	1 (2.3)	4 (12)	1 (2.9)	0	0	3 (9.1)	1 (3.0)	3 (4.8)	2 (3.2)	3 (5.3)	1 (1.8)
Febrile neutropenia	2 (4.5)	2 (4.5)	0	0	0	0	0	0	2 (3.2)	2 (3.2)	0	0
Disease progression	1 (2.3)	1 (2.3)	4 (12)	4 (12)	2 (10)	2 (10)	4 (12)	3 (9.1)	0	0	0	0

Spinal cord or nerve-root disorder[f]	1 (2.3)	1 (2.3)	4 (12)	3 (8.8)	1 (5.0)	1 (5.0)	0	0	4 (6.5)	1 (1.6)	5 (8.8)	2 (3.5)
Urinary tract obstruction	0	0	0	0	0	0	3 (9.1)	3 (9.1)	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	0	0	2 (3.2)	2 (3.2)	1 (1.8)	1 (1.8)

[a] The cut-off 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, musculoskeletal chest pain; [c] Including neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy; [d] Including acute kidney injury, renal failure, renal impairment, hydronephrosis and pyelocaliectasis; [e] Including hypertension, hypertensive crisis; [f] Including sciatica, radiculopathy, spinal cord compression.

TEAE, treatment-emergent adverse event.

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Title

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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Current counts

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Abstract: 311 (Limit: 300)
Tables and figure: 5 (Limit: 6)
References: 28 (Limit 40)

Key words: Elderly; Cabazitaxel; mCRPC; Prostate cancer

Abstract

Current word count: 311 (Limit: 300)

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 previously received docetaxel and progressed ≤12 months on the alternative agent (abiraterone/enzalutamide).

Objective:

Assess cabazitaxel versus abiraterone/enzalutamide in older (≥70 years) and younger (<70 years) patients in CARD.

Design, setting and participants:

Patients with mCRPC were randomized 1:1 to cabazitaxel (25mg/m^2 plus prednisone and granulocyte colony-stimulating factor) versus abiraterone (1000mg plus prednisone) or enzalutamide (160mg).

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:

Of 255 patients randomized, 135 were aged ≥70 years (median 76). Cabazitaxel, compared with abiraterone/enzalutamide, significantly improved median rPFS in older (8.2 vs 4.5

months; HR=0.58; 95% CI=0.38–0.89; p=0.012) and younger patients (7.4 vs 3.2 months; HR=0.47; 95% CI=0.30–0.74; p<0.001). Median OS of cabazitaxel versus abiraterone/enzalutamide was 13.9 versus 9.4 months in older patients (HR=0.66; 95% CI=0.41–1.06; p=0.084) and 13.6 versus 11.8 months in younger patients (HR=0.66; 95% CI=0.41–1.08; p=0.093). PFS, prostate-specific antigen, 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 AEs 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:

Using clinical trial data, cabazitaxel improved survival versus abiraterone/enzalutamide with manageable side effects in patients with mCRPC who previously received docetaxel and the alternative agent (abiraterone/enzalutamide), irrespective of age.

Take home message

Word count: 38 (limit: 40 words)

From the CARD study, we demonstrate that cabazitaxel improves efficacy outcomes versus abiraterone/enzalutamide in patients with metastatic castration-resistant prostate cancer who previously received docetaxel and progressed ≤12 months on the alternative androgen receptor-targeted agent (abiraterone/enzalutamide), irrespective of age.

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 years 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 years [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 is little data informing the optimal treatment choice with respect to both 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 months while receiving the 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

abirateronе/enzalutamide on the primary endpoint (rPFS) in older (≥70 years of age) and younger (<70 years of age) patient subgroups. Post hoc analyses of other secondary endpoints were also assessed in these patient subgroups. The cut-offs of ≥70 and <70 years of age were selected based on the International Society of Geriatric Oncology guidelines on prostate cancer [9].

Materials and Methods

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 previously described [8]. The study was designed to compare cabazitaxel with abiraterone or enzalutamide in patients with mCRPC who had been previously treated with ≥3 cycles of docetaxel and who had progressed within 12 months of treatment with the alternative AR-targeted agent, received before or after docetaxel. Eligible patients received intravenous cabazitaxel 25 mg/m^2 every 3 weeks, 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 weeks in each arm; treatment continued until radiographic progression, unacceptable toxicity or change in treatment.

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 cut-off 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 weeks apart. A tumor response was defined as a partial or complete

response according to RECIST v1.1, 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 weeks apart without an increase in analgesic usage score [11]. Treatment-emergent AEs (TEAEs), regardless of causality, were defined by first occurring or worsening of an AE after the first dose and up to 30 days after the last study drug administration. TEAEs were assessed using the National Cancer Institute Common Terminology Criteria for AEs v4.0.

Statistical analysis

For this analysis, patients were classified into two age subgroups, ≥70 (older) and <70 years of age (younger). This age cut-off was selected based upon the International Society of Geriatric Oncology guidelines on prostate cancer [9]. rPFS analysis by age subgroup (≥70 vs <70 years of age) was pre-specified; analyses of secondary endpoints (OS, PFS, PSA, tumor and pain responses) by these age subgroups were post hoc. Analyses conducted in patients aged ≥75 years 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-hazards 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, tumor and pain response comparisons between treatment groups a stratified Cochran-Mantel Haenszel test was used. The log-rank tests, Cox proportional-hazards 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 months) and timing of AR-targeted agent as specified at the time of randomization (before vs after docetaxel).

Results

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) (**Figure 1**). Of them, 135 patients were aged ≥70 years (cabazitaxel arm, n = 66; abiraterone or enzalutamide arm, n = 69) with a median age of 76 years. Compared with patients aged ≥70 years, younger patients had higher rates of Gleason's 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 years, those receiving abiraterone or enzalutamide versus cabazitaxel had higher rates of Gleason score 8–10 (58% vs 42%) and metastatic disease (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 months and the median event free time for rPFS, OS and PFS was 5.4, 10.6 and 5.2 months, respectively. The median duration of treatment was longer for patients receiving cabazitaxel compared with patients receiving abiraterone or enzalutamide, regardless of age (patients aged ≥70 years: 5.1 vs 3.0 months; younger patients: 5.5 vs 2.8 months). The proportion of patients discontinuing treatment was similar among patients receiving cabazitaxel versus abiraterone or enzalutamide both in patients aged ≥70 years (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**).

Efficacy

As previously reported, the median rPFS for the overall population was 8.0 months with cabazitaxel versus 3.7 months with abiraterone or enzalutamide (HR [95% CI] = 0.54 [0.40–0.73]; p < 0.001) [8]. In patients aged ≥70 years, the median rPFS was 8.2 months with cabazitaxel versus 4.5 months with abiraterone or enzalutamide (HR [95% CI] = 0.58 [0.38–0.89]; p = 0.012; **Figure 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 years, the median rPFS was also significantly improved with cabazitaxel versus abiraterone or enzalutamide (7.4 vs 3.2 months; HR [95% CI] = 0.47 [0.30–0.74]; p < 0.001; **Figure 2a**).

The median OS (main secondary endpoint) was numerically longer for cabazitaxel compared with abiraterone or enzalutamide in patients aged ≥70 years (13.9 vs 9.4 months; HR [95% CI] = 0.66 [0.41–1.06]; p = 0.084) and younger patients (13.6 vs 11.8 months; HR [95% CI] = 0.66 [0.41–1.08]; p = 0.093) but differences did not reach statistical significance (**Figure 2b**); the sensitivity analysis HR (95% CI) was 0.69 (0.42–1.15). In patients aged ≥70 years, the median PFS was 4.5 months with cabazitaxel versus 2.8 months with abiraterone or enzalutamide (HR [95% CI] = 0.57 [0.39–0.84]; p = 0.003; **Figure 2c**); the sensitivity analysis HR (95% CI) was 0.55 (0.36–0.83). Among patients aged <70 years, a significant improvement in median PFS was also observed with cabazitaxel versus abiraterone or enzalutamide (4.4 vs 2.5 months; HR [95% CI] = 0.45 [0.30–0.68]; p < 0.001; **Figure 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 years (**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 years, 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, regardless of age (**Figure 3**). Tumor response in patients aged ≥70 years numerically favored cabazitaxel versus abiraterone or enzalutamide but this difference did not reach statistical significance.

Safety

Almost all patients had a TEAE of any grade, irrespective of age and treatment (**Table 2** and **Supplementary Table 4**). Serious TEAEs of any grade were more frequent in patients aged ≥70 years compared with younger patients, both in the cabazitaxel (45% vs 32%) and abiraterone or enzalutamide arms (45% vs 33%). Any grade ≥3 TEAEs were also more frequent in patients aged ≥70 years compared with younger patients, both in the cabazitaxel (58% vs 48%) and abiraterone or enzalutamide arms (49% vs 42%). Grade ≥3 TEAEs that occurred more frequently in patients aged ≥70 years receiving cabazitaxel compared with 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 years receiving abiraterone or enzalutamide compared with 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 compared with patients receiving abiraterone or enzalutamide among patients aged ≥70 years (25% vs 12%) and younger patients (15% vs

5.3%). TEAEs leading to death were less frequent in patients receiving cabazitaxel compared with abiraterone or enzalutamide among patients aged ≥70 years (9.4% vs 15%) and younger patients (1.6% vs 7.0%). In patients aged ≥70 years, grade 5 TEAEs occurred in six patients receiving cabazitaxel (disease progression [n = 2], urinary tract infection [n = 1], head injury [n = 1], septic shock [n = 1] or aspiration [n = 1]) and 10 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 ≥1 dose reduction was lower among patients receiving cabazitaxel compared with abiraterone or enzalutamide among patients aged ≥70 years (20% vs 39%) and younger patients (23% vs 37%). The TEAE profiles of cabazitaxel and abiraterone/enzalutamide were further investigated using three different age cut-offs (≥75, 70–74 and <70; **Supplementary Table 5**).

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 10 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 they 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 years 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 months on the alternative AR-targeted agent. The results demonstrate that cabazitaxel provides a greater benefit compared with 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 aged ≥70 years (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 and PSA, tumor and pain responses) consistently favored cabazitaxel compared with abiraterone or enzalutamide, regardless of age [19].

Interestingly, median rPFS was slightly shorter for patients aged <70 years (cabazitaxel: 7.4 months; abiraterone/enzalutamide: 3.2 months) compared with patients aged ≥70 years (cabazitaxel: 8.2 months; abiraterone/enzalutamide: 4.5 months). This might be a reflection of the more aggressive baseline clinical features of the younger patient population (higher rates of Gleason's 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 years receiving cabazitaxel (21% vs 12%). As liver and lung metastases are often associated with more aggressive disease, this may be a contributing factor for the shorter rPFS observed [20].

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

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

315

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

323

324 The CARD results are important for several reasons. Firstly, they provide additional
325 confirmation that patients with mCRPC progressing following receipt of an AR-targeted
326 agent respond sub-optimally to a second alternative AR-targeted agent, as already shown by
327 several prospective randomized trials [24, 25]. Secondly, the results demonstrate that
328 cabazitaxel is superior to abiraterone or enzalutamide in delaying disease progression,
329 prolonging OS and relieving pain among patients with mCRPC previously treated with
330 docetaxel and the alternative AR-targeted agent. Finally, the safety profile of cabazitaxel is
331 manageable when prophylactic G-CSF is administered at each cycle. The incidence of febrile
332 neutropenia in patients receiving cabazitaxel in CARD (3.2%) is lower than in previous Phase
333 III 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 years), 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 years 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.

Conclusions

In this analysis of the CARD study, cabazitaxel significantly improved rPFS (pre-specified analysis) compared with abiraterone or enzalutamide among patients aged ≥70 years 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 years experienced a higher frequency of grade 3 TEAEs compared with 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 standard of care, irrespective of age, in patients with mCRPC previously treated with docetaxel and the alternative AR-targeted agent.

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436 **Tables and figures**

437

438 ***Table 1. Patient baseline and disease characteristics***

	≥70 years of age		<70 years of age	
	Cabazitaxel n = 66	Abiraterone or enzalutamide n = 69	Cabazitaxel n = 63	Abiraterone or enzalutamide n = 57
Median age at screening, years (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 (58.0)	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)

439

440 *AR, androgen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status;*

441 *PSA; prostate-specific antigen.*

Table 2. Treatment-emergent adverse events according to age

	≥70 years of age				<70 years of age			
Patients, n (%)	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)

[a] The cut-off 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, musculoskeletal chest pain; [c] Including neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy; [d] Including acute kidney injury, renal failure, renal impairment, hydronephrosis and pyelocaliectasis; [e] Including hypertension, hypertensive crisis; [f] Including sciatica, radiculopathy, spinal cord compression.

TEAE, treatment-emergent adverse event.

Figure 1. CONSORT diagram

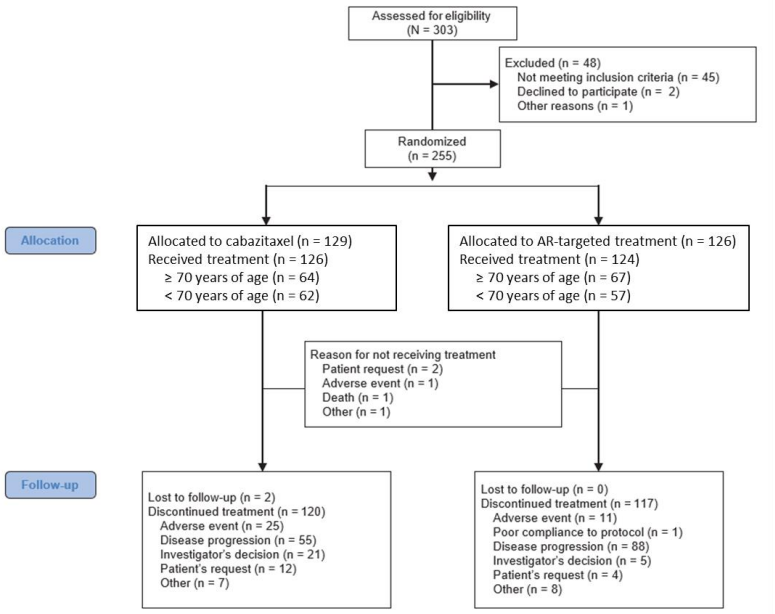
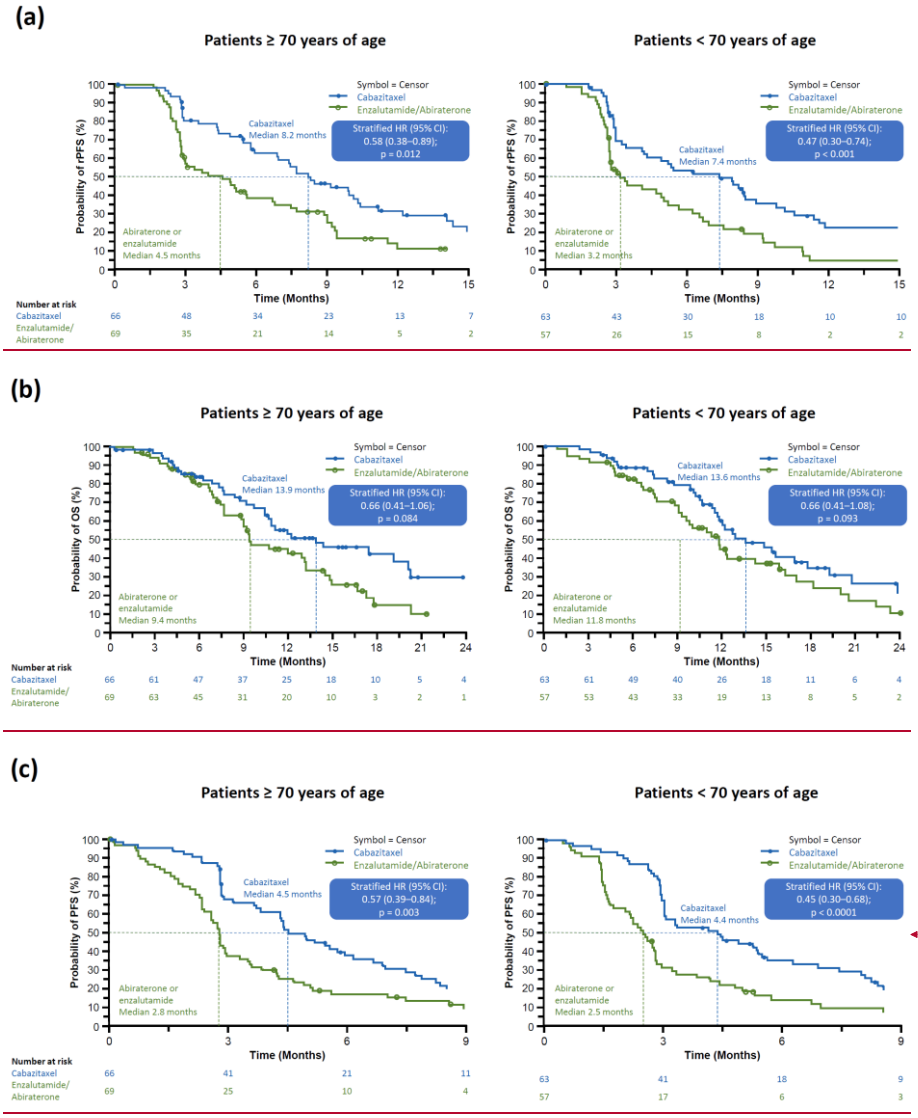


Figure 2. Kaplan–Meier estimates. (a) Radiographic progression-free survival according to age, (b) Overall survival according to age and (c) Progression-free survival according to age.



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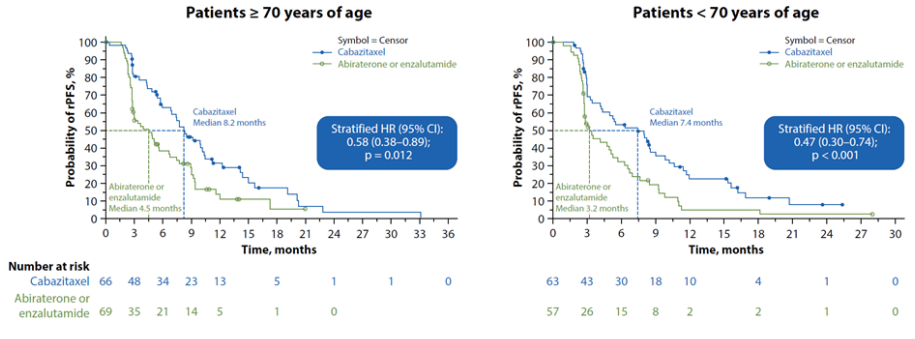

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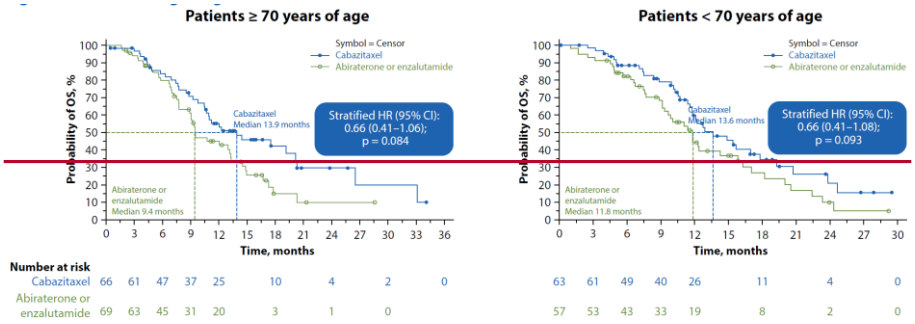

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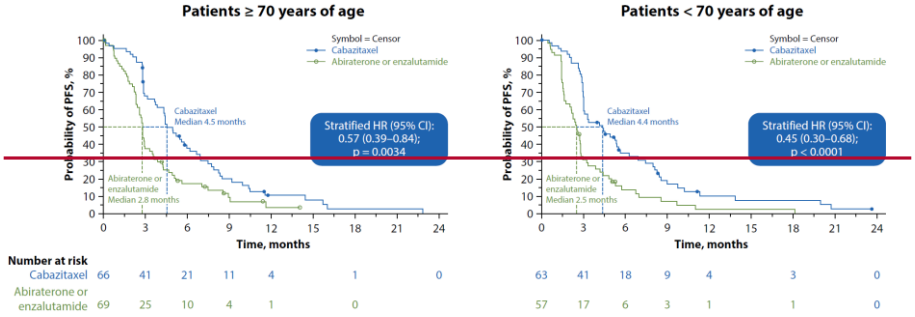
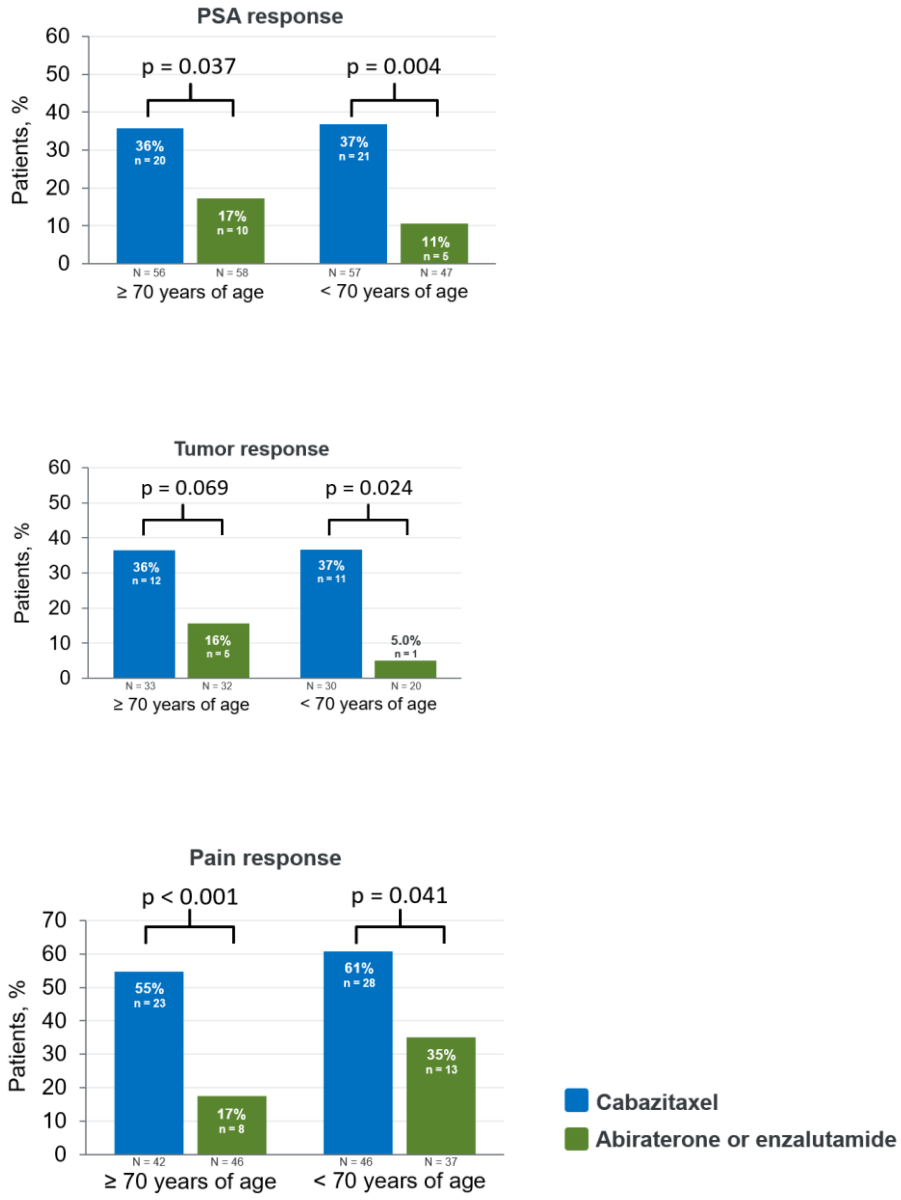


Kaplan-Meier estimates at later time points should be interpreted with caution due to small samples sizes. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Figure 3. Prostate-specific antigen, tumor and pain response according to age



PSA, prostate-specific antigen.

Supplementary Table 1. Treatment exposure according to age

	≥70 years of age		<70 years of age	
	Cabazitaxel n = 64[a]	Abiraterone or enzalutamide n = 67[a]	Cabazitaxel n = 62[a]	Abiraterone or enzalutamide n = 57[a]
Treatment duration				
Median duration of treatment exposure, weeks (range)	22.0 (3.0–63.4)	12.9 (3.0–87.3)	24.0 (6.0–87.9)	12.0 (2.0–141.3)
Median number of cycles, n (range)	7.0 (1.0–20.0)	4.0 (1.0–28.0)	7.5 (2.0–29.0)	4.0 (1.0–45.0)
Treatment reduction				
Patients with ≥1 cycle administered at a reduced dose, n (%)	13 (20)	26 (39)	14 (23)	21 (37)
	Cabazitaxel n = 66[b]	Abiraterone or enzalutamide n = 69[b]	Cabazitaxel n = 63[b]	Abiraterone or enzalutamide n = 57[b]
Treatment discontinuation				
Patients with discontinued treatment, n (%)	63 (96)	64 (93)	57 (91)	53 (93)
Reasons for discontinuation, n (%)				
Disease progression	21 (32)	49 (71)	34 (54)	39 (68)
Adverse event	16 (24)	8 (12)	9 (14)	3 (5.3)
Investigator's decision	16 (24)[c]	2 (2.9)	5 (7.9)	3 (5.3)
Patient's request	8 (12)	2 (2.9)	4 (6.3)	2 (3.5)
Other	2 (3.0)	3 (4.3)	5 (7.9)	5 (8.8)
Lost to follow-up	0	0	0	0
Poor compliance to protocol	0	0	0	1 (1.8)

[a] Safety population (randomized and received at least one dose of study treatment); [b] Randomized population; [c] Often following patient receipt of 10 cycles of cabazitaxel.

Supplementary Table 2. Summary of efficacy endpoints in patients ≥75 versus <75 years of age

	≥75 years of age		<75 years of age	
Median, months (95% CI)	Cabazitaxel n = 45	Abiraterone or enzalutamide n = 34	Cabazitaxel n = 84	Abiraterone or enzalutamide n = 92
rPFS	8.3 (6.9–10.4)	4.9 (3.0–9.0)	8.0 (5.0–9.0)	3.2 (2.8–5.1)
OS	14.4 (9.8–26.5)	9.2 (7.5–16.7)	12.9 (11.7–17.7)	11.8 (9.4–13.2)
PFS	5.4 (3.7–6.9)	2.9 (2.4–4.2)	4.4 (3.0–5.3)	2.6 (2.2–2.8)

CI, confidence interval; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Supplementary Table 3. Patient event and censoring data

	Overall		≥70 years of age		<70 years of age	
Patients,[a] n (%)	Cabazitaxel n = 129	Abiraterone or enzalutamide n = 126	Cabazitaxel n = 66	Abiraterone or enzalutamide n = 69	Cabazitaxel n = 63	Abiraterone or enzalutamide n = 57
rPFS						
Events	95 (74)	101 (80)	48 (73)	53 (77)	47 (75)	48 (84)
Censored	34 (26)	25 (20)	18 (27)	16 (23)	16 (25)	9 (16)
OS						
Events	70 (54)	83 (66)	35 (53)	43 (62)	35 (56)	40 (70)
Censored	59 (46)	43 (34)	31 (47)	26 (38)	28 (44)	17 (30)
PFS						
Events	111 (86)	115 (91)	57 (86)	61 (88)	54 (86)	54 (95)
Censored	18 (14)	11 (8.7)	9 (14)	8 (12)	9 (14)	3 (5.3)

[a] *Cut-off date: March 27th, 2019.*

OS, overall survival; PFS, progression-free survival; rPFS, radiological PFS.

Supplementary Table 4. Laboratory abnormalities of clinical interest according to age

	≥70 years of age				<70 years of age			
Patients, n (%)	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
Anemia	62 (98)	2 (3.2)	66 (99)	3 (4.5)	62 (100)	8 (13)	52 (91)	3 (5.3)
Leukopenia	53 (84)	25 (40)	20 (30)	1 (1.5)	40 (65)	16 (26)	21 (37)	1 (1.8)
Neutropenia	49 (79)	30 (48)	6 (9.0)	2 (3.0)	32 (53)	25 (41)	2 (3.5)	2 (3.5)
Thrombocytopenia	26 (41)	2 (3.2)	12 (18)	1 (1.5)	25 (40)	2 (3.2)	8 (14)	1 (1.8)

Supplementary Table 5. Treatment-emergent adverse events according to age

	≥75 years of age				70–74 years of age				<70 years of age			
Patients, n (%)	Cabazitaxel n = 44		Abiraterone or enzalutamide n = 34		Cabazitaxel n = 20		Abiraterone or enzalutamide n = 33		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 grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	44 (100)	29 (66)	33 (97)	18 (53)	20 (100)	8 (40)	30 (91)	15 (46)	60 (97)	30 (48)	54 (95)	24 (42)
Any serious TEAE	26 (59)	21 (48)	18 (53)	18 (53)	3 (15)	3 (15)	12 (36)	12 (36)	20 (32)	16 (26)	19 (33)	17 (30)
Any TEAE leading to treatment discontinuation	14 (32)	-	6 (18)	-	2 (10)	-	2 (6.1)	-	9 (15)	–	3 (5.3)	–
Any TEAE leading to death	5 (11)	-	7 (21)	-	1 (5.0)	-	3 (9.1)	-	1 (1.6)	–	4 (7.0)	–
Frequent TEAEs (grade ≥3 TEAEs reported in ≥3% in any subgroup)[a]												
Asthenia or fatigue	26 (59)	3 (6.8)	16 (47)	1 (2.9)	12 (60)	1 (5.0)	13 (39)	0	29 (47)	1 (1.6)	16 (28)	2 (3.5)
Diarrhea	21 (48)	4 (9.1)	2 (5.9)	1 (2.9)	6 (30)	0	1 (3.0)	0	23 (37)	0	6 (11)	0
Infection	14 (32)	3 (6.8)	9 (27)	4 (12)	5 (25)	0	8 (24)	2 (6.1)	21 (34)	6 (9.7)	9 (16)	3 (5.3)
Nausea or vomiting	11 (25)	0	8 (24)	0	4 (20)	0	13 (39)	1 (3.0)	18 (29)	0	8 (14)	1 (1.8)
Decreased appetite	10 (23)	1 (2.3)	4 (12)	0	2 (10)	0	9 (27)	1 (3.0)	5 (8.1)	0	6 (11)	2 (3.5)
Musculoskeletal pain or discomfort[b]	9 (21)	0	12 (35)	1 (2.9)	9 (45)	1 (5.0)	14 (42)	2 (6.1)	16 (26)	1 (1.6)	23 (40)	4 (7.0)
Peripheral neuropathy[c]	7 (16)	3 (6.8)	1 (2.9)	0	4 (20)	0	1 (3.0)	0	14 (23)	1 (1.6)	2 (3.5)	0
Hematuria	5 (11)	0	3 (8.8)	1 (2.9)	2 (10)	0	1 (3.0)	1 (3.0)	12 (19)	1 (1.6)	3 (5.3)	0
Renal disorder[d]	4 (9.1)	2 (4.5)	6 (18)	2 (5.9)	1 (5.0)	0	3 (9.1)	3 (9.1)	3 (4.8)	2 (3.2)	5 (8.8)	5 (8.8)
Cardiac disorder	4 (9.1)	0	8 (24)	6 (18)	0	0	0	0	4 (6.5)	1 (1.6)	2 (3.5)	0
Hypertensive disorder[e]	2 (4.5)	1 (2.3)	4 (12)	1 (2.9)	0	0	3 (9.1)	1 (3.0)	3 (4.8)	2 (3.2)	3 (5.3)	1 (1.8)
Febrile neutropenia	2 (4.5)	2 (4.5)	0	0	0	0	0	0	2 (3.2)	2 (3.2)	0	0
Disease progression	1 (2.3)	1 (2.3)	4 (12)	4 (12)	2 (10)	2 (10)	4 (12)	3 (9.1)	0	0	0	0

Spinal cord or nerve-root disorder[f]	1 (2.3)	1 (2.3)	4 (12)	3 (8.8)	1 (5.0)	1 (5.0)	0	0	4 (6.5)	1 (1.6)	5 (8.8)	2 (3.5)
Urinary tract obstruction	0	0	0	0	0	0	3 (9.1)	3 (9.1)	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	0	0	2 (3.2)	2 (3.2)	1 (1.8)	1 (1.8)

[a] The cut-off 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, musculoskeletal chest pain; [c] Including neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy; [d] Including acute kidney injury, renal failure, renal impairment, hydronephrosis and pyelocaliectasis; [e] Including hypertension, hypertensive crisis; [f] Including sciatica, radiculopathy, spinal cord compression.

TEAE, treatment-emergent adverse event.

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