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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

Karim Fizazi, Gero Kramer, Jean-Christophe Eymard, Cora N. Sternberg, Johann De Bono, Daniel Castellano, Bertrand Tombal, Christian Wülfing, Michael Lontos, Joan Carles, Roberto Iacovelli, Bohuslav Melichar, Ásgerður Sverrisdóttir, Christine Theodore, Susan Feyerabend, Carole Helissey, Stéphane Oudard, Gaetano Facchini, Elizabeth M. Poole, Ayse Ozatilgan, Christine Geffriaud-Ricouard, Samira Bensfia, Ronald de Wit

Affiliations

Institut Gustave Roussy and University of Paris Saclay, Villejuif, France (Prof K Fizazi MD); Department of Urology, Medical University of Vienna, Vienna, Austria (Prof G Kramer MD); Institut Jean Godinot, Reims, France (J-C Eymard MD); Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, USA (Prof C N Sternberg MD); The Institute of Cancer Research and the Royal Marsden Hospital, London, UK (Prof J de Bono MD); 12 de Octubre University Hospital, Madrid, Spain (D Castellano MD); Institut de Recherche Clinique, Université Catholique de Louvain, Louvain, Belgium (Prof B Tombal MD); Asklepios Tumorzentrum Hamburg, Asklepios Klinik Altona, Department of Urology, Hamburg, Germany (Prof C Wülfing MD); Department of Clinical Therapeutics, Oncology Unit, Alexandra Hospital, Athens, Greece (M Lontos MD); Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain (J Carles MD); Azienda Ospedaliera Universitaria Integrata (AOUI) Verona, Verona, Italy (Prof R Iacovelli MD); Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy (Prof R Iacovelli MD); Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic (Prof B Melichar MD); Landspítali University Hospital, Reykjavik, Iceland (Á Sverrisdóttir MD); Foch Hospital, Suresnes, France (C Theodore MD); Studienpraxis Urologie, Nürtingen, Germany (S Feyerabend MD); Hôpital d'Instruction des Armées BÉGIN, Saint Mandé, France (C Helissey MD); Georges Pompidou European Hospital, Paris Descartes University, Paris, France (Prof S Oudard MD); Istituto Nazionale Tumori-IRCCS-Fondazione, Naples, Italy (G Facchini MD);

Sanofi, Global Medical Oncology, Cambridge, USA (E Poole PhD, A Ozatilgan MD); Sanofi, Europe Medical Oncology, Paris, France (C Geffriaud-Ricouard MD, S Bensfia MD); Erasmus Medical Center, Rotterdam, The Netherlands (Prof R de Wit MD).

Corresponding author

Karim Fizazi

Department of Cancer Medicine

Institut Gustave Roussy and University of Paris Saclay

114 rue Edouard Vaillant

94800 Villejuif

France

Karim.fizazi@gustaveroussy.fr

+33 1 22 42 11 43 17

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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 (≥ 18 years, ECOG PS ≤ 2) with confirmed mCRPC were randomized 1:1
7 using an interactive voice/Web response system to receive cabazitaxel (25 mg/m²
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/m² 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.¹ Many studies have evaluated
71 treatment sequencing, however these were small retrospective studies, carried out using
72 different inclusion, exclusion and outcome criteria.² Although survival increases with the
73 number of life-extending therapies received, the optimal treatment sequence is unclear.² 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.^{3,4} However, many studies suggest there is cross-resistance between these
77 novel androgen-signaling-targeted inhibitors.^{2,3,5}

78 Since cabazitaxel retains activity in patients progressing on docetaxel, abiraterone, or
79 enzalutamide,⁶ 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.⁷ Cabazitaxel was associated with
82 improved radiographic progression-free survival (rPFS) and overall survival compared with
83 abiraterone or enzalutamide.⁷

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.⁸
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.⁹ 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.¹⁰⁻¹³ 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.⁷ 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 ≥ 2 new bone lesions or rising prostate-specific antigen (PSA) level per Prostate Cancer
108 Working Group 2 (PCWG2) criteria, had received ≥ 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 (≤ 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/m² 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/m², then 15 mg/m²;
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.⁷ 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).¹⁴ 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).¹⁵ 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.^{16,17} FACT-P is a 39-item self-report tool designed

189 to evaluate quality of life in patients with prostate cancer.¹⁸ 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 ≥ 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).¹⁹ 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.¹⁷

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 previously⁷
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.²⁰

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.^{13,21} Androgen
377 suppression is associated with loss of bone mineral density and increased risk of fracture.²²
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.²³⁻²⁵ 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.²⁶ 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.²⁷ 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.²⁸ 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.^{23,24}
397 Since pain progression is consistently associated with aggressive disease and worse overall
398 survival, it is important to adequately manage such patients.^{12,28} 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.^{16,17,29} 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.¹⁷ 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.¹⁶ 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.⁷ 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.^{30,31}
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.³² 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.³³
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.⁷

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,
476 Genmab, GlaxoSmithKline, Orion Pharma GmbH, Eisai, and BioXcel Therapeutics. DC
477 received personal fees from Pfizer, Roche, Sanofi, Janssen, Astellas, Bayer, Bristol Myers
478 Squibb, Merck Sharp & Dohme, Merck Serono, Pierre Fabre, AstraZeneca, and Lilly. BT has
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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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

515 **References**

- 516 1. Nuhn P, De Bono JS, Fizazi K, et al. Update on Systemic Prostate Cancer Therapies:
517 Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision
518 Oncology. *Eur Urol* 2019; **75**(1): 88-99.
- 519 2. Maines F, Caffo O, Veccia A, Bria E. Sequential use of new agents (NAs) after
520 docetaxel (DOC) first line in metastatic castration-resistant prostate cancer (mCRPC)
521 patients (pts): A pooled-analysis of the published studies. *J Clin Oncol* 2015; **33**(suppl 7):
522 Abstract 258.
- 523 3. Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with
524 enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific
525 antigen during enzalutamide treatment. *J Clin Oncol* 2018; **36**(25): 2639-46.
- 526 4. Anido-Herranz U, Fernández-Núñez N, Afonso-Afonso J, et al. Chemotherapy
527 management for unfit patients with metastatic castration-resistant prostate cancer. *Clin*
528 *Transl Oncol* 2019; **21**(3): 249-58.
- 529 5. Oh WK, Cheng WY, Miao R, et al. Real-world outcomes in patients with metastatic
530 castration-resistant prostate cancer receiving second-line chemotherapy versus an
531 alternative androgen receptor-targeted agent (ARTA) following early progression on a first-
532 line ARTA in a US community oncology setting. *Urol Oncol* 2018; **36**(11): 500.e1-.e9.
- 533 6. Al Nakouzi N, Le Moulec S, Albiges L, et al. Cabazitaxel remains active in patients
534 progressing after docetaxel followed by novel androgen receptor pathway targeted
535 therapies. *Eur Urol* 2015; **68**(2): 228-35.
- 536 7. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or
537 enzalutamide in metastatic prostate cancer. *The New England journal of medicine* 2019;
538 **381**: 2506-18.
- 539 8. Holm M, Doveson S, Lindqvist O, Wennman-Larsen A, Fransson P. Quality of life in
540 men with metastatic prostate cancer in their final years before death – a retrospective
541 analysis of prospective data. *BMC Palliative Care* 2018; **17**(1): 126.
- 542 9. Nussbaum N, George DJ, Abernethy AP, et al. Patient experience in the treatment of
543 metastatic castration-resistant prostate cancer: state of the science. *Prostate Cancer*
544 *Prostatic Dis* 2016; **19**(2): 111-21.
- 545 10. Mierzynska J, Piccinin C, Pe M, et al. Prognostic value of patient-reported outcomes
546 from international randomised clinical trials on cancer: a systematic review. *Lancet Oncol*
547 2019; **20**(12): e685-e98.
- 548 11. Cella D, Traina S, Li T, et al. Relationship between patient-reported outcomes and
549 clinical outcomes in metastatic castration-resistant prostate cancer: post hoc analysis of
550 COU-AA-301 and COU-AA-302. *Annals of Oncology* 2017; **29**(2): 392-7.
- 551 12. Robbrecht DG, Delanoy N, Tannock IF, et al. Impact of progression at baseline and
552 on-treatment progression events in three large prostate cancer trials. *Eur J Cancer* 2020;
553 **125**: 142-52.
- 554 13. Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively
555 correlate with overall survival in men with prostate cancer. *J Urol* 2002; **168**(3): 1005-7.
- 556 14. NPCRC. Brief Pain Inventory (Short Form). 1991.
557 http://www.npcrc.org/files/news/briefpain_short.pdf (accessed March 30 2020).
- 558 15. WHO. WHO's cancer pain ladder for adults. 2020.
559 <https://www.who.int/cancer/palliative/painladder/en/> (accessed March 30 2020).
- 560 16. Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus
561 prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate

562 cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol* 2013;
563 **14**(12): 1193-9.

564 17. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related
565 quality of life, pain, and skeletal-related events in asymptomatic and minimally
566 symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate
567 cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol* 2015; **16**(5): 509-
568 21.

569 18. Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful
570 changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical
571 trial of patients with metastatic hormone-refractory prostate cancer. *Value Health* 2009;
572 **12**(1): 124-9.

573 19. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the
574 new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36.

575 20. Behl AS, Ellis LA, Pilon D, Xiao Y, Lefebvre P. Medication Adherence, Treatment
576 Patterns, and Dose Reduction in Patients with Metastatic Castration-Resistant Prostate
577 Cancer Receiving Abiraterone Acetate or Enzalutamide. *American health & drug benefits*
578 2017; **10**(6): 296-303.

579 21. McKay R, Haider B, Duh MS, et al. Impact of symptomatic skeletal events on health-
580 care resource utilization and quality of life among patients with castration-resistant prostate
581 cancer and bone metastases. *Prostate Cancer Prostatic Dis* 2017; **20**(3): 276-82.

582 22. Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive
583 osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol* 2000; **163**(1):
584 181-6.

585 23. Gillessen S, Attard G, Beer TM, et al. Management of Patients with Advanced
586 Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur*
587 *Urol* 2020; **77**(4): 508-47.

588 24. Mottet N, van den Bergh RCN, Briers E, et al. EAU-ESTRO-ESUR-SIOG guidelines on
589 prostate cancer. European Association of Urology. 2018.
590 <https://uroweb.org/guideline/prostate-cancer/>.

591 25. Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced
592 prostate cancer: The report of the Advanced Prostate Cancer Consensus Conference APCCC
593 2017. *Eur Urol* 2018; **73**(2): 178-211.

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

598 27. Tombal BF, Loriot Y, Saad F, et al. Decreased fracture rate by mandating bone-
599 protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223
600 versus enzalutamide alone: An interim safety analysis. *Journal of Clinical Oncology* 2019;
601 **37**(15 suppl): Abstract 5007.

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

605 29. Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the
606 quality of life of patients with metastatic castration-resistant prostate cancer after failure of
607 docetaxel chemotherapy. *Eur J Cancer* 2013; **49**(17): 3648-57.

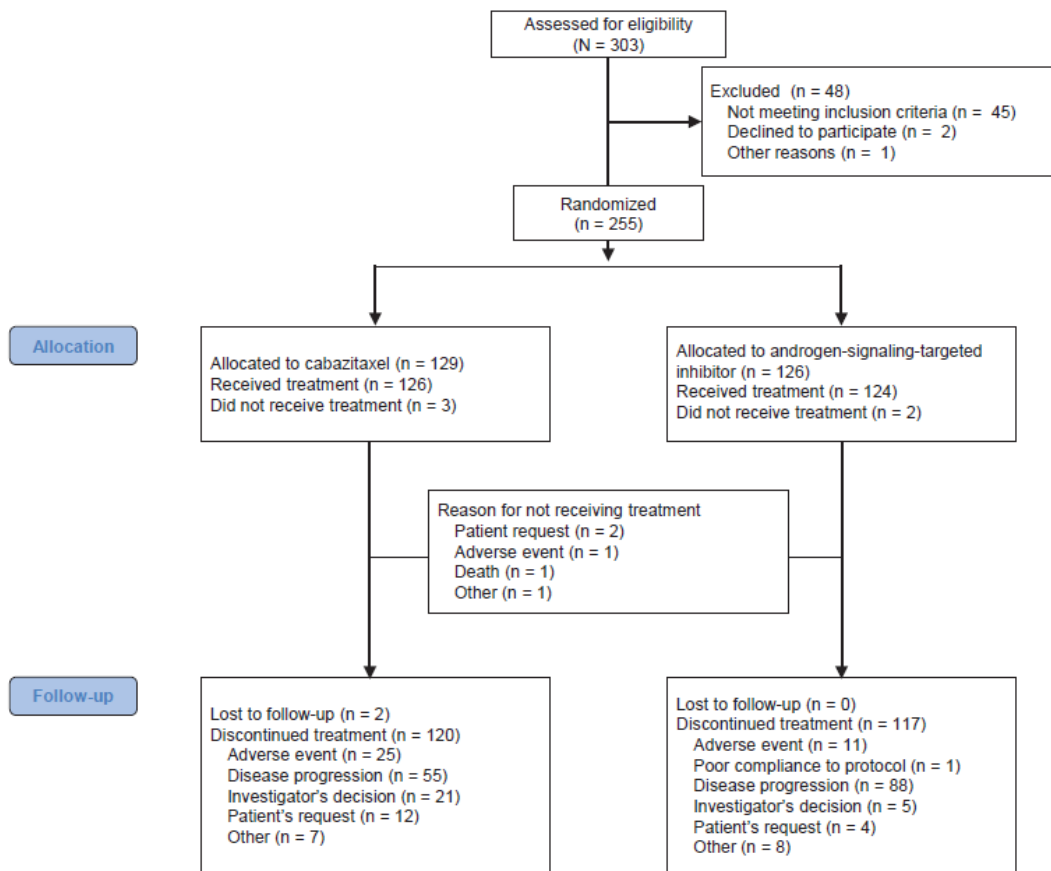
- 608 30. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer
609 without previous chemotherapy. *The New England journal of medicine* 2013; **368**(2): 138-48.
- 610 31. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate
611 cancer before chemotherapy. *The New England journal of medicine* 2014; **371**(5): 424-33.
- 612 32. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant
613 Prostate Cancer. *The New England journal of medicine* 2020.
- 614 33. Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-
615 life and patient-reported outcome endpoints in cancer randomised controlled trials:
616 recommendations of the SISAQOL Consortium. *The Lancet Oncology* 2020; **21**(2): e83-e96.

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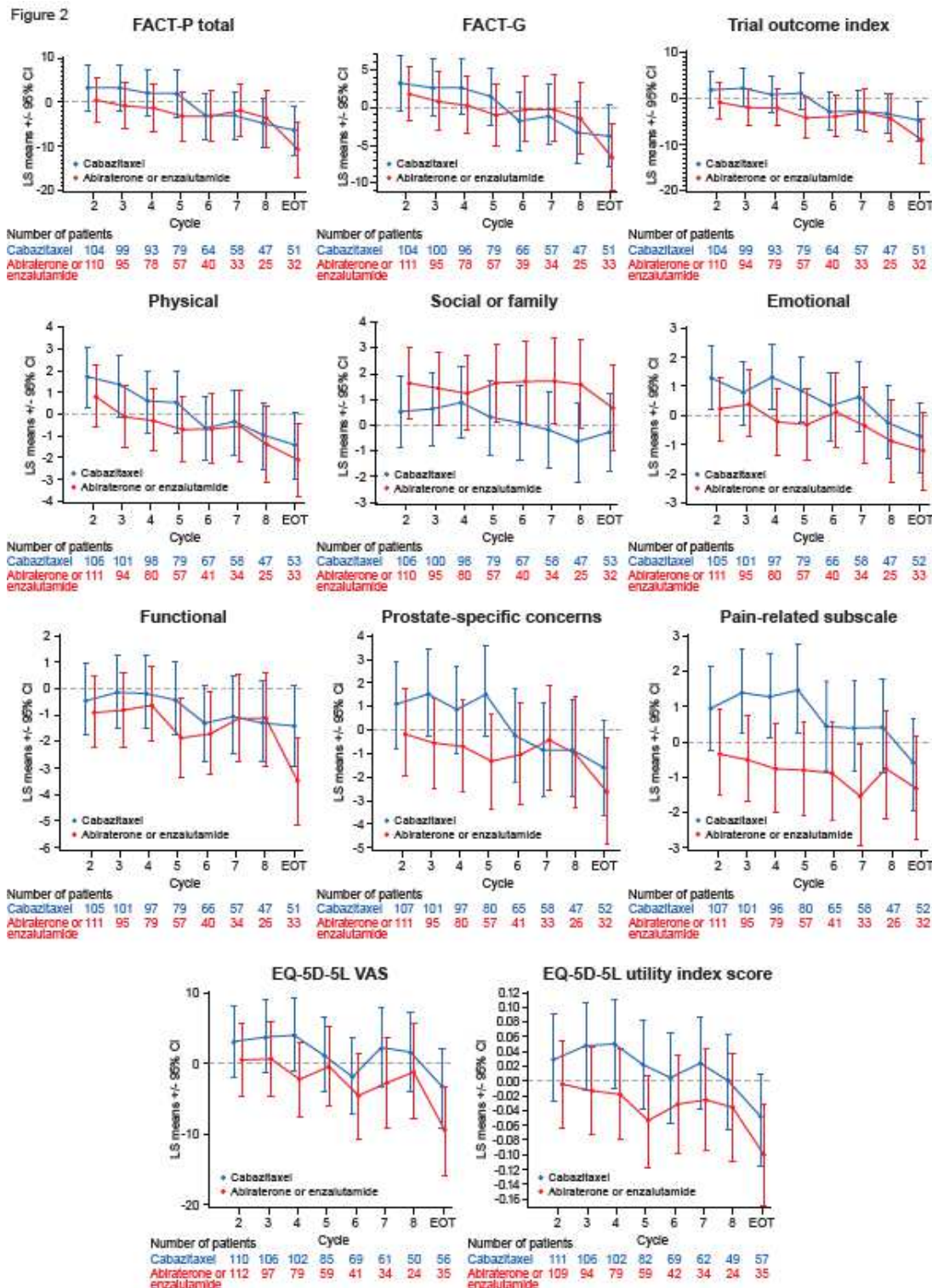
619 **Figures and Tables**

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

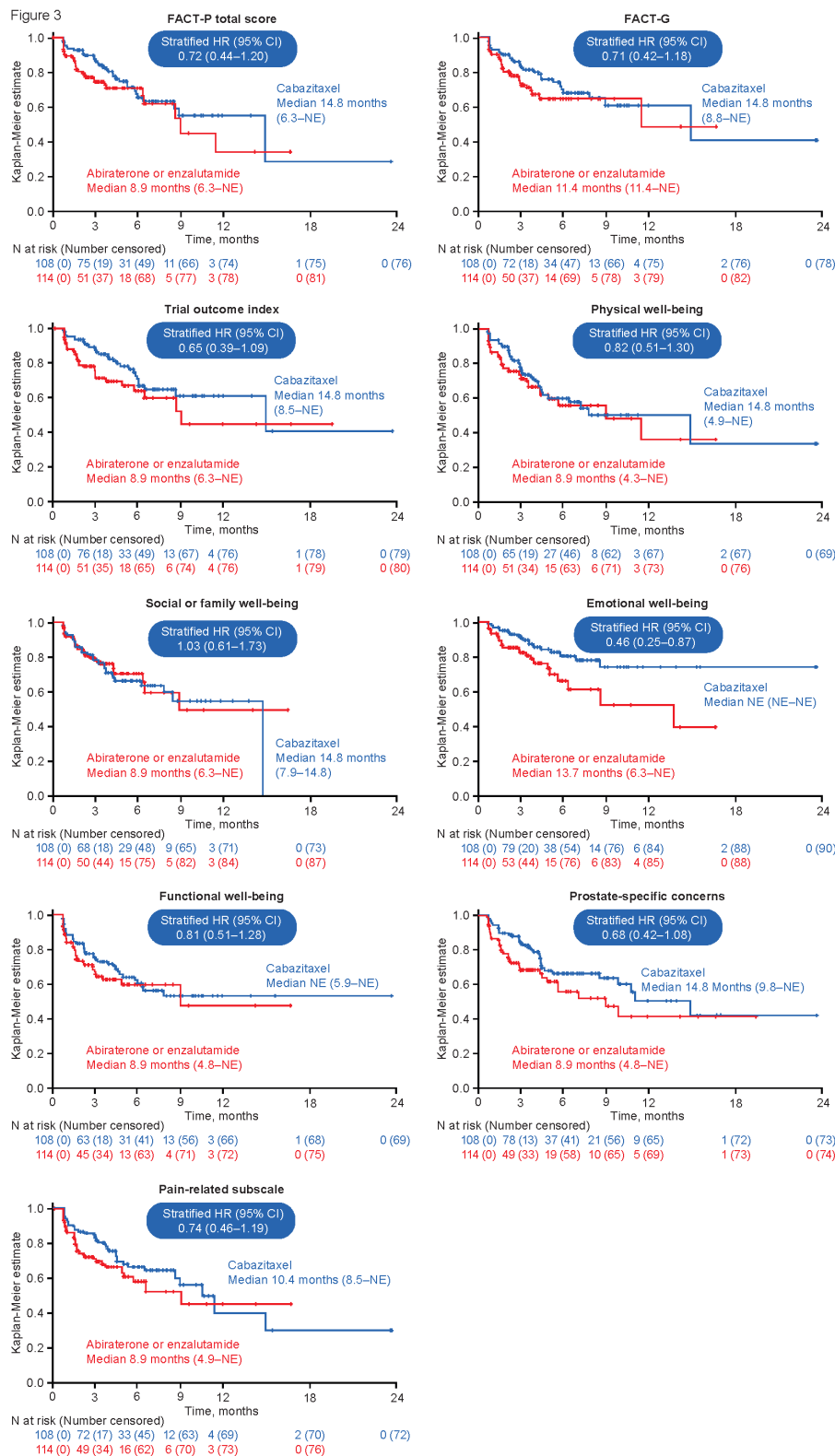
630 Abbreviations: CI, confidence interval; EOT, end of treatment; FACT-G, Functional

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 ^a Lymph nodes ^b Visceral metastases ^c	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 ^d Pain ^e 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 ^aBone metastases (+/- lymph nodes, +/- visceral metastases).; ^blymph node only – no bone
642 or visceral metastases; ^clung and/or liver metastases (+/- lymph nodes, +/- bone metastasis);
643 ^d+/- PSA, no pain; ^e+/- 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)
FACT-P questionnaire							
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*

	Cabazitaxel (n=129)	Abiraterone or enzalutamide (n=126)
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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