Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study

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Summary

Background In the CARD study, cabazitaxel significantly improved radiographic progression-free survival and overall survival versus abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and the alternative androgen signalling-targeted inhibitor. Here, we report the quality-of-life outcomes from the CARD study.

Methods CARD was a randomised, multicentre, open-label, phase 4 study involving 62 clinical sites across 13 European countries. Patients (aged ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2) with confirmed metastatic castration-resistant prostate cancer were randomly assigned (1:1) by means of an interactive voice–web response system to receive cabazitaxel (25 mg/m^2 intravenously every 3 weeks, 10 mg daily prednisone, and granulocyte colony-stimulating factor) versus abiraterone (1000 mg orally once daily plus 5 mg prednisone twice daily) or enzalutamide (160 mg orally daily). Stratification factors were ECOG performance status, time to disease progression on the previous androgen signalling-targeted inhibitor, and timing of the previous androgen signalling-targeted inhibitor. The primary endpoint was radiographic progression-free survival; here, we present more detailed analyses of pain (assessed using item 3 on the Brief Pain Inventory-Short Form [BPI-SF]) and symptomatic skeletal events, alongside preplanned patient-reported outcomes, assessed using the Functional Assessment of Cancer Therapy—Prostate (FACT-P) questionnaire and the EuroQoL—5 dimensions, 5 level scale (EQ-5D-5L). Efficacy analyses were done in the intention-to-treat population. Pain response was analysed in the intention-to-treat population with baseline and at least one post-baseline assessment of BPI-SF item 3, and patient-reported outcomes (PROs) were analysed in the intention-to-treat population with baseline and at least one post-baseline assessment of either FACT-P or EQ-5D-5L (PRO population). Analyses of skeletal-related events were also done in the intention-to-treat population. The CARD study is registered with ClinicalTrials.gov, NCT02485691, and is no longer enrolling.

Findings Between Nov 17, 2015, and Nov 28, 2018, of 303 patients screened, 255 were randomly assigned to cabazitaxel (n=129) or abiraterone or enzalutamide (n=126). Median follow-up was 9·2 months (IQR 5·6–13·1). Pain response was observed in 51 (46%) of 111 patients with cabazitaxel and 21 (19%) of 109 patients with abiraterone or enzalutamide (p<0·0001). Median time to pain progression was not estimable (NE; 95% CI NE–NE) with cabazitaxel and 8·5 months (4·9–NE) with abiraterone or enzalutamide (hazard ratio [HR] 0·55, 95% CI 0·32–0·97; log-rank p=0·035). Median time to symptomatic skeletal events was NE (95% CI 20·0–NE) with cabazitaxel and 16·7 months (10·8–NE) with abiraterone or enzalutamide (HR 0·59, 95% CI 0·35–1·01; log-rank p=0·050). Median time to FACT-P total score deterioration was 14·8 months (95% CI 6·3–NE) with cabazitaxel and 8·9 months (6·3–NE) with abiraterone or enzalutamide (HR 0·72, 95% CI 0·44–1·20; log-rank p=0·21). There was a significant treatment effect seen in changes from baseline in EQ-5D-5L utility index score in favour of cabazitaxel over abiraterone or enzalutamide (p=0·030) but no difference between treatment groups for change from baseline in EQ-5D-5L visual analogue scale (p=0·060).

Interpretation Since cabazitaxel improved pain response, time to pain progression, time to symptomatic skeletal events, and EQ-5D-5L utility index, clinicians and patients with metastatic castration-resistant prostate cancer can be reassured that cabazitaxel will not reduce quality of life when compared with treatment with a second androgen signalling-targeted inhibitor.

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Research in context

Evidence before this study

Results from the CARD study showed improved radiographic progression-free survival and overall survival with cabazitaxel versus abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and who progressed within 12 months on the alternative androgen signalling-targeted inhibitor. Many patients with advanced metastatic castration-resistant prostate cancer have bone metastases, which can cause pain and deterioration of quality of life. Therefore, it is crucial to balance clinical activity and adverse events of therapies administered with their effect on patient quality of life. We searched PubMed using the terms "metastatic castration-resistant prostate cancer", "quality of life", "pain", "skeletal-related events", "cabazitaxel", "abiraterone," and "enzalutamide" for studies published after Jan 1, 2010, and before Jan 1, 2020. We identified two phase 3 studies showing that both abiraterone and enzalutamide reduce pain, delay pain progression and skeletal-related events, and improve patient-reported outcomes (PROs; as assessed by the Functional Assessment of Cancer Therapy-Prostate questionnaire) versus placebo in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel. Our search did not identify any randomised studies directly comparing abiraterone or enzalutamide with cabazitaxel, which strengthened the rationale for reporting these preplanned secondary endpoints of the CARD study related to patient quality of life.

Added value of this study

Our results show that, in addition to the previously reported survival benefits, cabazitaxel improves pain response, delays time to pain progression and time to symptomatic skeletal events, and has no deleterious effect on PROs when compared with abiraterone or enzalutamide. The study provides reassurance that cabazitaxel 25 mg/m^2 administered with systematic granulocyte colony-stimulating factor prophylaxis is a relevant treatment option for patients with metastatic castration-resistant prostate cancer previously treated with one androgen signalling-targeted inhibitor and docetaxel.

Implications of all the available evidence

This analysis further clarifies the optimal treatment sequence in metastatic castration-resistant prostate cancer by highlighting the value of cabazitaxel in patients previously treated with docetaxel and progressed within 12 months on an androgen signalling-targeted inhibitor. The available evidence supports the use of cabazitaxel over abiraterone or enzalutamide as a standard of care in this patient population in terms of both clinical outcomes and quality of life.

Introduction

Several new therapies have been shown to improve survival for patients with metastatic castration-resistant prostate cancer during the past 10 years, including taxanes (docetaxel and cabazitaxel), androgen signalling-targeted inhibitors (abiraterone and enzalutamide), a radiopharmaceutical (radium-223 [^{223}Ra]), and an immunotherapy (sipuleucel-T). Bone-targeted agents have shown activity in preventing skeletal-related events in patients with metastatic castration-resistant prostate cancer.[1] Many studies have evaluated treatment sequencing, but these were small retrospective studies, which used different inclusion, exclusion, and outcome criteria.[2] Although survival time generally increases with the number of life-extending therapies received, the optimal treatment sequence remains unclear.[2] In daily practice, many patients receive both abiraterone and enzalutamide before taxanes, mostly owing to age, patient choice, and because these agents are considered less toxic than chemotherapy.[3,4] However, many studies suggest there is cross-resistance between these novel androgen signalling-targeted inhibitors.[2,3,5]

Since cabazitaxel retains activity in patients progressing on docetaxel, abiraterone, or enzalutamide,[6] the CARD study evaluated cabazitaxel versus abiraterone or enzalutamide in patients who had received previous docetaxel and progressed within 12 months on an alternative androgen signalling-targeted inhibitor.[7] Cabazitaxel was associated with improved radiographic progression-free survival and overall survival compared with abiraterone or enzalutamide.[7]

As the prognosis for metastatic castration-resistant prostate cancer has improved, treatment goals have broadened from merely prolonging survival to minimising symptoms and enabling patients to live fulfilled lives.[8] Maintaining or improving quality of life has become increasingly important when selecting treatment regimens, owing to the high symptom and treatment burdens associated with metastatic castration-resistant prostate cancer. The value of patient-reported outcomes (PROs) is well established in prostate cancer, with several validated prostate cancer-specific questionnaires available to assess physical and psychological symptoms.[9] Pain, symptomatic skeletal events, and physical and functional wellbeing have been shown to predict overall survival and other clinical outcomes in patients with metastatic castration-resistant prostate cancer,[10–13] underscoring the importance of evaluating such parameters during interventional studies in order to establish optimal patient-centred care. In this prespecified analysis of the CARD trial, we describe the effect of cabazitaxel versus abiraterone or enzalutamide on preplanned endpoints associated with quality of life.

Methods

Study design and participants

CARD was a randomised, multicentre, open-label study involving 62 clinical sites across 13 European countries

(appendix pp 10–11). The full study design and eligibility criteria have been described previously.[7] Briefly, patients with prostate cancer were eligible if they had castrate amounts of testosterone (<0·5 ng/mL), had disease progression per Response Evaluation Criteria in Solid Tumors version 1.1, or had at least two new bone lesions or a rising prostate-specific antigen (PSA) concentration according to Prostate Cancer Working Group 2 criteria, had received at least three cycles of docetaxel, and had progressed within 12 months of androgen signalling-targeted inhibitor treatment. Use of abiraterone and docetaxel in metastatic hormone-sensitive disease was allowed. Exclusion criteria included age younger than 18 years, Eastern Cooperative Oncology Group (ECOG) performance status higher than 2, previous chemotherapy (except docetaxel), history of seizure, inadequate organ or bone marrow function, history of previous malignancy within 5 years, history of mineralocorticoid excess or deficiency, and uncontrolled severe illness or medical condition. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Patients provided written informed consent before participation and the study received ethics approval from the relevant bodies. The protocol is in the appendix.

Randomisation and masking

Eligible patients were allocated through a centralised, stratified randomisation process to receive cabazitaxel or one of the two androgen signalling-targeted inhibitors (either abiraterone or enzalutamide) in a 1:1 ratio by an interactive voice–web response system. Stratifying criteria at randomisation included ECOG performance status (0–1 *vs* 2), time to disease progression on previous androgen signalling-targeted inhibitor (≤6 months *vs* 6–12 months), and timing of the previous androgen signalling-targeted inhibitor (before *vs* after docetaxel). An independent organisation (Almac Group, Craigavon, UK) with no other involvement in the trial was responsible for generating the allocation sequence, enrolling participants, and assigning them to trial groups.

The study was open label and participants and investigators were not masked to treatment allocation. However, the study team, excluding individuals who had access to patient documents (eg, monitoring team and auditors), remained masked to the treatment group of individual patients until the database lock.

Procedures

Patients were screened 4 weeks before randomisation for eligibility and baseline measurements. Cabazitaxel 25 mg/m² was administered intravenously over 1 h every 3 weeks with prophylactic granulocyte colony-stimulating factor at each cycle and prednisone 10 mg daily. Abiraterone 1000 mg was given orally once daily with prednisone 5 mg twice daily. Enzalutamide 160 mg was given orally once daily. A treatment cycle was 3 weeks. Patients who had previously received enzalutamide received abiraterone, and vice versa. Two dose reductions were permitted as per labelling recommendations before treatment discontinuation (cabazitaxel to 20 mg/m², then 15 mg/m²; abiraterone to 750 mg, then 500 mg; enzalutamide to 120 mg, then 80 mg). The 750 mg abiraterone dose reduction amount was discontinued on March 14, 2018, to align with updated European labelling.[14] Treatment interruptions of less than 2 weeks were permitted to allow acute toxicity recovery as per investigator judgment. Treatment continued until criteria for permanent discontinuation were reached: imaging-based progression, unacceptable toxicity, investigator decision (including non-compliance) or patient request to stop the study, or loss to follow-up.

No masked central review was done on standard imaging (bone scans, and CT and MRI of the pelvis, abdomen, and chest). Chest, abdomen, and pelvic CT-scan or MRI and bone scan were performed at baseline and then every 12 weeks until radiological tumour progression or whenever disease progression was suspected, using the same method for each assessment to follow all target or non-target lesions present at baseline. In case of doubtful lesions on bone scan, a bone-centred x-ray or MRI scan was performed to establish the nature of those lesions (metastatic or not). Adverse events were monitored every 3 weeks during treatment, at the end-of-treatment visit, and every 12 weeks during follow-up until disease progression, start of other anticancer treatment, or data cutoff, and were reported in compliance with regulations. Type of treatment-emergent adverse event was defined according to MedDRA (Medical Dictionary for Regulatory Activities). Severity of treatment-emergent adverse events and laboratory abnormalities were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Laboratory tests were obtained before treatment administration, at every cycle, and up to 30 days after the last study treatment administration. Study protocol and all amendments affecting recruitment to, or conduct of, the study were approved by the review boards of the participating institutions.

Pain and PRO assessments were carried out at baseline, every 3 weeks at each visit before treatment administration, at the end of treatment visit, and then every 12 weeks until disease progression, start of subsequent cancer therapy, or data cutoff date, whichever came first. Pain intensity was assessed using item 3 (progression of worst pain intensity) of the validated Brief Pain Inventory–Short Form (BPI-SF), which rates pain at its worst in the last 24 h on a scale of 0 (no pain) to 10 (worst imaginable pain).[15] Analgesic consumption was reported by local investigators and coded by the WHO analgesic ladder (0=no analgesic; 1=non-opioid analgesics; 2=opioid analgesics for moderate pain; 3=opioids for severe pain).[16] PROs were assessed by means of the Functional Assessment of Cancer Therapy-Prostate

See **Online** for appendix

For more on the **organisation responsible for generating the allocation sequence** see www.almacgroup.com

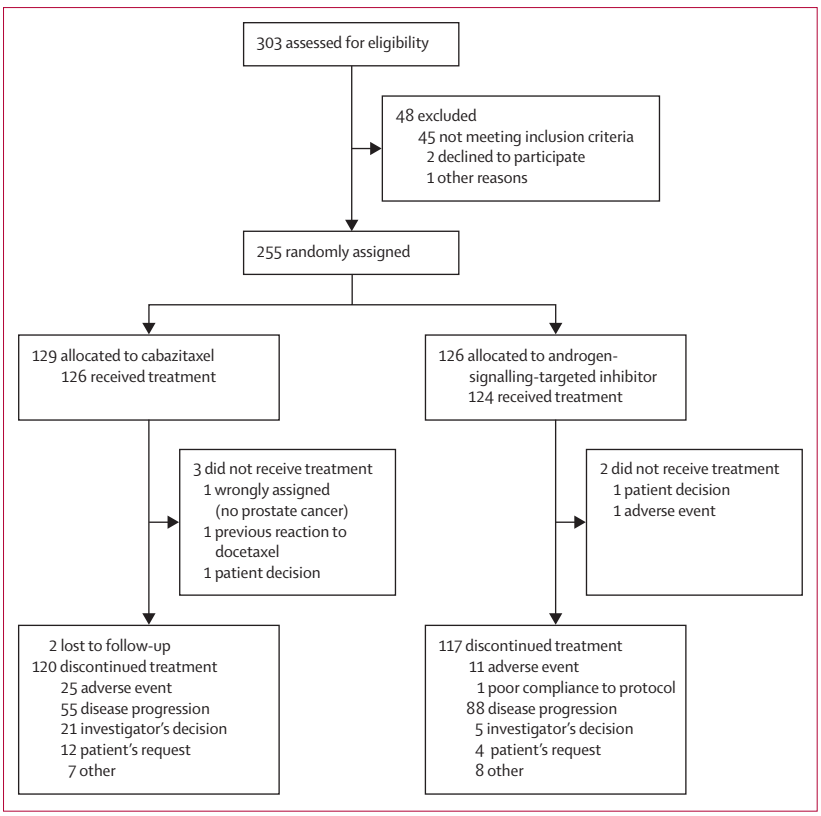


Figure 1: **Trial profile**

(FACT-P) questionnaire (version 4; FACT-General [G] is a subscale of FACT-P) and the EuroQoL—5 dimensions, 5 level scale (EQ-5D-5L). We used these instruments because they were standard tools to measure quality of life in prostate cancer at the time the CARD protocol was developed and have been shown to be reliable and valid in this patient population.[17,18] FACT-P is a 39-item self-report tool designed to evaluate quality of life in patients with prostate cancer.[19] Full ranges and definitions for FACT-P subscales are in the appendix (p 3). A higher FACT-P score indicates better quality of life. EQ-5D-5L describes five health dimensions: mobility, self-care, usual activities, pain–discomfort, and anxiety–depression. Patients rate each domain on a 1–5 Likert-type scale (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, 5=extreme problems).[20] Each PRO questionnaire was done by means of paper and pencil versions and no assistance was given to patients while they were completing the forms. Patients were not advised on a specific order in which to complete the forms.

Symptomatic skeletal events were evaluated at baseline, at each visit, at the end of treatment, and every 12 weeks during follow-up. Standard imaging was scheduled at baseline and every 12 weeks until imaging-based disease progression. Pathological fractures and spinal cord compression were assessed by imaging as needed throughout the study.

Outcomes

The primary endpoint of the CARD trial was radiographic progression-free survival, as reported previously.[7] Key secondary endpoints, tested hierarchically, and reported previously were overall survival, progression-free survival, PSA response, and objective tumour response. Pain response and symptomatic skeletal events were partially described in the primary CARD publication.[7] Here, we report more detailed analyses of preplanned endpoints affecting quality of life.

Pain response was defined as at least a 30% decrease from baseline in average BPI-SF pain intensity score (item 3) observed at two consecutive evaluations at least 3 weeks apart without an increased analgesic usage score. Pain progression was defined as at least a 30% increase from baseline in BPI-SF pain intensity score observed at two consecutive evaluations at least 3 weeks apart without at least a 30% increase or decrease in analgesic usage score. Time to pain progression was defined as time from randomisation until first documented pain progression.

Symptomatic skeletal events were defined as either the use of external beam radiotherapy to relieve bone pain, occurrence of new symptomatic pathological fractures, occurrence of spinal cord compression, or tumour-related orthopaedic surgical intervention. Time to symptomatic skeletal event was defined as time from randomisation until first documented symptomatic skeletal event.

A deterioration in health-related quality of life (HRQOL) was defined as at least a ten-point change in FACT-P total or a specified change in subscale score (as described in the appendix p 4) on two consecutive evaluations, more than 3 weeks apart. The minimally important difference for EQ-5D-5L utility index was 0·14 and 11 for the EQ–visual analogue scale (EQ–VAS). To ensure we did not overestimate the clinically meaningful effect of treatment, we used the upper values of the established range for both the utility index, which is 0·04–0·14, and the VAS, which is 7–11.[18]

Statistical analysis

The study was designed to have 80% power to detect a hazard ratio [HR] of 0·67 (cabazitaxel *vs* abiraterone or enzalutamide) in the analysis of the primary endpoint (radiographic progression-free survival), with the use of a stratified log-rank test at a two-sided α level of 5%. Approximately 234 patients needed to be enrolled and randomly assigned to collect data on 196 events (achieved at the cutoff date of March 27, 2019). There was no interim analysis. The study was not powered for the secondary quality-of-life endpoints reported here. All analyses reported were obtained at the cutoff date, as planned in the protocol (appendix). The statistical analysis plan for the assessment of PROs is in the appendix.

Efficacy analyses were done in the intention-to-treat population, defined as all patients who were randomly assigned to a treatment group. Pain response was

analysed in the intention-to-treat population with baseline and at least one post-baseline assessment of BPI-SF item 3. Symptomatic skeletal events were analysed in the intention-to-treat population. PROs were analysed in the intention-to-treat population with baseline and at least one post-baseline assessment of either FACT-P or EQ-5D-5L (PRO population). p values of less than 0·05 were deemed significant for the primary analysis and for all analyses presented. The p values for these endpoints are purely descriptive.

Stratified log-rank tests were used to analyse time to event and time to progression data. Time to progression at 3 months and 9 months, and time to symptomatic skeletal events at 3, 6, 12, and 18 months was determined by pre-specified Kaplan-Meier analyses. HRs and associated 95% CIs were estimated by means of a stratified Cox proportional hazards model. The proportional hazards assumptions were checked by visual inspection of negative log graphs (appendix p 12–22). Patients with no progression or deterioration at the time of the analysis were censored on the last date on which they were known to have not progressed or deteriorated.

Descriptive statistics for the FACT-P subscale and EQ-5D-5L scores were provided for all cycles for which the number of evaluable patients reached at least 20% in each treatment group in the PRO population, and for the end-of-treatment visit. For qualitative parameters, proportions of patients with deterioration, no change, and improvement were provided.

PRO changes from baseline were analysed by means of a mixed ANCOVA linear repeated measures model where treatment is a fixed-effect variable and patient is a random-effect variable. Stratification variables were included in the model as covariates, as well as the interaction treatment visit. The least squares means by treatment group with corresponding 95% CIs obtained from the mixed model were presented graphically. No adjustments for multiplicity were made. Post-hoc exploratory analyses were done to ascertain whether the PRO results were related to the overall survival or pain relief outcomes.

Compliance with the planned assessment schedule was calculated at baseline and for each cycle as the proportion of patients receiving study treatment at that timepoint. No formal imputation for missing data was done, and reasons for missing data were not centrally recorded. FACT-P total score was evaluable when more than 80% of questions were answered. For FACT-P subscales, a score was evaluable when more than 50% of the questions in the subscale domain were answered. If less than 50% of the questions were missing in any FACT-P subscale, the score could be imputed by means of the following formula:

Prorated subscale score=[Sum of question scores]× [number of questions in subscale]/[number of questions answered]

Data were analysed with SAS version 9.2. The study is registered with ClinicalTrials.gov, NCT02485691.

Role of the funding source

The funder of the study provided the study treatments, and collaborated with the authors on study design, data analysis, data interpretation, and writing of the report. The funder had no role in data collection. The manuscript was written with editorial support from medical writers, funded by the sponsor. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Between Nov 17, 2015, and Nov 28, 2018, of 303 patients assessed for eligibility, 255 with metastatic castration-resistant prostate cancer were randomly assigned

	Cabazitaxel group (n=129)	Abiraterone or enzalutamide group (n=126)
Median age, years	70 (65–76)	71 (64–75)
≥75 years	45 (35%)	34 (27%)
Total Gleason score ≥8 at diagnosis	73 (57%)	81 (64%)
Eastern Cooperative Oncology Group performance status at baseline		
0 or 1	123 (95%)	119 (94%)
2	6 (5%)	7 (6%)
Patients with metastatic disease at diagnosis	49 (38%)	60 (48%)
Disease location at baseline		
Bone*	105/126† (83%)	110/125† (88%)
Lymph nodes‡	8/126 (6%)	6/125 (5%)
Visceral metastases§	21/126 (16%)	25/125 (20%)
Previous life-extending therapy		
Docetaxel	129 (100%)	126 (100%)
Abiraterone	56 (43%)	67 (53%)
Enzalutamide	72 (56%)	59 (47%)
Bisphosphonate or denosumab use at baseline	27 (21%)	46 (37%)
Type of progression at randomisation		
Prostate-specific antigen only	11 (9%)	10 (8%)
Imaging-based¶	23 (18%)	15 (12%)
Pain‖	86 (67%)	90 (71%)
Missing	9 (7%)	11 (9%)
Pain intensity at randomisation (Brief Pain Inventory—Short Form, item 3)		
0 or 1	36 (28%)	28 (22%)
2 or 3	28 (22%)	32 (25%)
≥4	56 (43%)	56 (44%)
Missing	9 (7%)	10 (8%)
Analgesics consumption for cancer pain at randomisation		
No analgesics	57 (44%)	53 (42%)
Non-opioid analgesics (mild pain)	24 (19%)	30 (24%)
Opioids for moderate pain	16 (12%)	15 (12%)
Opioids for severe pain	31 (24%)	27 (21%)
Missing	1 (1%)	1 (1%)

(Table 1 continues on next page)

	Cabazitaxel group (n=129)	Abiraterone or enzalutamide group (n=126)
(Continued from previous page)		
Baseline Functional Assessment of Cancer Therapy—Prostate scores		
Number of patients	108 (84%)	114 (90%)
Total Functional Assessment of Cancer Therapy—Prostate	103·8 (22·0)	105·4 (21·2)
Total Functional Assessment of Cancer Therapy—General	73·7 (16·5)	75·1 (16·6)
Trial outcome index	66·5 (16·7)	68·1 (15·7)
Prostate-specific concerns	30·0 (7·1)	30·1 (6·9)
Pain-related subscale	9·8 (4·4)	10·2 (3·9)
Emotional wellbeing	16·2 (4·5)	16·8 (4·7)
Functional wellbeing	15·6 (6·1)	16·9 (6·0)
Physical wellbeing	20·9 (5·6)	21·0 (5·3)
Social or family wellbeing	21·1 (4·8)	20·6 (5·2)
Baseline EuroQol—5 dimensions, 5 level scores		
Number of patients with baseline health status score on visual analogue scale	113 (88%)	112 (89%)
Health status score (visual analogue scale)	65·8 (20·4)	66·3 (18·5)
Number of patients with baseline health utility index score	112 (87%)	115 (91%)
Health utility index score	0·70 (0·26)	0·70 (0·22)

Data are median (IQR), n (%), or mean (SD). *Bone metastases (possibly including lymph nodes or visceral metastases). †Some patients had missing information regarding disease location. ‡Lymph node only, no bone or visceral metastases. §Lung or liver metastases (possibly including lymph nodes or bone metastasis). ¶Possible prostate-specific antigen increase, no pain; ||Possible prostate-specific antigen increase, possibly imaging-based.

Table 1: **Baseline characteristics**

(129 to cabazitaxel and 126 to abiraterone or enzalutamide) and 250 (98%) of 255 were treated (126 of 129 with cabazitaxel, 124 of 126 with abiraterone or enzalutamide; figure 1). The 255 patients randomly assigned constituted the intention-to-treat population. At the cutoff date (March 27, 2019), median follow-up was 9·2 months (IQR 5·6–13·1). Median duration of treatment was 22·0 weeks (IQR 13·1–30·4) with cabazitaxel versus 12·5 weeks (9·9–23·4) with abiraterone or enzalutamide. The median number of cycles of treatment received was seven (IQR 4–10) with cabazitaxel versus four (3–8) with abiraterone or enzalutamide. More patients in the abiraterone or enzalutamide group than in the cabazitaxel group discontinued treatment early because of disease progression (figure 1).

Patient demographics and clinical characteristics at baseline have been reported previously[7] and are shown in table 1. At least one dose reduction was required as per labelling recommendations for 27 (21%) of 126 patients receiving cabazitaxel and 47 (38%) of 124 patients receiving an androgen signalling-targeted inhibitor (17 [29%] of 58 patients with abiraterone and 30 [46%] of 66 patients with enzalutamide).

Pain response was evaluable in 220 (86%) of 255 patients (111 of 129 with cabazitaxel and 109 of 126 with abiraterone or enzalutamide); 35 (14%) of 255 patients (18 of 129 with cabazitaxel and 17 of 126 with abiraterone or enzalutamide) were not evaluable because of incomplete BPI-SF questionnaires. As previously reported, confirmed pain response was observed in 51 (46%) of 111 patients receiving cabazitaxel and 21 (19%) of 109 patients receiving abiraterone or enzalutamide (p<0·0001). At data cutoff, 25 (23%) of 111 patients receiving cabazitaxel had pain progression, compared with 27 (25%) of 109 with abiraterone or enzalutamide. The median time to pain progression was not estimable (NE; 95% CI NE–NE) with cabazitaxel and 8·5 months (4·9–NE) with abiraterone or enzalutamide (HR 0·55, 95% CI 0·32–0·97; log-rank p=0·035). The Kaplan-Meier estimates of not having pain progression with cabazitaxel versus abiraterone or enzalutamide at 3 months and 9 months are shown in table 2.

Symptomatic skeletal events were observed in 24 (19%) of 129 patients in the cabazitaxel group and 35 (28%) of 126 patients in the abiraterone or enzalutamide group, which were the numbers with an event included in analyses of time to symptomatic skeletal events (table 3). There was a lower use of denosumab or bisphosphonates in patients treated with cabazitaxel (27 [21%] of 129) than in those who received abiraterone or enzalutamide (46 [37%] of 126) and the median time to symptomatic skeletal events was NE (95% CI 20·0–NE) with cabazitaxel and 16·7 months (10·8–NE) with abiraterone or enzalutamide (HR 0·59, 95% CI 0·35–1·01; log-rank p=0·050). The Kaplan-Meier estimates of not having symptomatic skeletal events with cabazitaxel versus abiraterone or enzalutamide at 3, 6, 12, and 18 months are shown in table 3. Estimates at 3 months and 9 months are provided by Kaplan-Meier analyses. All were preplanned.

FACT-P was evaluable in 108 (84%) of 129 patients receiving cabazitaxel and 114 (91%) of 126 patients receiving abiraterone or enzalutamide, with 21 (16%) of 129 patients in the cabazitaxel group and 12 (10%) of 126 in the abiraterone or enzalutamide group excluded because of incomplete FACT-P questionnaires. At least one item in the FACT-P questionnaire was completed by at least 88% of patients in each treatment group at each visit (appendix pp 5, 7).

Mean FACT-P total scores at baseline are in table 1. At the cutoff date, FACT-P deterioration was recorded in 32 (30%) of 108 patients receiving cabazitaxel and 33 (29%) of 114 patients receiving abiraterone or enzalutamide. Data are shown for up to eight cycles and at end of treatment owing to small patient numbers for later cycles (figures 2 and 3). The median time to FACT-P total score deterioration was 14·8 months (95% CI 6·3 to NE) with cabazitaxel and 8·9 months (6·3 to NE) with abiraterone or enzalutamide (HR 0·72, 95% CI 0·44–1·20; log-rank p=0·21; table 2; figure 3). In repeated-analysis measures by means of a mixed-effect model, no significant differences between groups were observed (figure 2; appendix p 9). Mean changes

	Time to deterioration, months			Kaplan-Meier probability of no deterioration at 3 months (95% CI)		Kaplan-Meier probability of no deterioration at 9 months (95% CI)	
	Cabazitaxel	Abiraterone or enzalutamide	Hazard ratio	Cabazitaxel	Abiraterone or enzalutamide	Cabazitaxel	Abiraterone or enzalutamide
Overall survival	13·6 (11·5–17·5); 70/129 (54%)	11·0 (9·2–12·9); 83/126 (66%)	0·64* (0·46–0·89)	0·976 (0·950–1·00)	0·936 (0·893–0·979)	0·748 (0·668–0·828)	0·646 (0·556–0·735)
Pain progression (Brief Pain Inventory—Short Form)	NE (NE–NE); 25/111 (23%)	8·5 (4·9–NE); 27/109 (25%)	0·55* (0·32–0·97)	0·878 (0·813–0·943)	0·746 (0·649–0·843)	0·662 (0·546–0·779)	0·453 (0·221–0·686)
Functional Assessment of Cancer Therapy—Prostate, total	14·8 (6·3–NE); 32/108 (30%)	8·9 (6·3–NE); 33/114 (29%)	0·72 (0·44–1·20)	0·862 (0·795–0·930)	0·740 (0·652–0·827)	0·542 (0·395–0·690)	0·437 (0·208–0·667)
Functional Assessment of Cancer Therapy—General, total	14·8 (8·8–NE); 30/108 (28%)	11·4 (11·4–NE); 32/114 (28%)	0·71 (0·42–1·18)	0·823 (0·749–0·898)	0·723 (0·632–0·814)	0·607 (0·471–0·742)	0·644 (0·533–0·755)
Trial outcome index	14·8 (8·5–NE); 29/108 (27%)	8·9 (6·3–NE); 34/114 (30%)	0·65 (0·39–1·09)	0·861 (0·793–0·929)	0·714 (0·662–0·806)	0·610 (0·479–0·740)	0·447 (0·241–0·652)
Physical wellbeing	14·8 (4·9–NE); 39/108 (36%)	8·9 (4·3–NE); 38/114 (33%)	0·82 (0·51–1·30)	0·760 (0·675–0·844)	0·714 (0·624–0·804)	0·501 (0·363–0·640)	0·480 (0·298–0·661)
Social or family wellbeing	14·8 (7·9–14·8); 35/108 (32%)	8·9 (6·3–NE); 27/114 (24%)	1·03 (0·61–1·73)	0·787 (0·708–0·867)	0·794 (0·712–0·876)	0·547 (0·398–0·695)	0·494 (0·266–0·721)
Emotional wellbeing	NE (NE–NE); 18/108 (17%)	13·7 (6·3–NE); 26/114 (23%)	0·46† (0·25–0·87)	0·911 (0·855–0·967)	0·826 (0·749–0·903)	0·741 (0·619–0·863)	0·525 (0·317–0·733)
Functional wellbeing	NE (5·9–NE); 39/108 (36%)	8·9 (4·8–NE); 39/114 (34%)	0·81 (0·51–1·28)	0·737 (0·652–0·823)	0·653 (0·557–0·749)	0·530 (0·409–0·652)	0·474 (0·248–0·700)
Prostate-specific concerns	14·8 (9·8–NE); 35/108 (32%)	8·9 (4·8–NE); 40/114 (35%)	0·68 (0·42–1·08)	0·836 (0·764–0·907)	0·684 (0·591–0·776)	0·636 (0·525–0·747)	0·473 (0·320–0·626)
Pain-related subscale	10·4 (8·5–NE); 36/108 (33%)	8·9 (4·9–NE); 38/114 (33%)	0·74 (0·46–1·19)‡	0·816 (0·741–0·891)	0·696 (0·605–0·787)	0·562 (0·422–0·702)	0·451 (0·264–0·638)

Data are median (95% CI) and n/N (%), unless otherwise indicated. NE=not estimable. *Stratified log-rank test p=0·03. †Stratified log-rank test p=0·015. ‡ p<0.001.

Table 2: **Overall survival, pain, and patient-reported outcomes**

from baseline at end of treatment in FACT-P total score were –6·33 (SE 2·81) with cabazitaxel and –10·91 (3·13) with abiraterone or enzalutamide (least squares mean difference 4·58, 95% CI –1·36 to 10·52, p=0·13; figure 2).

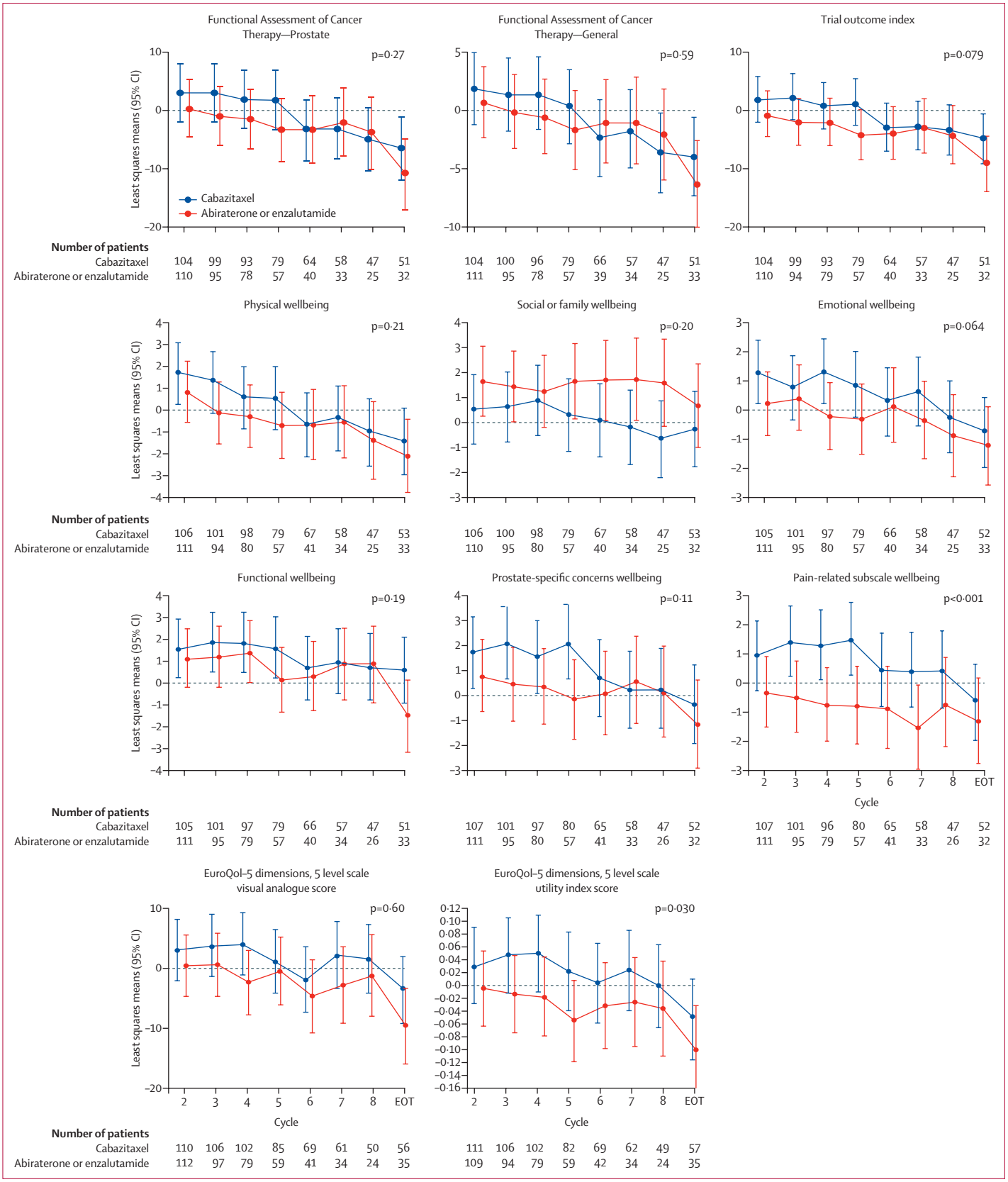
For FACT-P subscale scores, time to deterioration was significantly longer in patients receiving cabazitaxel than in patients receiving abiraterone or enzalutamide for the emotional wellbeing subscale; however, there were no significant differences between groups for the other subscores; table 2; figure 3). When looking at overall treatment effects by a mixed ANCOVA linear model, there was a significant difference between groups (p<0·001) favouring cabazitaxel for pain-related subscale with least squares mean difference ranging from 1·12 (95% CI –0·38 to 2·61) to 2·26 (1·06 to 3·47) (figure 2). The proportion of patients reporting improvement, maintainence or deterioration for the pain-related subscale are shown in the appendix (p1). Conversely, changes in social or family wellbeing significantly favoured abiraterone or enzalutamide over cabazitaxel. For the other dimensions (FACT-P total score, FACT-G, trial outcome index, physical, emotional, and functional wellbeing, and prostate-specific concerns) no significant between-group differences were observed.

Exploratory analyses were done to ascertain whether the quality-of-life results were related to the prolonged overall survival or greater pain relief associated with cabazitaxel compared wtih abiraterone or enzalutamide in the primary trial report. As previously reported, median overall survival was 13·6 months (95% CI 11·5–17·5) in the cabazitaxel group versus 11·0 months (9·2–12·9) in the abiraterone or enzalutamide group (HR 0·64 [95% CI 0·46–0·89]; table 2). Estimated overall survival was relatively high in both groups at 3 months but lower in both groups at 9 months. Estimates of pain progression and time to FACT-P deterioration at

	Cabazitaxel group (n=129)	Abiraterone or enzalutamide group (n=126)
Any symptomatic skeletal event	24 (19%)	35 (28%)
Radiation to relieve bone pain	14 (11%)	23 (18%)
Spinal cord compression	4 (3%)	4 (3%)
New symptomatic pathological fracture	6 (5%)	8 (6%)
Surgery to the bone	0	0
Kaplan-Meier probability of not having symptomatic skeletal events		
3 months	0·926 (0·880–0·973)	0·814 (0·744–0·885)
6 months	0·858 (0·792–0·923)	0·771 (0·693–0·849)
12 months	0·794 (0·709–0·880)	0·629 (0·511–0·748)
18 months	0·712 (0·594–0·830)	0·486 (0·286–0·685)

Data are n (%) and % (95% CI).

Table 3: **Distribution of first symptomatic skeletal events and probability of not having symptomatic skeletal events in the intention-to-treat population**


Functional Assessment of Cancer Therapy—Prostate
p=0·27
Functional Assessment of Cancer Therapy—General
p=0·59
Trial outcome index
p=0·079
Least squares means (95% CI)
Cabazitaxel
Abiraterone or enzalutamide
Number of patients
Cabazitaxel 104 99 93 79 64 58 47 51
Abiraterone or enzalutamide 110 95 78 57 40 33 25 32
Cabazitaxel 104 100 96 79 66 57 47 51
Abiraterone or enzalutamide 111 95 78 57 39 34 25 33
Cabazitaxel 104 99 93 79 64 57 47 51
Abiraterone or enzalutamide 110 94 79 57 40 33 25 32
Physical wellbeing
p=0·21
Social or family wellbeing
p=0·20
Emotional wellbeing
p=0·064
Number of patients
Cabazitaxel 106 101 98 79 67 58 47 53
Abiraterone or enzalutamide 111 94 80 57 41 34 25 33
Cabazitaxel 106 100 98 79 67 58 47 53
Abiraterone or enzalutamide 110 95 80 57 40 34 25 32
Cabazitaxel 105 101 97 79 66 58 47 52
Abiraterone or enzalutamide 111 95 80 57 40 34 25 33
Functional wellbeing
p=0·19
Prostate-specific concerns wellbeing
p=0·11
Pain-related subscale wellbeing
p<0·001
Number of patients
Cabazitaxel 105 101 97 79 66 57 47 51
Abiraterone or enzalutamide 111 95 79 57 40 34 26 33
Cabazitaxel 107 101 97 80 65 58 47 52
Abiraterone or enzalutamide 111 95 80 57 41 33 26 32
Cabazitaxel 107 101 96 80 65 58 47 52
Abiraterone or enzalutamide 111 95 79 57 41 33 26 32
Cycle
EuroQol–5 dimensions, 5 level scale visual analogue score
p=0·60
EuroQol–5 dimensions, 5 level scale utility index score
p=0·030
Number of patients
Cabazitaxel 110 106 102 85 69 61 50 56
Abiraterone or enzalutamide 112 97 79 59 41 34 24 35
Cabazitaxel 111 106 102 82 69 62 49 57
Abiraterone or enzalutamide 109 94 79 59 42 34 24 35
Cycle

3 months and 9 months were similar for each group (table 2), suggesting that differences in FACT-P values between the cabazitaxel and abiraterone or enzalutamide groups were more closely related to pain relief than to overall survival. Median time from FACT-P definitive deterioration to death was 7·5 months (IQR 0–10·2) with cabazitaxel versus 4·8 months (0–8·7) with abiraterone or enzalutamide. Median time from confirmed pain progression to death was 8·6 months (IQR 6·7–14·2) with cabazitaxel versus 7·0 months (5·2–12·0) with abiraterone or enzalutamide.

EQ-5D-5L was evaluable in 115 (89%) of 129 patients receiving cabazitaxel, with 14 (11%) patients excluded because of missing EQ-5D-5L questionnaires, and evaluable in 115 (91%) of 126 patients receiving abiraterone or enzalutamide, with 11 (9%) excluded because of missing EQ-5D-5L questionnaires. Data are shown for up to eight cycles and end of treatment because the number of patients receiving subsequent cycles in the control group was too small (figure 2). At least one item in the EQ-5D-5L questionnaire was completed by at least 82% of patients in each treatment group at each visit (appendix pp 6, 8). Mean values for EQ-5D-5L health status (VAS) at baseline are shown in table 1. Figure 2 shows the changes from baseline in VAS, with least squares mean difference between cabazitaxel and abiraterone or enzalutamide ranging from 1·6 (95% CI −3·65 to 6·85) to 6·4 (1·49 to 11·25; 0·060).

Mean baseline values for EQ-5D-5L utility index are shown in table 1). There was a significant treatment effect seen in changes from baseline in EQ-5D-5L utility index score in favour of cabazitaxel over abiraterone or enzalutamide (p=0·030; mixed ANCOVA linear model), with least squares mean difference between cabazitaxel and abiraterone or enzalutamide ranging from 0·03 (95% CI −0·04 to 0·11) to 0·08 (0·02 to 0·14) during treatment and 0·05 (−0·02 to 0·11) at the end of treatment in favour of cabazitaxel (figure 2).

Moderate, severe, or extreme pain or discomfort per EQ-5D-5L was reported by 45 (39%) of 115 patients receiving cabazitaxel and 47 (41%) of 115 receiving abiraterone or enzalutamide at baseline. Between-group differences in the number of patients reporting improvement in pain or discomfort from baseline are shown in the appendix (p 2); tests for statistical significance were not done.

Figure 2: **Adjusted mean (95% CI) change from baseline in health-related quality-of-life scores**
Mean changes from baseline were assessed by means of a mixed linear repeated measures model adjusted for baseline stratification variables as well as the interaction between treatment and visit. Only results for cycles with data for at least 20% of patients in each treatment group in the patient-reported outcomes population, and for the end-of-treatment (EOT) visit, are shown. p values calculated from a mixed ANCOVA linear model for overall treatment effect.

Discussion

To our knowledge, this prospective, randomised study is the first to directly compare cabazitaxel and abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and the alternative androgen signalling-targeted inhibitor. In these preplanned analyses, cabazitaxel significantly improved pain response and prolonged time to pain progression versus abiraterone or enzalutamide. Cabazitaxel also reduced the probability of developing symptomatic skeletal events, despite lower use of denosumab or bisphosphonates compared with patients receiving abiraterone or enzalutamide. Lastly, cabazitaxel had no deleterious effect on PROs compared with a second androgen signalling-targeted inhibitor. In the past 10 years, many patients received back-to-back androgen signalling-targeted inhibitors in daily practice owing to concerns surrounding the toxicity of chemotherapy. This analysis can provide reassurance to physicians and patients that receiving cabazitaxel chemotherapy will not negatively affect HRQOL or induce additional toxicity when compared with oral androgen signalling-targeted inhibitors. Notably, a high number of patients in the abiraterone or enzalutamide group required a dose reduction, which is in line with clinical experience in metastatic castration-resistant prostate cancer.[21]

Since it is known that HRQOL deteriorates close to death, we attempted to ascertain whether differences in time to deterioration in FACT-P total score and subscale scores with cabazitaxel versus abiraterone or enzalutaimide were related to the greater pain relief or longer overall survival also seen in patients receiving cabazitaxel. Post-hoc exploratory landmark analyses at 3 and 9 months suggest that estimates of FACT-P deterioration were similar to those of pain deterioration, with the probability of disease-related death being relatively small during the initial months. Nevertheless, it is difficult to ascertain whether the numerical differences in HRQOL reflect the effect of cabazitaxel on symptoms, overall survival, or both.

In metastatic castration-resistant prostate cancer, metastases are frequently located in the bone, resulting in substantial pain and fractures that contribute to HRQOL deterioration and increased mortality.[13,22] Androgen suppression is associated with loss of bone mineral density and increased risk of fracture.[23] In CARD, concomitant use of bisphosphonates or denosumab was lower in the cabazitaxel group at baseline than in the abiraterone or enzalutamide group, underlining the substantial under-use of these medications by treating physicians. International guidelines and consensus conferences consistently provide recommendations for monitoring and maintaining bone health, including baseline evaluation of bone mineral density, supplementation with calcium and vitamin D, and use of denosumab or bisphosphonates in patients with metastatic castration-resistant prostate

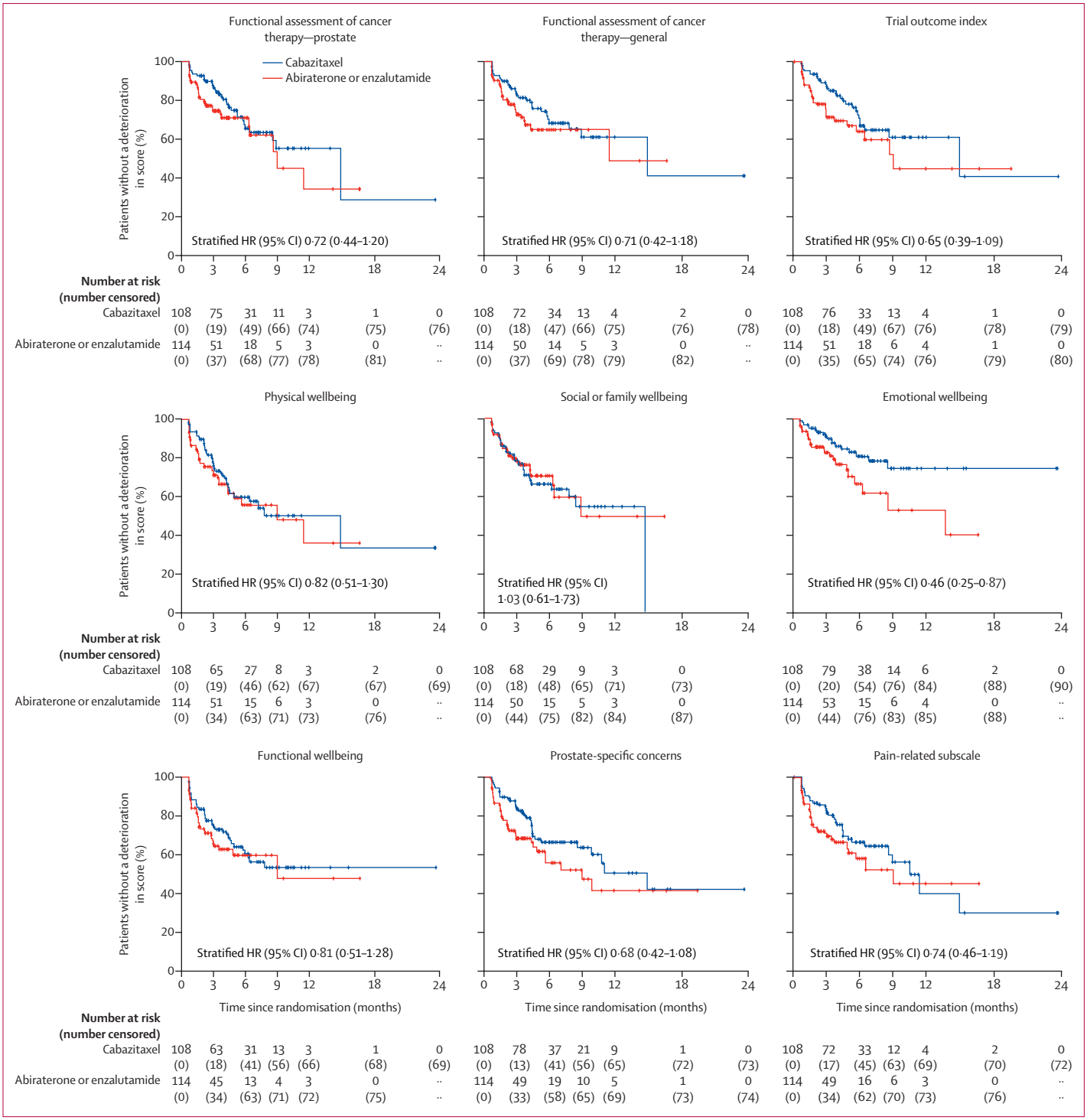


Figure 3: **Time to deterioration in Functional Assessment of Cancer Therapy—Prostate total score and subscales**
HR=hazard ratio. NE=not estimable.

cancer and bone metastases at high risk of fracture.[24–26] A phase 3 study combining abiraterone and ^{223}Ra reported a decreased risk of fractures and mortality with the addition of bone-health agents, highlighting the importance of these prophylactic measures in daily practice.[27] Additionally, a decreased fracture rate by mandating bone-protecting agents was observed in the EORTC 1333–PEACEIII trial combining ^{223}Ra with enzalutamide versus enzalutamide

alone.[28] Despite the imbalance between groups in bone-targeted agents in CARD, cabazitaxel decreased the probability of developing symptomatic skeletal events versus abiraterone or enzalutamide.

In the CARD study, most patients had pain progression at randomisation. Similar findings were reported in a large retrospective registry of 661 patients with metastatic castration-resistant prostate cancer treated in clinical practice.[29] This situation possibly reflects recommendations of international guidelines and consensus conferences to continue androgen signalling-targeted inhibitors until unequivocal signs of progression (ie, imaging-based or clinical progression) before switching therapy.[24,25] Since pain progression is consistently associated with aggressive disease and worse overall survival, it is important to adequately manage such patients.[12,29] Our results show that patients receiving cabazitaxel have a greater pain response and longer time to pain progression than patients receiving a second androgen signalling-targeted inhibitor.

Patients in the CARD study had advanced metastatic disease, which might contribute to their lower baseline FACT-P scores and shorter treatment durations compared with studies of patients with less advanced prostate cancer.[17,18,30] In the phase 3 PREVAIL study,[18] which evaluated enzalutamide in asymptomatic or minimally symptomatic chemotherapy-naive patients with metastatic castration-resistant prostate cancer, mean FACT-P total score at baseline was 119·59 (SD 17·78) in patients receiving enzalutamide and 119·41 (17·92) in patients receiving placebo.[18] By the end of treatment, mean changes from baseline were –5·08 (95% CI –6·87 to –3·28) in the enzalutamide group and –10·87 (–13·49 to –8·25) in the placebo group. Similarly, in the phase 3 COU-AA-302 study of abiraterone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer, baseline FACT-P scores were 122·1 (SD 17·0) in the abiraterone group and 122·6 (17·7) in the placebo group. Mean changes from baseline were not reported.[17] In comparison, patients in CARD had lower FACT-P scores at baseline with mean changes from baseline to the end of treatment similar to those of PREVAIL. This shows that despite worse HRQOL at baseline, based on FACT-P total baseline scores, changes at end of treatment in patients receiving cabazitaxel were similar to those observed at earlier disease stages with a first androgen signalling-targeted inhibitor.

There are several limitations to this study that must be considered. CARD was an open-label trial with a relatively small number of patients and was not powered for the quality-of-life analyses presented here. Despite this, the primary endpoint (radiographic progression-free survival) and the main secondary endpoint (overall survival) were significantly improved with cabazitaxel, reinforcing the validity of our findings.[7] Furthermore, CARD enrolled patients who had progressed within 12 months on the alternative androgen signalling-targeted inhibitor, which might limit the generalisability of the data in the era of combination systemic therapy in metastatic hormone-sensitive and non-metastatic castration-resistant prostate cancer. Importantly, patients with PSA progression within 12 months were eligible for enrolment, even if treatment continued for a longer period. In phase 3 studies of abiraterone and enzalutamide in patients with asymptomatic chemotherapy-naive metastatic castration-resistant prostate cancer, median time to PSA progression was less than 12 months.[31,32] Additionally, in the PROfound study[33] of olaparib versus abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer and DNA repair abnormalities, a second androgen signalling-targeted inhibitor was associated with a short radiographic progression-free survival of 3·55 months (compared with 3·7 months in CARD), despite no eligibility restrictions in relation to time to progression with the first androgen signalling-targeted inhibitor. There are also inherent multiplicity issues with recording outcomes at multiple timepoints throughout treatment, and issues relating to lower patient numbers at the end of the study. The mixed linear repeated measures model that was used attempted to reduce the probability of type 1 errors introduced as the result of dropout bias. However, there are two issues that might introduce bias in either direction: reasons for missing data were not centrally recorded and therefore not well characterised, and there was an imbalance between groups in FACT-P and EQ-5D-5L completion rates during treatment (appendix pp 5–6). Lastly, as is the case with any PRO analysis, it is not possible to isolate the effects of treatment and disease burden from other factors influencing patients' lives.

One strength of this analysis is the use of validated and reliable PRO questionnaires (FACT-P and EQ-5D-5L). Adherence to each of the BPI-SF, FACT-P, and EQ-5D-5L questionnaires was quite high at baseline and during treatment. Although the CARD study was done in accordance with the appropriate guidelines when it was designed, it also satisfies several recommendations of the SISAQOL Consortium for the analysis of PROs in cancer trials.[34] Specifically, CARD used valid within-group PRO objectives, predefined PRO analysis populations, and clearly defined criteria for improvement, stable, or deterioration based on predefined thresholds. Additionally, overall effect endpoints were used with caution, and Cox proportional hazard and linear mixed model tests were chosen where appropriate.

In medical oncology, effective interventions are often not the best choice from the patient's perspective owing to adverse events affecting HRQOL. Here, we show that cabazitaxel significantly improves pain response and time to pain progression and reduces the risk of developing symptomatic skeletal events compared with abiraterone or enzalutamide, and is not associated with a detrimental effect on HRQOL in patients with metastatic castration-resistant prostate cancer who have received previous docetaxel and progressed on the alternative androgen

signalling-targeted inhibitor within the previous year. These findings, combined with the previously published overall survival benefit, should help to guide treatment decisions and reassure patients and treating physicians that they should not be reluctant to receive or prescribe chemotherapy.[7]

Contributors

KF, CNS, JdB, DC, BT, CW, AO, CG-R and RdW contributed to study design. KF, CNS, JdB, DC, GK, J-CE, ML, JC, RI, BM, ÁS, CT, SF, CH, SO, GF and RdW contributed to data collection. KF, CNS, JdB, DC, BT, CW, AO, CG-R, SB and RdW contributed to data interpretation. EMP contributed to data analysis. All authors critically revised and provided approval for each submitted version and are accountable for the accuracy and integrity of the manuscript.

Declaration of interests

KF has received honoraria from and provided an advisory role for Astellas, AAA, Bayer, Essa, Janssen, Orion, CureVac, Clovis, Sanofi, and Endocyte. GK has received personal fees from Sanofi, Astellas, Takeda, Bayer, Janssen, Novartis, Ipsen, and AstraZeneca, and has received grants from Sanofi and Bayer. J-CE has received honoraria from and provided an advisory role for Astellas, Bristol-Myers Squibb, Ipsen, Janssen, Pfizer, and Sanofi Aventis, and has received travel and accommodation fees from Pfizer and Bristol-Myers Squibb. CNS has received honoraria from Janssen, AstraZeneca, Sanofi, and Astellas; consultancy fees from Sanofi, Bayer, and Pfizer; and institutional funding from Genentech–Roche, Bayer, Sanofi Genzyme, Janssen, Medivation, Merck Sharp and Dohme, and Exelixis. JdB has received honoraria from AstraZeneca, Sanofi, Astellas Pharma, Pfizer, Genentech–Roche, Janssen Oncology, Menarini Silicon Biosystems, Daiichi Sankyo, Sierra Oncology, and BioXcel Therapeutics, and provided an advisory role for AstraZeneca, Sanofi, Genentech–Roche, Astellas Pharma, Bayer, Pfizer, Merck Sharp and Dohme, Merck Serono, Boehringer Ingelheim, Sierra Oncology, Menarini Silicon Biosystems, Celgene, Taiho Pharmaceutical, Daiichi Sankyo, Janssen Oncology, Genmab, GlaxoSmithKline, Orion Pharma GmbH, Eisai, and BioXCel Therapeutics. DC has received personal fees from Pfizer, Roche, Sanofi, Janssen, Astellas, Bayer, Bristol-Myers Squibb, Merck Sharp and Dohme, Merck Serono, Pierre Fabre, AstraZeneca, and Lilly. BT has received personal fees and research grants from Astellas, Janssen, Sanofi Genzyme, Amgen, and Ferring, and received non-financial support from Sanofi Genzyme. ML has received personal fees from Sanofi, Janssen, Amgen, Bristol-Myers Squibb, MSD Oncology, AstraZeneca, GSK, and Roche. JC has provided an advisory role for Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, MSD Oncology, Johnson and Johnson, Sanofi, Roche, and Pfizer, and has attended speaker bureaus for Asofarma, Astellas, Bayer, and Johnson & Johnson. RI has received honoraria and provided an advisory role for Sanofi, Janssen, Pfizer, Ipsen, Novartis, Bristol-Myers Squibb, and Merck Sharp and Dohme. BM has received travel fees, honoraria and provided an advisory role for Bristol-Myers Squibb and Merck Serono, and received honoraria and provided an advisory role for MSD, Oncology Sanofi, Roche, Janssen, Bayer, Astellas, Amgen, Novartis, Servier, AstraZeneca, Eisai, Eli Lilly, Ipsen, Pierre Fabre, and Pfizer. CH has received consultancy fees for Sanofi, Janssen, and Astellas. SO has received honoraria from Astellas, Bayer, Bristol-Myers Squibb, Janssen, Merck, Novartis, Pfizer, and Sanofi. AO and SB are employees and stockholders of Sanofi. CG-R and EMP are employees of Sanofi. RdW has provided an advisory role for Sanofi, Janssen, Merck, Bayer, Clovis, Astellas, and Roche and received institutional grants from Sanofi and Bayer. CW, ÁS, CT, SF and GF declare no competing interests.

Data sharing

Individual participant data (including data dictionaries) will not be made available. The full study protocol and statistical analysis plan will be available indefinitely in the appendix. No other data will be shared.

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References

1 Nuhn P, De Bono JS, Fizazi K, et al. Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. *Eur Urol* 2019; **75:** 88–99.

2 Maines F, Caffo O, Veccia A, Bria E. Sequential use of new agents (NAs) after docetaxel (DOC) first line in metastatic castration-resistant prostate cancer (mCRPC) patients (pts): a pooled-analysis of the published studies. *Proc Am Soc Clin Oncol* 2015; **33** (suppl 7): 258 (abstr).

3 Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. *J Clin Oncol* 2018; **36:** 2639–46.

4 Anido-Herranz U, Fernández-Núñez N, Afonso-Afonso J, et al. Chemotherapy management for unfit patients with metastatic castration-resistant prostate cancer. *Clin Transl Oncol* 2019; **21:** 249–58.

5 Oh WK, Cheng WY, Miao R, et al. Real-world outcomes in patients with metastatic castration-resistant prostate cancer receiving second-line chemotherapy versus an alternative androgen receptor-targeted agent (ARTA) following early progression on a first-line ARTA in a US community oncology setting. *Urol Oncol* 2018; **36:** 500.e1–9.

6 Al Nakouzi N, Le Moulec S, Albigès L, et al. Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. *Eur Urol* 2015; **68:** 228–35.

7 de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med* 2019; **381:** 2506–18.

8 Holm M, Doveson S, Lindqvist O, Wennman-Larsen A, Fransson P. Quality of life in men with metastatic prostate cancer in their final years before death – a retrospective analysis of prospective data. *BMC Palliat Care* 2018; **17:** 126.

9 Nussbaum N, George DJ, Abernethy AP, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. *Prostate Cancer Prostatic Dis* 2016; **19:** 111–21.

10 Mierzynska J, Piccinin C, Pe M, et al. Prognostic value of patient-reported outcomes from international randomised clinical trials on cancer: a systematic review. *Lancet Oncol* 2019; **20:** e685–98.

11 Cella D, Traina S, Li T, et al. Relationship between patient-reported outcomes and clinical outcomes in metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-301 and COU-AA-302. *Ann Oncol* 2018; **29:** 392–97.

12 Robbrecht DG, Delanoy N, Tannock IF, et al. Impact of progression at baseline and on-treatment progression events in three large prostate cancer trials. *Eur J Cancer* 2020; **125:** 142–52.

13 Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol* 2002; **168:** 1005–07.

14 Janssen-Cilag International. ZYTIGA® summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/zytiga-epar-product-information_en.pdf (accessed Aug 1, 2020).

15 National Palliative Care Research Center. Brief pain inventory (short form). 1991. http://www.npcrc.org/files/news/briefpain_short.pdf (accessed March 30, 2020).

16 WHO. WHO's cancer pain ladder for adults. 2020. https://www.who.int/cancer/palliative/painladder/en/ (accessed March 30, 2020).

17 Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol* 2013; **14:** 1193–99.

18 Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol* 2015; **16:** 509–21.

19 Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health* 2009; **12:** 124–29.

20 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–36.

21 Behl AS, Ellis LA, Pilon D, Xiao Y, Lefebvre P. Medication adherence, treatment patterns, and dose reduction in patients with metastatic castration-resistant prostate cancer receiving abiraterone acetate or enzalutamide. *Am Health Drug Benefits* 2017; **10:** 296–303.

22 McKay R, Haider B, Duh MS, et al. Impact of symptomatic skeletal events on health-care resource utilization and quality of life among patients with castration-resistant prostate cancer and bone metastases. *Prostate Cancer Prostatic Dis* 2017; **20:** 276–82.

23 Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol* 2000; **163:** 181–86.

24 Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol* 2020; **77:** 508–47.

25 Mottet N, van den Bergh RCN, Briers E, et al. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer. European Association of Urology. 2018. https://uroweb.org/guideline/prostate-cancer/ (accessed June 1, 2020).

26 Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: The report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol* 2018; **73:** 178–211.

27 Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20:** 408–19.

28 Tombal BF, Loriot Y, Saad F, et al. Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223 versus enzalutamide alone: an interim safety analysis. *Proc Am Soc Clin Oncol* 2019; **37** (suppl)**:** 5007 (abstr).

29 Delanoy N, Hardy-Bessard AC, Efstathiou E, et al. Clinical progression is associated with poor prognosis whatever the treatment line in metastatic castration resistant prostate cancer: The CATS international database. *Eur J Cancer* 2020; **125:** 153–63.

30 Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. *Eur J Cancer* 2013; **49:** 3648–57.

31 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; **368:** 138–48.

32 Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; **371:** 424–33.

33 de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **382:** 2091–102.

34 Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol* 2020; **21:** e83–96.