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# Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel vs abiraterone or enzalutamide: An analysis of the Phase 4 CARD randomized study

## Authors

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1 **Abstract (342/300)**

2 **Background:** In the CARD study, cabazitaxel significantly improved radiographic progression-  
3 free survival (rPFS) and overall survival versus abiraterone or enzalutamide in patients with  
4 metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel  
5 and the alternative androgen-signaling-targeted inhibitor.

6 **Methods:** Patients ( $\geq 18$  years, ECOG PS  $\leq 2$ ) with confirmed mCRPC were randomized 1:1  
7 using an interactive voice/Web response system to receive cabazitaxel (25 mg/m<sup>2</sup>  
8 intravenously every 3 weeks, 10 mg daily prednisone, and granulocyte colony-stimulating  
9 factor) versus abiraterone (1000 mg plus 5 mg prednisone twice daily) or enzalutamide (160  
10 mg daily). Stratification factors were ECOG PS, time to progression on, and timing of the  
11 prior androgen-signaling-targeted inhibitor. The primary endpoint was rPFS; here, we  
12 present more detailed analyses of pain and symptomatic skeletal events (SSEs), alongside  
13 pre-planned patient reported outcomes (PROs). CARD was open label (NCT02485691).

14 **Findings:** Between 17 Nov 2015 and 28 Nov 2018, 255 patients were randomly assigned to  
15 cabazitaxel (n=129) or abiraterone or enzalutamide (n=126). Median follow-up was 9·2  
16 months (IQR: 5·6–13·1). Pain response was observed in 51/111 patients (46%) with  
17 cabazitaxel and 21/109 (19%) with abiraterone or enzalutamide ( $p < 0\cdot0001$ ). Median time to  
18 pain progression was not reached (NE; 95% CI: NE–NE) with cabazitaxel and 8·5 months  
19 (95% CI: 4·9–NE) with abiraterone or enzalutamide (HR: 0·55; 95% CI: 0·32–0·97; log-rank  
20  $p = 0\cdot035$ ). Median time to SSEs was NE (95% CI: 20·0–NE) with cabazitaxel and 16·7 months  
21 (95% CI: 10·8–NE) with abiraterone or enzalutamide (HR: 0·59, 95% CI: 0·35–1·01; log-rank  
22  $p = 0\cdot050$ ). Median time to Functional Assessment of Cancer Therapy-Prostate (FACT-P) total  
23 score deterioration was 14·8 months (95% CI: 6·3–NE) with cabazitaxel and 8·9 months (95%  
24 CI: 6·3–NE) with abiraterone or enzalutamide (HR: 0·72, 95% CI: 0·44–1·20; log-rank  $p = 0\cdot21$ ).  
25 There was a significant treatment effect seen in changes from baseline in EQ-5D-5L utility  
26 index score in favor of cabazitaxel over abiraterone or enzalutamide ( $p = 0\cdot030$ ).

27 **Interpretation:** As cabazitaxel improved pain response, time to pain progression, time to  
28 SSEs and EQ5D-5L utility index, clinicians and patients with mCRPC can be reassured that  
29 cabazitaxel will not reduce quality of life when compared with a second androgen-signaling-  
30 targeted inhibitor.

31 **Funding:** This research was funded by Sanofi.

32 **Research in context**

33 *Evidence before this study*

34 Results from the CARD study demonstrated improved overall survival with cabazitaxel  
35 versus abiraterone or enzalutamide in patients with mCRPC previously treated with  
36 docetaxel and who failed within 12 months on the alternative androgen-signaling–targeted  
37 inhibitors. Many patients with advanced mCRPC have bone metastases, which can cause  
38 pain and deterioration of quality of life. Therefore, it is crucial to balance clinical activity and  
39 adverse events of therapies administered with their impact on patient quality of life. We  
40 searched PubMed using the terms “metastatic castration-resistant prostate cancer”,  
41 “quality of life”, “pain”, “skeletal-related events”, “cabazitaxel”, “abiraterone,” and  
42 “enzalutamide” for studies published before January 1st, 2020. We identified two Phase 3  
43 studies showing that both abiraterone and enzalutamide improve pain, delay pain  
44 progression and skeletal-related events, and improve PROs (as assessed by FACT-P) versus  
45 placebo in mCRPC patients previously treated with docetaxel. Our search did not identify  
46 any randomized studies directly comparing abiraterone or enzalutamide with cabazitaxel,  
47 which strengthened the rationale for reporting these preplanned secondary endpoints of  
48 the CARD study related to patient quality of life.

49 *Added value of this study*

50 CARD compared the impact of cabazitaxel versus abiraterone or enzalutamide on measures  
51 of PROs (as assessed by FACT-P and EQ-5D-5L), pain, and SSEs. Results demonstrate that, in  
52 addition to the previously reported survival benefits, cabazitaxel improves pain response,  
53 delays time to pain progression and time to SSEs, and has no deleterious impact on PROs.  
54 The study provides reassurance that cabazitaxel 25 mg/m<sup>2</sup> administered with systematic  
55 granulocyte colony-stimulating factor (G-CSF) prophylaxis is a relevant treatment option for  
56 mCRPC patients previously treated with one androgen-signaling–targeted inhibitor and  
57 docetaxel.

58 *Implications of all the available evidence*

59 This analysis further clarifies the optimal treatment sequence in mCRPC by highlighting the  
60 value of cabazitaxel in patients previously treated with docetaxel and an androgen-  
61 signaling–targeted inhibitor and who progressed within 12 months with the alternative  
62 androgen-signaling-targeted inhibitor. The available evidence supports the use of

63 cabazitaxel over abiraterone or enzalutamide as a standard of care in this patient population  
64 in terms of both clinical outcomes and quality of life.

65 **Introduction**

66 Several new therapies have been shown to improve survival for patients with mCRPC during  
67 the past few years, including taxanes (docetaxel, cabazitaxel), androgen-signaling-targeted  
68 inhibitors (abiraterone, enzalutamide), a radiopharmaceutical (radium-223), and an  
69 immunotherapy (sipuleucel-T). Bone-targeted agents have demonstrated activity in  
70 preventing skeletal-related events in patients with mCRPC.<sup>1</sup> Many studies have evaluated  
71 treatment sequencing, however these were small retrospective studies, carried out using  
72 different inclusion, exclusion and outcome criteria.<sup>2</sup> Although survival increases with the  
73 number of life-extending therapies received, the optimal treatment sequence is unclear.<sup>2</sup> In  
74 daily practice, many patients receive both abiraterone and enzalutamide before taxanes,  
75 mostly due to age, patient choice, and because these agents are considered less toxic than  
76 chemotherapy.<sup>3,4</sup> However, many studies suggest there is cross-resistance between these  
77 novel androgen-signaling-targeted inhibitors.<sup>2,3,5</sup>

78 Since cabazitaxel retains activity in patients progressing on docetaxel, abiraterone, or  
79 enzalutamide,<sup>6</sup> the CARD study evaluated cabazitaxel versus abiraterone or enzalutamide in  
80 patients who had received prior docetaxel and progressed within 12 months on an  
81 alternative androgen-signaling-targeted inhibitor.<sup>7</sup> Cabazitaxel was associated with  
82 improved radiographic progression-free survival (rPFS) and overall survival compared with  
83 abiraterone or enzalutamide.<sup>7</sup>

84 As the prognosis for mCRPC has improved, treatment goals have broadened from merely  
85 prolonging survival to minimizing symptoms and enabling patients to live fulfilled lives.<sup>8</sup>  
86 Maintaining or improving quality of life has become increasingly important when selecting  
87 treatment regimens, due to high symptom and treatment burdens associated with mCRPC.  
88 The value of patient-reported outcomes (PROs) is well established in prostate cancer, with  
89 several validated prostate cancer-specific questionnaires available to assess physical and  
90 psychologic symptoms.<sup>9</sup> Pain, symptomatic skeletal events (SSEs), and physical and  
91 functional well-being have been shown to predict overall survival and other clinical  
92 outcomes in patients with mCRPC.<sup>10-13</sup> This underscores the importance of evaluating such  
93 parameters during interventional studies in order to determine optimal patient-centered  
94 care.



95 In this analysis of CARD, we describe the impact of cabazitaxel versus abiraterone or  
96 enzalutamide on pre-planned endpoints associated with quality of life.

97

98 **Methods**

99 *Study design and participants*

100 CARD was a randomized, multicenter, open-label study involving 62 sites across 13  
101 European countries. It was designed to compare cabazitaxel with abiraterone and  
102 enzalutamide in patients with mCRPC who had received prior docetaxel and progressed  
103 within 12 months on the alternative androgen-signaling-targeted inhibitor. The full study  
104 design and eligibility criteria have been described previously.<sup>7</sup> Briefly, patients with prostate  
105 cancer were eligible if they had castrate levels of testosterone (<0.5 ng/mL), had disease  
106 progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or had  
107  $\geq 2$  new bone lesions or rising prostate-specific antigen (PSA) level per Prostate Cancer  
108 Working Group 2 (PCWG2) criteria, had received  $\geq 3$  docetaxel cycles and progressed within  
109 12 months of androgen-signaling-targeted inhibitor treatment. Docetaxel or abiraterone  
110 was allowed for metastatic hormone-sensitive disease. Exclusion criteria included age <18  
111 years, ECOG PS >2, prior chemotherapy (except docetaxel), history of seizure, inadequate  
112 organ or bone marrow function, history of prior malignancy within 5 years, history of  
113 mineralocorticoid excess or deficiency and uncontrolled severe illness or medical condition.  
114 The study was conducted in accordance with the Declaration of Helsinki and Good Clinical  
115 Practice guidelines. Patients provided written informed consent before participation and the  
116 study received ethics approval from the relevant bodies.

117 *Randomization and masking*

118 Eligible patients were allocated through a centralized, stratified randomization process to  
119 receive either cabazitaxel or abiraterone or enzalutamide in a 1:1 ratio by an interactive  
120 voice/Web response system. Stratifying criteria at randomization included ECOG PS (0–1  
121 versus 2), time to disease progression on prior androgen-signaling-targeted inhibitor ( $\leq 6$   
122 versus 6–12 months), and timing of the prior androgen-signaling-targeted inhibitor (before  
123 versus after docetaxel). An independent organization was responsible for generating the  
124 allocation sequence, enrolling participants and assigning trial groups that had no other  
125 involvement in the trial.

126 The study was open label and participants and investigators were not masked to treatment  
127 allocation. However the study team, excluding individuals who had access to patient

128 documents (e.g. monitoring team, auditors), remained blinded to the treatment arm of  
129 individual patients until the database lock.

### 130 *Procedures*

131 Patients were screened 4 weeks before randomization for eligibility and baseline  
132 measurements. Cabazitaxel 25 mg/m<sup>2</sup> was administered intravenously over 1 hour every 3  
133 weeks with prophylactic G-CSF at each cycle and prednisone 10 mg daily. Abiraterone 1000  
134 mg was given orally once daily with prednisone 5 mg twice daily. Enzalutamide 160 mg was  
135 given orally once daily. A treatment cycle was 3 weeks. Patients who had previously  
136 received enzalutamide received abiraterone, and vice versa. Two dose reductions were  
137 permitted before treatment discontinuation (cabazitaxel to 20 mg/m<sup>2</sup>, then 15 mg/m<sup>2</sup>;  
138 abiraterone to 750 mg, then 500 mg; enzalutamide to 120 mg, then 80 mg). The 750 mg  
139 abiraterone dose reduction level was discontinued on 14 March 2018 to align with updated  
140 European labelling. Treatment interruptions of <2 weeks were permitted to allow acute  
141 toxicity recovery. Treatment continued until criteria for permanent discontinuation were  
142 reached: imaging-based progression, unacceptable toxicity, investigator decision (including  
143 non-compliance) or patient request to stop the study, or loss to follow-up.

144 No blinded central review was performed on standard imaging (bone scans, CT and MRI of  
145 pelvis, abdomen, and chest). Adverse events were monitored every 3 weeks during  
146 treatment, at the end of treatment visit and every 12 weeks during follow-up until disease  
147 progression, start of other anticancer treatment or study cut-off, and reported in  
148 compliance with regulations. Laboratory tests were obtained prior to treatment  
149 administration, at every cycle and up to 30 days after the last study treatment  
150 administration. Study protocol and all amendments affecting recruitment to or conduct of  
151 the study were approved by review boards of participating institutions.

152 Pain, and PRO assessments were carried out at baseline, every 3 weeks at each visit before  
153 treatment administration and at the end of treatment visit, then every 12 weeks until  
154 disease progression, start of subsequent cancer therapy, or study cut-off date, whichever  
155 came first. SSEs were evaluated at baseline, each visit, end of treatment, and every 12  
156 weeks during follow-up. Standard imaging was scheduled at baseline and every 12 weeks  
157 until imaging-based disease progression. Pathologic fractures and spinal cord compression  
158 were assessed by imaging as needed throughout the study.

159 Each PRO questionnaire was conducted using paper/pencil versions and no assistance was  
160 given to patients whilst they were completing the forms. Patients were not advised on a  
161 specific order to complete the forms.

### 162 *Outcomes*

163 The primary endpoint was imaging-based progression-free survival (rPFS), as reported  
164 previously.<sup>7</sup> Key secondary endpoints tested hierarchically were overall survival,  
165 progression-free survival, PSA response, and objective tumor response. Pain response and  
166 SSEs were partially described in the primary CARD publication. Here, we report more  
167 detailed analyses of pre-planned endpoints affecting quality of life.

168 Pain intensity was defined using item 3 of the validated Brief Pain Inventory-Short Form  
169 (BPI-SF), which rates pain at its worst in the last 24 hours on a scale of 0 (no pain) to 10  
170 (worst imaginable pain).<sup>14</sup> Analgesic consumption was reported by local investigators and  
171 coded by the World Health Organization's analgesic ladder (0 = no analgesic; 1 = non-opioid  
172 analgesics; 2 = opioid analgesics for moderate pain; 3 = opioids for severe pain).<sup>15</sup> Pain  
173 response was defined as a  $\geq 30\%$  decrease from baseline in average BPI-SF pain intensity  
174 score observed at two consecutive evaluations at least 3 weeks apart without an increased  
175 analgesic usage score. Pain progression was defined as a  $\geq 30\%$  increase from baseline in  
176 BPI-SF pain intensity score (item 3) observed at two consecutive evaluations at least 3 weeks  
177 apart without a  $\geq 30\%$  increase or decrease in analgesic usage score. Time to pain  
178 progression was defined as time from randomization until first documented pain  
179 progression.

180 SSEs were defined as either the use of external beam radiation to relieve bone pain,  
181 occurrence of new symptomatic pathologic fractures, occurrence of spinal cord  
182 compression, or tumor-related orthopedic surgical intervention. Time to SSE was defined as  
183 time from randomization until first documented SSE.

184 PROs were assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P)  
185 questionnaire (version 4) and the generic health status/utility instrument EQ-5D-5L. We  
186 used these instruments because they were standard tools to measure quality of life in  
187 prostate cancer at the time the CARD protocol was developed and have been shown to be  
188 reliable and valid in this patient population.<sup>16,17</sup> FACT-P is a 39-item self-report tool designed

189 to evaluate quality of life in patients with prostate cancer.<sup>18</sup> Full ranges and definitions for  
190 FACT-P subscales can be found in **Supp Table 1**. A higher FACT-P score indicates better  
191 quality of life. A deterioration in HRQL was defined as a  $\geq 10$ -point change in FACT-P total or  
192 a specified change in subscale score (as described in **Supp Table 2**) on two consecutive  
193 evaluations,  $>3$  weeks apart. EQ-5D-5L describes five health dimensions: mobility, self-care,  
194 usual activities, pain/discomfort, and anxiety/depression. Patients rate each domain on a 1–  
195 5 Likert-type scale (1=no problems, 2=slight problems, 3=moderate problems, 4=severe  
196 problems, 5=extreme problems).<sup>19</sup> The minimally important difference for EQ-5D-5L utility  
197 index was 0.14 and 11 for VAS. To ensure we did not overestimate the clinically meaningful  
198 effect of treatment, we used the upper values of the established range for both utility index  
199 and VAS, which are 0.04–0.14 and 7–11, respectively.<sup>17</sup>

200

#### 201 *Statistical analysis*

202 The statistical analysis plan for the assessment of PROs is available in the appendix (**p143**).  
203 The study was designed to have 80% power to detect a HR of 0.67 (cabazitaxel versus  
204 abiraterone or enzalutamide) in the analysis of the primary endpoint (rPFS), with the use of  
205 a stratified log-rank test at a two-sided alpha level of 5%. Approximately 234 patients  
206 needed to be randomized to collect data on 196 events (achieved at the cut-off date of  
207 March 27, 2019). There was no interim analysis. The study was not powered for the  
208 secondary endpoints reported here. All analyses reported were obtained at the cut-off date,  
209 as planned in the protocol (**Appendix p23**).

210 Efficacy analyses were conducted in the intention-to-treat (ITT) population, defined as all  
211 patients who underwent randomization. Pain response was analyzed in the ITT population  
212 with baseline and at least one post-baseline assessment of BPI-SF item 3. PROs were  
213 analyzed in the ITT population with baseline and at least one post-baseline assessment of  
214 either FACT-P or EQ-5D-5L (PRO population). P values of  $<0.05$  were deemed significant for  
215 the primary analysis and all analyses presented.

216 Stratified log-rank tests were used to analyze time to event and time to progression data.  
217 Hazard ratios (HR) and associated 95% confidence intervals (CIs) were estimated using a  
218 stratified Cox proportional hazards model. Proportional hazards assumptions were checked

219 by visual inspection of negative log graphs (**Appendix p12**). Patients with no progression or  
220 deterioration at the time of the analysis were censored on the last date they were known to  
221 have not progressed or deteriorated.

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

226 PRO changes from baseline were analyzed using a mixed linear repeated measures model  
227 where treatment is a fixed effect variable and subject is a random effect variable.  
228 Stratification variables were included in the model as covariates as well as the interaction  
229 treatment visit. The least square means by treatment group with corresponding 95% CI  
230 obtained from the mixed model were presented graphically. No adjustments for multiplicity  
231 were made.

232 Compliance with the planned assessment schedule was calculated at baseline and for each  
233 cycle as the proportion of patients receiving study treatment at this time point. No formal  
234 imputation for missing data was carried out and reasons for missing data were not centrally  
235 recorded. FACT-P total score was evaluable when  $>80\%$  of questions were answered. For  
236 FACT-P subscales, a score was evaluable when  $>50\%$  of the questions in the subscale domain  
237 were answered. If  $<50\%$  of the questions were missing in any FACT-P subscale, the score  
238 could be imputed using the following formula: Prorated subscale score =  $[\text{Sum of question}$   
239  $\text{scores}] \times [\text{N of questions in subscale}] \div [\text{N of questions answered}]$ .

240 Data were analyzed with SAS version 9.2. The study is registered with Clinicaltrials.gov  
241 (NCT02485691).

242

#### 243 *Role of the funding source*

244 Sanofi Genzyme funded the CARD study, provided the study treatments, and collaborated  
245 with the co-authors on study design, data analysis, data interpretation, and writing of the  
246 report. The sponsor had no role in data collection. The manuscript was written with editorial  
247 support from medical writers, funded by the sponsor. The corresponding author (KF) had

248 full access to the data and had the final responsibility for the decision to submit for  
249 publication. Authors received no honoraria for development of this manuscript.

250 **Results**

251 Between 17 Nov 2015 and 28 Nov 2018, 255 patients with mCRPC were randomized (129 to  
252 cabazitaxel, 126 to abiraterone or enzalutamide) and 250/255 were treated (126/129 with  
253 cabazitaxel, 124/126 with abiraterone or enzalutamide) (**Figure 1**). The 255 patients  
254 randomized constituted the intention-to-treat population. At the cut-off date, median  
255 follow-up was 9.2 months (IQR: 5.6–13.1). Median duration of treatment was 22.0 weeks  
256 with cabazitaxel (IQR: 13.1–30.4) versus 12.5 weeks (IQR: 9.9–23.4) with abiraterone or  
257 enzalutamide. The median number of cycles received was 7 (IQR: 4–10) with cabazitaxel  
258 versus 4 (IQR: 3–8) with abiraterone or enzalutamide. More patients discontinued  
259 abiraterone or enzalutamide early due to disease progression compared with cabazitaxel.

260 Patient demographics and clinical characteristics at baseline have been reported previously<sup>7</sup>  
261 and are shown in **Table 1**. At least one dose reduction was required as per labelling  
262 recommendations for 27/126 patients (21%) receiving cabazitaxel and 47/124 patients  
263 (38%) receiving an androgen-signaling-targeted inhibitor (17/58 [29%] patients with  
264 abiraterone and 30/66 [46%] patients with enzalutamide). The significant number of  
265 patients in the androgen-signaling-targeted inhibitor group requiring a dose reduction is in  
266 line with clinical experience in mCRPC.<sup>20</sup>

267 Pain response was evaluable in 220/255 patients (111/129 with cabazitaxel and 109/126  
268 with abiraterone or enzalutamide), 35/255 patients (18/129 with cabazitaxel and 17/126  
269 with abiraterone or enzalutamide) were not evaluable due to incomplete BPI-SF  
270 questionnaires. As previously reported, confirmed pain response was observed in 51/111  
271 patients (46%) receiving cabazitaxel and 21/109 patients (19%) receiving abiraterone or  
272 enzalutamide ( $p < 0.0001$ ). At the cut-off date, 25/111 (23%) patients receiving cabazitaxel  
273 had pain progression, compared with 27/109 (25%) with abiraterone or enzalutamide. The  
274 median time to pain progression was NE with cabazitaxel (95% CI: NE–NE) and 8.5 months  
275 (95% CI: 4.9–NE) with abiraterone or enzalutamide (HR: 0.55; 95% CI: 0.32–0.97; log-rank  
276  $p = 0.035$ ). The Kaplan-Meier estimates of not having pain progression with cabazitaxel  
277 versus abiraterone or enzalutamide are shown in **Table 2**.

278



279 SSEs were observed in 24/129 patients (19%) in the cabazitaxel arm and 35/126 patients  
280 (28%) in the abiraterone or enzalutamide arm (**Table 3**), which were the numbers with an  
281 event included in analyses of time to SSEs. Despite a lower use of denosumab or  
282 bisphosphonates in patients treated with cabazitaxel (27/129 [21%]) versus abiraterone or  
283 enzalutamide (46/126 [37%]), the median time to SSEs was NE (95% CI: 20·0–NE) with  
284 cabazitaxel and 16·7 months (95% CI: 10·8–NE) with abiraterone or enzalutamide (HR: 0·59,  
285 95% CI: 0·35–1·01; log-rank p=0·050). The Kaplan-Meier estimates of not having SSEs with  
286 cabazitaxel versus abiraterone or enzalutamide are shown in **Table 3**.

287 FACT-P was evaluable in 108/129 patients (84%) receiving cabazitaxel and 114/126 patients  
288 (91%) receiving abiraterone or enzalutamide, with 21/129 and 12/129 patients excluded  
289 due to incomplete FACT-P questionnaires in each arm, respectively. At the cut-off date,  
290 FACT-P deterioration was recorded in 32/108 (30%) patients receiving cabazitaxel and  
291 33/114 (29%) patients receiving abiraterone or enzalutamide. Data are shown for up to  
292 eight cycles and end of treatment due to small patient numbers for later cycles. At least one  
293 item in the FACT-P questionnaire was completed by  $\geq 88\%$  of patients in each treatment  
294 arm at each visit (**Appendix p5, p7**).

295 Mean FACT-P total scores at baseline were 104 and 105 for patients who received  
296 cabazitaxel versus abiraterone or enzalutamide, respectively (**Table 1**). The median time to  
297 FACT-P total score deterioration was 14·8 months (95% CI: 6·3–NE) with cabazitaxel and 8·9  
298 months (95% CI: 6·3–NE) with abiraterone or enzalutamide (HR: 0·72; 95% CI: 0·44–1·20;  
299 log-rank p=0·21). In repeated-analysis measures using a mixed-effect model, no significant  
300 differences between arms were observed (**Figure 2; Appendix p9**). Mean changes from  
301 baseline at end of treatment in FACT-P total score were -6·33 (SE: 2·81) with cabazitaxel and  
302 -10·91 (SE: 3·13) with an androgen-signaling-targeted inhibitor (LS mean difference: 4·58;  
303 95% CI: -1·36 to +10·52; p=0·13). For FACT-P subscale scores, time to deterioration was  
304 numerically longer in patients receiving cabazitaxel compared with patients receiving  
305 abiraterone or enzalutamide, although significance was reached only for the emotional well-  
306 being subscale (HR=0·46 [95% CI 0·25–0·87], p=0·015) (**Table 2; Figure 3**). There was a  
307 significant difference between arms (p<0·001) favoring cabazitaxel for the pain-related  
308 subscale (referred to as “pain-PCS”) with least squares mean difference ranging from +1·12  
309 (95% CI: -0·38 to +2·61) to +2·26 (95% CI: +1·06 to +3·47); there were also numerical

310 between group differences in the percentage of patients with improved pain-related  
311 subscale, although tests for significance were not conducted (**Appendix p1**). Conversely,  
312 changes in social or family well-being significantly favored abiraterone or enzalutamide  
313 ( $p=0.02$ ). For the other dimensions (FACT-P total score, Functional Assessment of Cancer  
314 Therapy-General (FACT-G), trial outcome index, physical, emotional and functional well-  
315 being, and prostate-specific concerns) no significant between-group differences were  
316 observed.

317 Post hoc exploratory analyses to determine whether these results were related to the  
318 prolonged overall survival or greater pain relief associated with cabazitaxel were conducted.  
319 Overall survival estimates, estimates of experiencing pain progression, and FACT-P  
320 deterioration at 3 and 9 months are shown in **Table 2**. The differences in FACT-P values  
321 between the cabazitaxel and abiraterone or enzalutamide arms appeared more closely  
322 related to pain relief than overall survival. Median time from FACT-P definitive deterioration  
323 to death was 7.5 months (IQR 0–10.2) with cabazitaxel versus 4.8 months (IQR 0–8.7) with  
324 abiraterone or enzalutamide. Median time from confirmed pain progression to death was  
325 8.6 months (IQR 6.7–14.2) with cabazitaxel versus 7.0 months (IQR 5.2–12.0) with  
326 abiraterone or enzalutamide.

327

328 EQ-5D-5L was evaluable in 115/129 patients (89%) receiving cabazitaxel and 115/126  
329 patients (91%) receiving abiraterone or enzalutamide, with 14/129 (11%) and 11/126 (9%)  
330 patients excluded due to missing EQ-5D-5L questionnaires, respectively. Data are shown for  
331 up to 8 cycles and end of treatment because the number of patients receiving subsequent  
332 cycles in the control arm was too small. At least one item in the EQ-5D-5L questionnaire was  
333 completed by  $\geq 82\%$  of patients in each treatment arm at each visit (**Appendix p6, p8**).

334 Mean values for EQ-5D-5L health status (visual analogue score; VAS) at baseline were 65.8  
335 (SD: 20.4) for cabazitaxel and 66.3 (SD: 18.5) for abiraterone or enzalutamide (**Table 1**).

336 There was a non-significant treatment effect seen in changes from baseline in VAS  
337 ( $p=0.060$ ), with least squares mean difference between cabazitaxel and abiraterone or  
338 enzalutamide ranging from +1.6 (95% CI: -3.65 to +6.85) to +6.4 (95% CI: +1.49 to +11.25).  
339 (**Figure 2**).

340 At baseline, mean values for utility index were 0.70 (SD: 0.26) in the cabazitaxel arm and  
341 0.70 (SD: 0.22) in the abiraterone or enzalutamide arm (**Table 1**). There was a significant  
342 treatment effect seen in changes from baseline in EQ-5D-5L utility index score in favor of  
343 cabazitaxel over abiraterone or enzalutamide ( $p=0.030$ ), with least squares mean difference  
344 ranging from +0.03 (95% CI: -0.04 to +0.11) to +0.08 (95% CI: +0.02 to +0.14) during  
345 treatment and +0.05 (95% CI: -0.02 to +0.11) at end of treatment in favor of cabazitaxel  
346 (**Figure 2**).

347 Moderate, severe, or extreme pain/discomfort per EQ-5D-5L was reported by 45 of 115  
348 patients (39%) receiving cabazitaxel and 47 of 115 patients (41%) receiving abiraterone or  
349 enzalutamide at baseline. There were numerical between-group differences in the number  
350 of patients reporting improvement in pain/discomfort from baseline in favor of cabazitaxel  
351 (**Appendix p2**); however, tests for significance were not conducted.

## 352 **Discussion**

353 To our knowledge, this prospective, randomized study is the first to directly compare  
354 cabazitaxel and abiraterone or enzalutamide in patients with mCRPC previously treated with  
355 docetaxel and the alternative androgen-signaling-targeted inhibitor. In these pre-planned  
356 analyses, cabazitaxel significantly improved pain response and prolonged time to pain  
357 progression versus abiraterone or enzalutamide. Cabazitaxel also reduced the probability of  
358 developing SSEs despite lower use of denosumab or bisphosphonates compared with  
359 patients receiving abiraterone or enzalutamide. Lastly, cabazitaxel had no deleterious  
360 impact on PROs compared with a second androgen-signaling-targeted inhibitor. In the  
361 recent past, many patients received back-to-back androgen-signaling-targeted inhibitors in  
362 daily practice due to concerns surrounding the toxicity of chemotherapy. This analysis can  
363 provide reassurance to physicians and patients that receiving cabazitaxel chemotherapy will  
364 not reduce HRQL or induce additional toxicity when compared with oral androgen-signaling-  
365 targeted inhibitors.

366

367 Since it is known that HRQL deteriorates close to death, we attempted to determine  
368 whether numerically longer time to deterioration in FACT-P total score and subscale scores  
369 with cabazitaxel were related to the greater pain relief or longer survival also seen in

370 patients receiving cabazitaxel. Post hoc exploratory landmark analyses at 3 and 9 months  
371 suggest that estimates of FACT-P deterioration were comparable to those of pain  
372 deterioration, with the probability of disease-related death being relatively small during the  
373 initial months. Nevertheless, it is difficult to ascertain whether the numerical differences in  
374 HRQL reflect the impact of cabazitaxel on symptoms, overall survival, or both.

375 In mCRPC, metastases are frequently located in the bone, resulting in significant pain and  
376 fractures that contribute to HRQL deterioration and increased mortality.<sup>13,21</sup> Androgen  
377 suppression is associated with loss of bone mineral density and increased risk of fracture.<sup>22</sup>  
378 In CARD, concomitant use of bisphosphonates or denosumab was lower in the cabazitaxel  
379 arm at baseline versus the abiraterone or enzalutamide arm, underlining the significant  
380 under-usage of these medications by treating physicians. International guidelines and  
381 consensus conferences consistently provide recommendations for monitoring and  
382 maintaining bone health, including baseline evaluation of bone mineral density,  
383 supplementation with calcium and vitamin D, and use of denosumab or bisphosphonates in  
384 patients with mCRPC and bone metastases at high risk of fracture.<sup>23-25</sup> A Phase 3 study  
385 combining abiraterone and radium-223 observed a decreased risk of fractures and mortality  
386 with the addition of bone-health agents, highlighting the importance of these prophylactic  
387 measures in daily practice.<sup>26</sup> In addition, a decreased fracture rate by mandating bone-  
388 protecting agents was observed in the EORTC 1333/PEACEIII trial combining radium-223  
389 with enzalutamide versus enzalutamide alone.<sup>27</sup> Despite the imbalance between arms in  
390 bone-targeted agents in CARD, cabazitaxel decreased the probability of developing SSEs  
391 versus abiraterone or enzalutamide.

392 In the CARD study, most patients had pain progression at randomization. Similar findings  
393 were reported in a large retrospective registry of 661 patients with mCRPC treated in clinical  
394 practice.<sup>28</sup> This possibly reflects recommendations of international guidelines and consensus  
395 conferences to continue androgen-signaling-targeted inhibitors until unequivocal signs of  
396 progression (i.e. imaging-based and/or clinical progression) before switching therapy.<sup>23,24</sup>  
397 Since pain progression is consistently associated with aggressive disease and worse overall  
398 survival, it is important to adequately manage such patients.<sup>12,28</sup> The present results  
399 demonstrate that patients receiving cabazitaxel have a greater pain response and longer

400 time to pain progression compared with patients receiving a second androgen-signaling-  
401 targeted inhibitor.

402 Patients in the CARD study had advanced metastatic disease, which may contribute to their  
403 lower baseline FACT-P scores and shorter treatment durations compared with studies of  
404 patients with less advanced prostate cancer.<sup>16,17,29</sup> In the Phase 3 PREVAIL study, which  
405 evaluated enzalutamide in asymptomatic or minimally symptomatic chemotherapy-naïve  
406 patients with mCRPC, mean FACT-P total score at baseline was 119.59 (SD: 17.78) in patients  
407 receiving enzalutamide and 119.41 (SD: 17.92) in patients receiving placebo. By end of  
408 treatment, mean changes from baseline were -5.08 (95% CI: -6.87 to -3.28) in the  
409 enzalutamide arm and -10.87 (95% CI: -13.49 to -8.25) in the placebo arm.<sup>17</sup> Similarly, in the  
410 Phase 3 COU-AA-302 study of abiraterone in chemotherapy-naïve patients with mCRPC,  
411 baseline FACT-P scores were 122.1 (SD: 17.0) in the abiraterone arm and 122.6 (SD: 17.7) in  
412 the placebo arm. Mean changes from baseline were not reported.<sup>16</sup> In comparison, patients  
413 in CARD had lower FACT-P scores at baseline with mean changes from baseline at end of  
414 treatment comparable to those of PREVAIL. This shows that despite worse HRQL at  
415 baseline, based on FACT-P total baseline scores, changes at end of treatment in patients  
416 receiving cabazitaxel were comparable with those observed at earlier disease stages with a  
417 first androgen-signaling-targeted inhibitor.

418 There are several limitations that must be considered. CARD was open label with a relatively  
419 small number of patients (n=255) and not powered for the secondary analyses presented  
420 here. Despite this, the primary endpoint (rPFS) and the main secondary end-point (overall  
421 survival) were significantly improved with cabazitaxel, reinforcing the validity of our  
422 findings.<sup>7</sup> Furthermore, CARD enrolled patients who had progressed within 12 months on  
423 the alternative androgen-signaling-targeted inhibitor, which may limit the generalizability of  
424 the data in the era of combination systemic therapy in metastatic hormone-sensitive and  
425 nonmetastatic castration resistant prostate cancer . Importantly, patients with PSA  
426 progression within 12 months were eligible, even if treatment continued for a longer period.  
427 In Phase 3 studies of abiraterone and enzalutamide in patients with asymptomatic  
428 chemotherapy-naïve mCRPC, median time to PSA progression was <12 months.<sup>30,31</sup>  
429 Additionally, in the PROfound study of olaparib versus abiraterone or enzalutamide in  
430 mCRPC patients with DNA repair abnormalities, a second androgen-signaling-targeted

431 inhibitor was associated with a short rPFS of 3.55 months (compared with 3.7 months in  
432 CARD), despite no eligibility restrictions in relation to time to progression with the first  
433 androgen-signaling-targeted inhibitor.<sup>32</sup> There are also inherent multiplicity issues with  
434 recording outcomes at multiple time points throughout treatment, and issues relating to  
435 lower patient numbers at the end of the study. The mixed linear repeated measures model  
436 that was used attempted to reduce the probability of type 1 errors introduced as the result  
437 of dropout bias. However, there are two issues that may introduce bias in either direction:  
438 reasons for missing data were not centrally recorded and therefore not well characterized,  
439 and there was an imbalance between arms in FACT-P and EQ-5D-5L completion rates during  
440 treatment. Lastly, as with any PRO analysis, it is not possible to isolate the effects of  
441 treatment and disease burden from other factors influencing patients' lives.

442 One strength of this analysis is the use of validated and reliable PRO questionnaires (FACT-P  
443 and EQ-5D-5L). Adherence to each of the BPI-SF, FACT-P, and EQ-5D-5L questionnaires was  
444 quite high at baseline and during treatment. Although the CARD study was conducted in  
445 accordance with the appropriate guidelines when it was designed, it also satisfies several  
446 recommendations of the SISAQOL consortium for the analysis of PROs in cancer trials.<sup>33</sup>  
447 Specifically, CARD used valid within-group PRO objectives, predefined PRO analysis  
448 populations, and clearly defined criteria for improvement/stable/deterioration based on  
449 predefined threshold levels. Additionally, overall effect endpoints were used with caution,  
450 and Cox proportional hazard and linear mixed model tests were chosen where appropriate.

451 In the field of medical oncology, it is often the case that effective interventions may not be  
452 the best choice from the patient's perspective due to adverse events impacting HRQL. Here,  
453 we demonstrate that cabazitaxel significantly improves pain response and time to pain  
454 progression reduces the risk of developing SSEs compared with abiraterone or  
455 enzalutamide, and is not associated with a detrimental impact on HRQL in patients with  
456 mCRPC who have received prior docetaxel and progressed on the alternative androgen-  
457 signaling-targeted inhibitor within a year. These findings, combined with the overall survival  
458 benefit previously published, should help to guide treatment decisions and reassure  
459 patients and treating physicians that they should not be reluctant to receive or prescribe  
460 chemotherapy.<sup>7</sup>

461 **Declaration of interests**

462 KF has received honoraria and provided an advisory role for Astellas, AAA, Bayer, Essa,  
463 Janssen, Orion, CureVac, Clovis, Sanofi, and Endocyte. GK received personal fees from  
464 Sanofi, Astellas, Takeda, Bayer, Janssen, Novartis, Ipsen, and AstraZeneca, and has received  
465 grants from Sanofi and Bayer. J-CE has received honoraria from and provided an advisory  
466 role for Astellas, BMS, Ipsen, Janssen, Pfizer and Sanofi Aventis, and has received travel and  
467 accommodation fees from Pfizer and BMS. CNS has received honoraria from Janssen,  
468 AstraZeneca, Sanofi, and Astellas, received consultancy fees from Sanofi, Bayer, and Pfizer,  
469 and received institutional funding from Genentech/Roche, Bayer, Sanofi Genzyme, Janssen,  
470 Medivation, Merck Sharp & Dohme, and Exelixis. JdB has received honoraria from  
471 AstraZeneca, Sanofi, Astellas Pharma, Pfizer, Genentech/Roche, Janssen Oncology, Menarini  
472 Silicon Biosystems, Daiichi Sankyo, Sierra Oncology, and BioXcel Therapeutics, and provided  
473 an advisory role for AstraZeneca, Sanofi, Genentech/Roche, Astellas Pharma, Bayer, Pfizer,  
474 Merck Sharp & Dohme, Merck Serono, Boehringer Ingelheim, Sierra Oncology, Menarini  
475 Silicon Biosystems, Celgene, Taiho Pharmaceutical, Daiichi Sankyo, Janssen Oncology,  
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477 received personal fees from Pfizer, Roche, Sanofi, Janssen, Astellas, Bayer, Bristol Myers  
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479 received personal fees and research grants from Astellas, Janssen, Sanofi Genzyme, Amgen,  
480 and Ferring, and received non-financial support from Sanofi Genzyme. ML has received  
481 personal fees from Sanofi, Janssen, Amgen, BMS, MSD, AstraZeneca, GSK, and Roche. JC has  
482 provided an advisory role for Astellas, AstraZeneca, Bayer, BMS, MSD Oncology, Johnson &  
483 Johnson, Sanofi, Roche and Pfizer and has attended speaker bureaus for Asofarma, Astellas,  
484 Bayer, and Johnson & Johnson. RI received honoraria and provided an advisory role for  
485 Sanofi, Janssen, Pfizer, IPSEN, Novartis, Bristol Myers Squibb, and Merck Sharp & Dohme.  
486 BM received travel fees, honoraria and provided an advisory role for Bristol Myers Squibb  
487 and Merck Serono, and received honoraria and provided an advisory role for MSD, Sanofi,  
488 Roche, Janssen, Bayer, Astellas, Amgen, Novartis, Servier, AstraZeneca, Eisai, E. Lilly, Ipsen,  
489 Pierre Fabre, and Pfizer. CH received consultancy fees for Sanofi, Janssen and Astellas. SO  
490 has received honoraria for Astellas, Bayer, Bristol Myers Squibb, Janssen, Merck, Novartis,  
491 Pfizer, and Sanofi. AO and SB are employees and stock holders of Sanofi. CW, JC, AS, CT, SF  
492 and GF report no conflicts of interest. CGR and EMP are employees of Sanofi. RdW provided

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495

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501

#### 502 **Author contributions**

503 KF, CNS, JbB, DC, BT, CW, AO, CGR and RdW contributed to study design. KF, CNS, JdB, DC,  
504 GK, JCE, ML, JC, RI, BM, AS, CT, SF, CH, SO, GF and RdW contributed to data collection. KF,  
505 CNS, JdB, DC, BT, CW, AO, CGR, SB and RdW contributed to data interpretation. EP  
506 contributed to data analysis. All authors critically revised and provided approval for each  
507 submitted version and are accountable for the accuracy and integrity of the manuscript.

508

#### 509 **Data sharing statement**

510 Individual participant data (including data dictionaries) will not be made available. The full  
511 study protocol and statistical analysis plan will be available indefinitely in the web appendix  
512 PDF. There will not be any other data shared.

513

514



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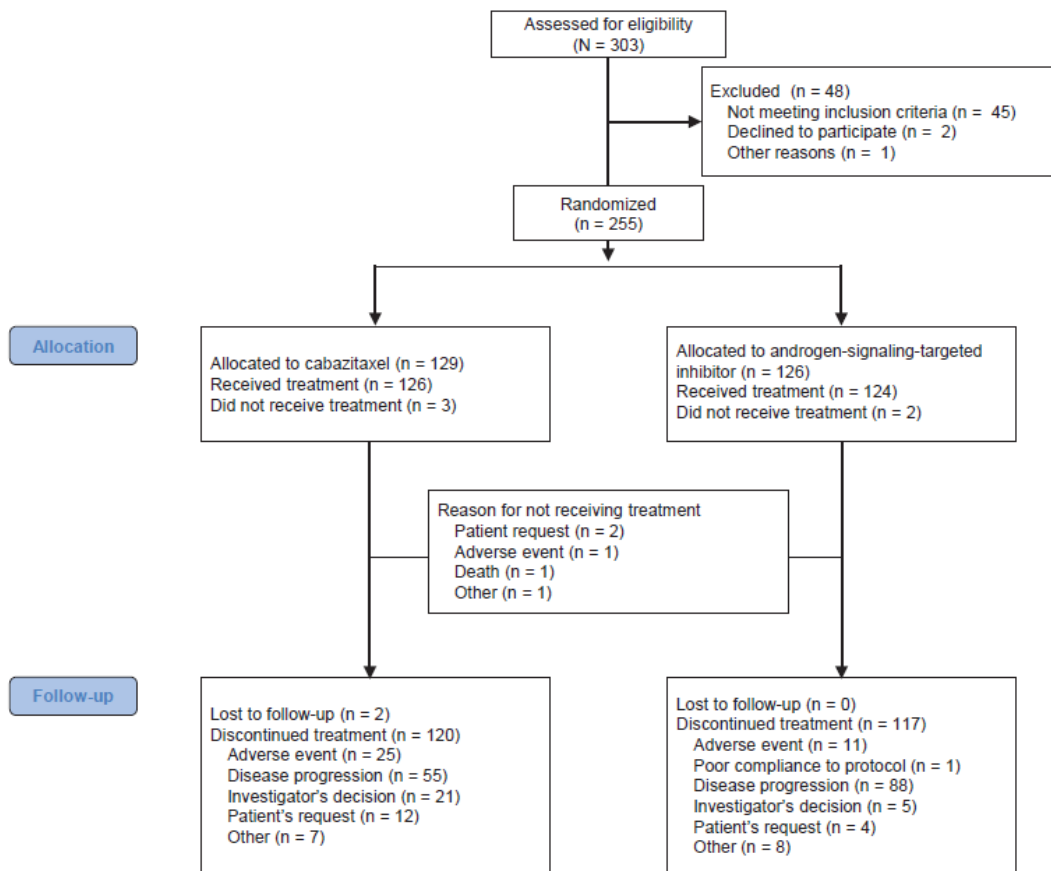
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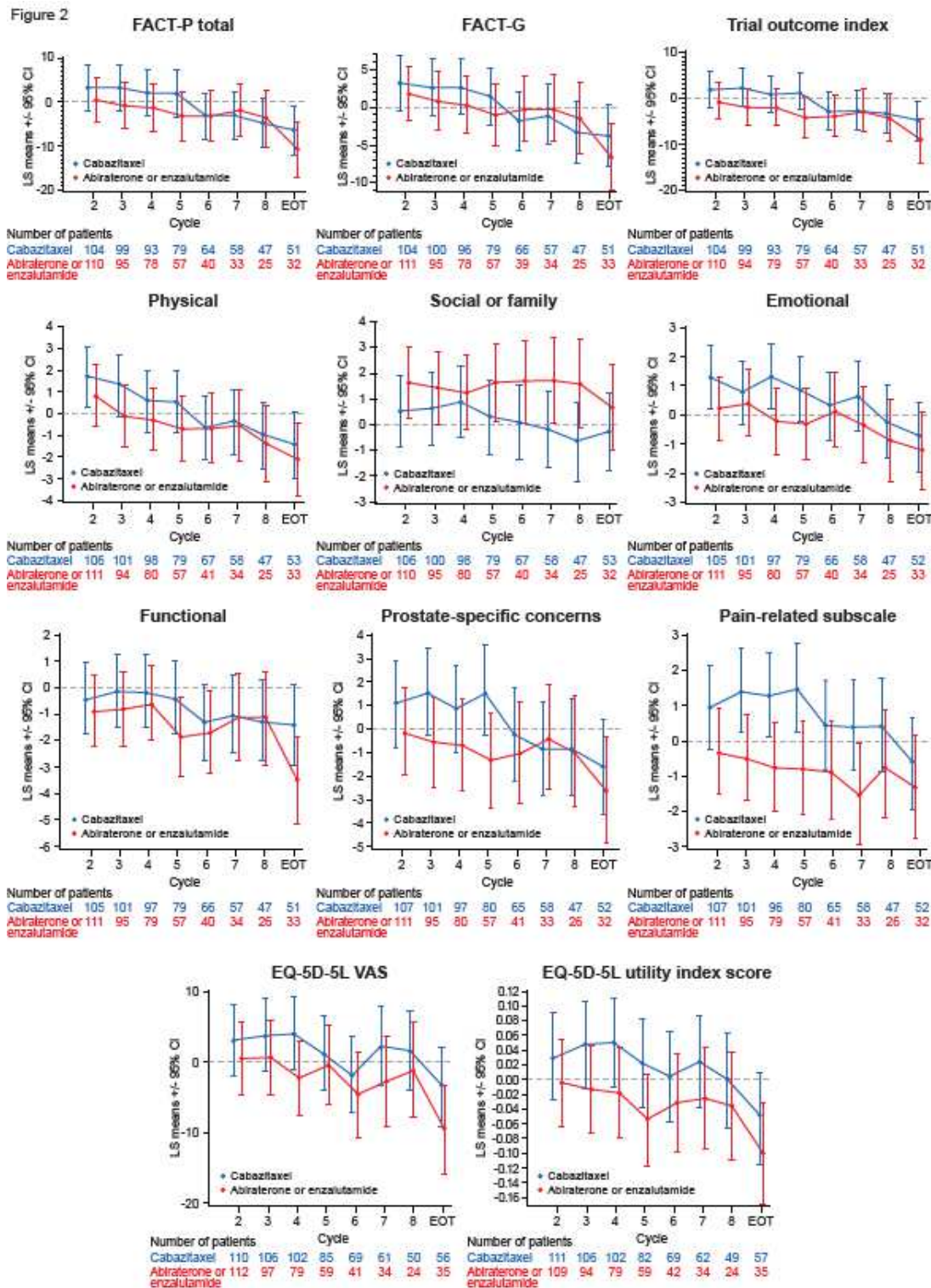
619 **Figures and Tables**

620 **Figure 1. CONSORT diagram**



621  
622

623 **Figure 2.** Adjusted mean (95% CI) change from baseline in FACT-P total and subscale scores.  
 624 Mean changes from baseline were assessed using a mixed linear repeated measures model  
 625 adjusted for baseline stratification variables as well as the interaction treatment\*visit. Only  
 626 results for cycles where  $n \geq 20\%$  in each treatment group in the PRO population, and for the  
 627 end-of-treatment visit, are shown.



629

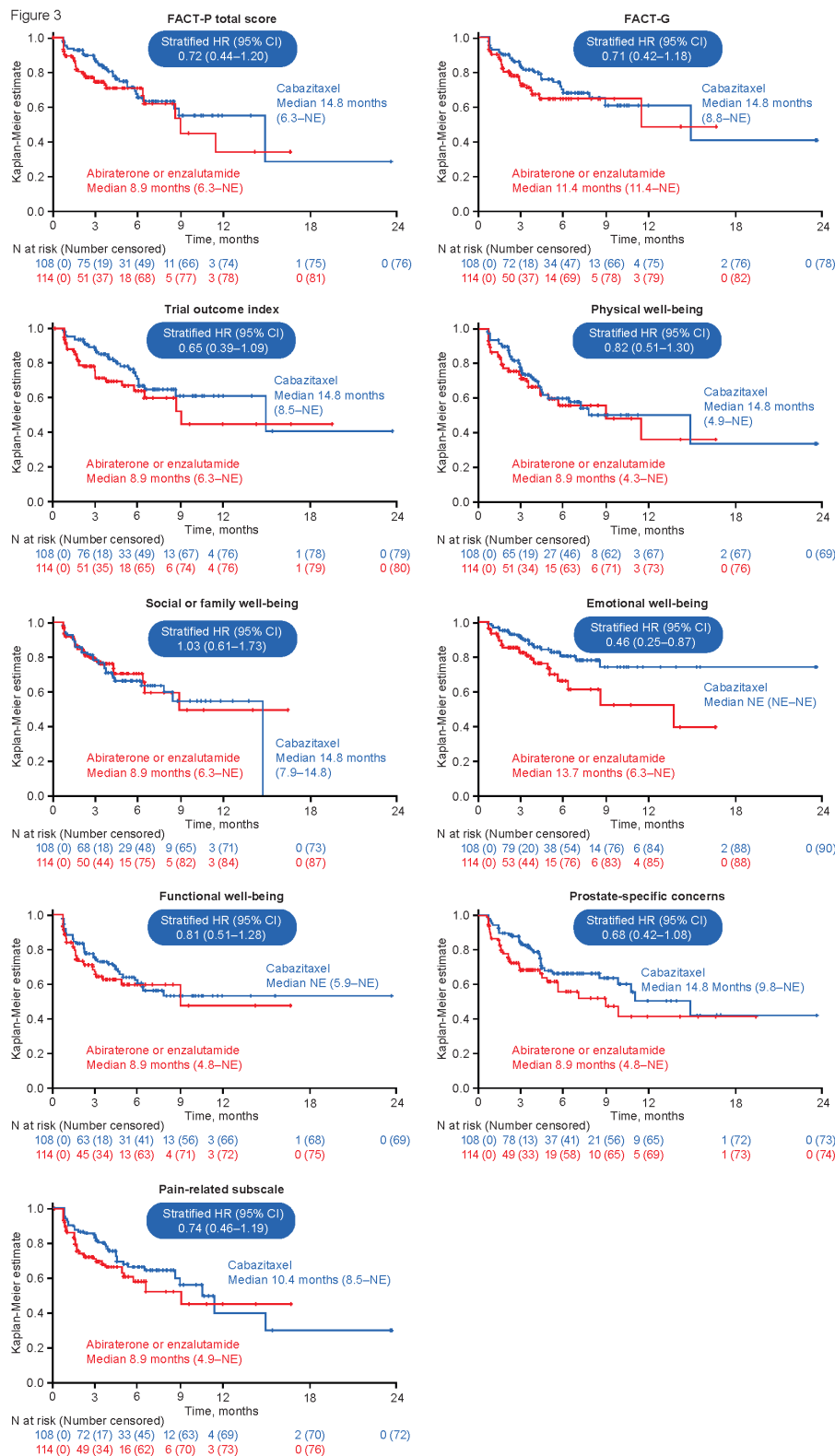
630 Abbreviations: CI, confidence interval; EOT, end of treatment; FACT-G, Functional

631 Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-

632 Prostate; LS, least squares.

633

634 **Figure 3. Time to progression in FACT-P total score and subscales**



635

636 Abbreviations: CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-  
 637 General; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; NR,  
 638 not reached.

640 **Table 1.** Baseline demographics and clinical characteristics

Total population	Cabazitaxel (n=129)	Abiraterone or enzalutamide (n=126)
Median age, years (range) ≥75 years, n/N (%)	70.0 (46–85) 45 (35)	71.0 (45–88) 34 (27)
Total Gleason score ≥8 at diagnosis, n/N (%)	73/129 (57)	81/126 (64)
ECOG performance status at baseline, n/N (%) 0 or 1 2	123/129 (95) 6/129 (5)	119/126 (94) 7/126 (6)
Patients with M1 disease at diagnosis, n/N (%)	49/129 (38)	60/126 (48)
Disease location at baseline, n/N (%) Bone <sup>a</sup> Lymph nodes <sup>b</sup> Visceral metastases <sup>c</sup>	105/126 (83) 8/129 (6) 21/129 (16)	110/125 (88) 6/126 (5) 25/126 (20)
Prior life-extending therapy, n/N (%) Docetaxel Abiraterone Enzalutamide	129/129 (100) 56/129 (43) 72/129 (56)	126/126 (100) 67/126 (53) 59/126 (47)
Bisphosphonate or denosumab use at baseline, n/N (%)	27/129 (21)	46/126 (37)
Type of progression at randomization, n/N (%) PSA only Imaging-based <sup>d</sup> Pain <sup>e</sup> Missing	11/129 (9) 23/129 (18) 86/129 (67) 9/129 (7)	10/126 (8) 15/126 (12) 90/126 (71) 11/126 (9)
Pain intensity at randomization (BPI-SF, item 3), n/N (%) 0 or 1 2 or 3 ≥ 4 Missing	36/129 (28) 28/129 (22) 56/129 (43) 9/129 (7)	28/126 (22) 32/126 (25) 56/126 (44) 10/126 (8)
Analgesics consumption for cancer pain at randomization, n/N (%) No analgesics Non-opioid analgesics (mild pain) Opioids for moderate pain Opioids for severe pain Missing	57/129 (44) 24/129 (19) 16/129 (12) 31/129 (24) 1/129 (1)	53/126 (42) 30/126 (24) 15/126 (12) 27/126 (21) 1/126 (1)
Baseline FACT-P scores Number of patients, n/N (%) Total FACT-P, mean (SD) Total FACT-G, mean (SD)	108/129 (84) 104 (22.0) 73.7 (16.5)	114/126 (91) 105 (21.2) 75.1 (16.6)



Total population	Cabazitaxel (n=129)	Abiraterone or enzalutamide (n=126)
Trial outcome index, mean (SD)	66.5 (16.7)	68.1 (15.7)
Prostate-specific concerns, mean (SD)	30.0 (7.1)	30.1 (6.9)
Pain-related subscale, mean (SD)	9.8 (4.4)	10.2 (3.9)
Emotional well-being, mean (SD)	16.2 (4.5)	16.8 (4.7)
Functional well-being, mean (SD)	15.6 (6.1)	16.9 (6.0)
Physical well-being, mean (SD)	20.9 (5.6)	21.0 (5.3)
Social and family well-being, mean (SD)	21.1 (4.8)	20.6 (5.2)
Baseline EQ-5D-5L scores		
Number of patients, n/N (%)	113/129 (88)	112/126 (89)
Health status score (VAS), mean (SD)	65.8 (20.4)	66.3 (18.5)
Number of patients, n/N (%)	112/129 (87)	115/126 (91)
Health utility index, mean (SD)	0.7 (0.26)	0.7 (0.22)

641 <sup>a</sup>Bone metastases (+/- lymph nodes, +/- visceral metastases).; <sup>b</sup>lymph node only – no bone  
642 or visceral metastases; <sup>c</sup>lung and/or liver metastases (+/- lymph nodes, +/- bone metastasis);  
643 <sup>d</sup>+/- PSA, no pain; <sup>e</sup>+/- PSA, +/- imaging-based.

644 Abbreviations: BPI-SF, Brief Pain Inventory-Short Form, ECOG, Eastern Cooperative  
645 Oncology Group; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P,  
646 Functional Assessment of Cancer Therapy-Prostate; PSA, prostate-specific antigen; SD,  
647 standard deviation; VAS, visual analogue score.

648 **Table 2.** Median time to pain progression and deterioration of FACT-P total and subscale scores

	Median time to deterioration, months (95% CI) n/nT events, (%)			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	HR (95% CI)	Cabazitaxel	Abiraterone or Enzalutamide	Cabazitaxel	Abiraterone or Enzalutamide
Overall survival	13.6 (11.5–17.5) 70/129 (54.3)	11.0 (9.2–12.9) 83/126 (65.9)	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 (BPI-SF)	NE (NE–NE) 25/111 (22.5)	8.5 (4.9–NE) 27/109 (24.8)	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)
<b>FACT-P questionnaire</b>							
FACT-P total	14.8 (6.3–NE) 32/108 (29.6)	8.9 (6.3–NE) 33/114 (28.9)	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)
FACT-G total	14.8 (8.8–NE) 30/108 (27.8)	11.4 (11.4–NE) 32/114 (28.1)	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 (26.9)	8.9 (6.3–NE) 34/114 (29.8)	0.65 (0.39–1.09)	0.861 (0.793–0.929)	0.714 (0.662–0.806)	0.610 (0.47.9–0.74.0)	0.447 (0.241–0.652)

Physical well-being	14·8 (4·9–NE) 39/108 (36·1)	8·9 (4·3–NE) 38/114 (33·3)	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 well-being	14·8 (7·9–14·8) 35/108 (32·4)	8·9 (6·3–NE) 27/114 (23·7)	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 well-being	NE (NE–NE) 18/108 (16·7)	13·7 (6·3–NE) 26/114 (22·8)	0·46** (0·25–0·87)	0·91·1 (0·855–0·967)	0·826 (0·749–0·903)	0·741 (0·619–0·863)	0·525 (0·317–0·733)
Functional well-being	NE (5·9–NE) 39/108 (36·1)	8·9 (4·8–NE) 39/114 (34·2)	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 (PCS)	14·8 (9·8–NE) 35/108 (32·4)	8·9 (4·8–NE) 40/114 (35·1)	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 (33·3)	8·9 (4·9–NE) 38/114 (33·3)	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)

649 Stratified log rank test: \*p=0·03; \*\*p=0·015

650 Abbreviations: BPI-SF, Brief Pain Inventory-Short Form, CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General;

651 FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; NE, not estimable.

652 **Table 3.** *Distribution of first symptomatic skeletal events and probability of not having*  
 653 *symptomatic skeletal events in the intention to treat population*

	<b>Cabazitaxel (n=129)</b>	<b>Abiraterone or enzalutamide (n=126)</b>
Any symptomatic skeletal event, n (%)	24/129 (19)	35/126 (28)
Radiation to relieve bone pain, n (%)	14/129 (11)	23/126 (18)
Spinal cord compression, n (%)	4/129 (3)	4/126 (3)
New symptomatic pathologic fracture, n (%)	6/129 (5)	8/126 (6)
Surgery to the bone, n (%)	0/129 (0)	0/126 (0)
Kaplan–Meier probability of not having symptomatic skeletal events, % (95% CI)		
- At 3 months	0.926 (0.880–0.973)	0.814 (0.744–0.885)
- At 6 months	0.858 (0.792–0.923)	0.771 (0.693–0.849)
- At 12 months	0.794 (0.709–0.880)	0.629 (0.511–0.748)
- At 18 months	0.712 (0.594–0.830)	0.486 (0.286–0.685)

654 Abbreviation: CI, confidence interval.

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