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# Impact of Abiraterone Acetate plus Prednisone or Enzalutamide on Patient-reported Outcomes in Patients with Metastatic Castration-resistant Prostate Cancer: Final 12-mo Analysis from the Observational AQUARiUS Study

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**Impact of Abiraterone Acetate plus Prednisone or Enzalutamide on Patient-reported Outcomes in Patients with Metastatic Castration-resistant Prostate Cancer: Final 12-month Analysis from the Observational AQUARiUS Study**

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cancer; Patient-reported outcomes; Prednisone; Quality of life

## **Abstract**

**Background:** Few studies have examined patient-reported outcomes (PROs) with  
abiraterone acetate plus prednisone (abiraterone) versus enzalutamide in metastatic  
castration-resistant prostate cancer (mCRPC).

**Objective:** To determine the impact of abiraterone and enzalutamide on PROs.

**Design, setting, and participants:** AQUARiUS (NCT02813408) was a prospective, 12-mo,  
observational study in patients with mCRPC from Denmark, France, and the UK.

**Intervention:** Abiraterone or enzalutamide treatment according to routine practice.

**Outcome measurements and statistical analysis:** PROs were collected over 12 mo using Functional Assessment of Cancer Therapy—Cognitive Function (FACT-Cog), Brief Fatigue Inventory—Short Form (BFI-SF), Brief Pain Inventory—Short Form, and European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire (QLQ-C30) at baseline and routine visits. Outcomes included mean change in PROs, patients with clinically meaningful worsening (CMW) in PROs, and safety. Data were analysed using repeated measures linear and logistic models adjusted for baseline characteristics.

**Results and limitations:** Abiraterone-treated ( $N = 105$ ) and enzalutamide-treated ( $N = 106$ ) patients were included. Key PRO items (cognitive impairments and fatigue) were significantly ( $p < 0.05$ ) in favour of abiraterone versus enzalutamide during the study. “Perceived cognitive impairment” and “comments from others” (FACT-Cog); “fatigue right now”, “usual level of fatigue”, and “worst level of fatigue” (BFI-SF); and “cognitive functioning” and “fatigue” (QLQ-C30) were significantly in favour of abiraterone over enzalutamide for three or more consecutive periods up to month 12. From study initiation, significantly fewer patients receiving abiraterone experienced one or more CMW episode in cognition and fatigue. Fatigue and asthenia (adverse events) were lower with abiraterone than with enzalutamide (5% vs 15% and 10% vs 11%, respectively). There were no treatment-related deaths. Limitations included lack of randomisation.

**Conclusions:** In a real-world setting, this 12-mo analysis suggests an advantage of abiraterone acetate plus prednisone over enzalutamide in reducing fatigue and cognitive function; this finding occurred early after treatment initiation. This difference should be considered when choosing treatment.

**Patient summary:** This study looked at the effect of two treatments (abiraterone acetate plus prednisone and enzalutamide) for metastatic castration-resistant prostate cancer on

patient quality of life over 12 mo. Using established questionnaires, patients reported that they experienced less fatigue and cognitive impairments (including memory loss and reduced thinking abilities) with abiraterone acetate plus prednisone than with enzalutamide.

## **1. Introduction**

Approximately 90% of patients with metastatic prostate cancer respond well to initial androgen deprivation therapy (ADT) [1]. However, 20% of patients progress to castration-resistant prostate cancer within 5 yr [2]. Metastatic castration-resistant prostate cancer (mCRPC) has a 5-yr survival rate of ~30% [3]. Metastatic CRPC is characterised by worsening symptoms, progressive decline in health-related quality of life (HRQoL), and increasing pain [4,5].

Until 2010, docetaxel was the standard treatment for mCRPC, but life-extending noncytotoxic therapies that may have positive impacts on patient-reported outcomes (PROs) are now available [5]. Abiraterone acetate plus prednisone (abiraterone) and enzalutamide target androgen signalling, delay radiographic progression, increase survival, and improve HRQoL and pain outcomes in chemotherapy-naïve patients with mCRPC compared with placebo ± prednisone [6–8]. However, few studies have examined the impact of these treatments on HRQoL under real-world conditions.

AQUARiUS was a 12-mo phase IV study to evaluate the effect of abiraterone versus enzalutamide on PROs in patients with chemotherapy-naïve mCRPC in a real-world setting. Results from interim 3- and 6-mo analyses of AQUARiUS showed that more favourable

outcomes were achieved with abiraterone than with enzalutamide for PROs of cognition and fatigue [9,10]. We report the final 12-mo results of AQUARiUS.

## **2. Patients and methods**

### **2.1. Study design**

AQUARiUS (NCT02813408) was a 12-mo, two-cohort, prospective, observational, nonrandomised, multicentre, phase IV study conducted by office- or hospital-based urology and/or oncology specialists in Denmark ( $n = 3$ ), France ( $n = 14$ ), and the UK ( $n = 10$ ). An independent ethics committee or institutional review board reviewed/received study notification, in all countries, as required by local regulations. The study was conducted in accordance with the Declaration of Helsinki. The design has been reported [9,10].

### **2.2. Patients**

Patients were eligible if they were  $\geq 18$  yr old with a histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate, and with documented metastatic disease and castration resistance, and if they were initiated on abiraterone or enzalutamide for asymptomatic or mildly symptomatic mCRPC after ADT failure.

Patients were excluded if they had prior chemotherapy to treat mCRPC or prior chemotherapy/cytotoxic agent to treat metastatic hormone-sensitive prostate cancer in the previous 12 mo. Inclusion and exclusion criteria have been described [9]. All patients provided informed consent to participate. Patients meeting the study criteria were consecutively invited to participate in the study to minimise recruitment bias.

### **2.3. Intervention**

The decision to prescribe abiraterone or enzalutamide was made by the treating physician in accordance with their usual practice.

### **2.4. Data collection**

Medical records were used to capture clinical and demographic data. PRO data were collected prospectively using paper questionnaires completed by the patient at baseline and during routine visits to the clinic over 12 mo (the cut-off date was 21 March 2018).

Questionnaires included the Functional Assessment of Cancer Therapy—Cognitive Function (FACT-Cog) [11], Brief Fatigue Inventory—Short Form (BFI-SF) [12], Brief Pain Inventory—Short Form (BPI-SF) [13], and European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire (EORTC QLQ-C30) [14] (see Supplementary Table 1 for further details on questionnaires). Questionnaire data were entered onto electronic case report forms (eCRFs) by an external vendor in accordance with quality control policies for data entry.

### **2.5. Outcomes**

Two primary analyses were performed: (1) mean change from baseline in PRO item scores (continuous outcome), with treatment differences summarised by the mean (95% confidence intervals [CIs]); and (2) the percentage of patients who experienced at least one clinically meaningful (ie,  $0.5 \times$  standard deviation [SD] of the baseline PRO) worsening

(CMW) versus improvement/no change in PRO items (binary outcome) in the 12-mo period, for which odds ratios (ORs; 95% CI) were reported. An additional analysis was performed to determine the time (in months) to the first PRO item showing CMW of symptoms.

Secondary analyses included patient-reported adverse events (AEs), monitored from the 1st day of treatment to 30 d after last treatment exposure. Cause, severity, possible relationship to study drug, and outcome of AEs were recorded in eCRFs by the treating physician during routine visits. Medical resource use data were not source document verified and were inconsistent with visit dates reported in the eCRFs, so meaningful conclusions could not be made, and these data were not reported.

## **2.6. Statistical analyses**

It was estimated that a sample size of 211 patients, balanced equally between cohorts, would be required to detect a CMW value of  $\geq 0.5$  SD between treatment cohorts, with 85% power at the 5% level of significance ( $p < 0.05$ ). CMW ( $\geq 0.5$  SD) was based on published minimally important difference ranges (0.5–1.0 SD) for the questionnaires used in the study [12,15,16].

Collection of PRO data began before baseline visit (abiraterone and enzalutamide initiation) and continued until termination of treatment or for ~12 mo, whichever occurred first. Questionnaire data were collected during routine visits and analysed by periods 1, 2, 3, 4–6, 7–9, and 10–12 (see tables and figures for day ranges used per period).

Primary analyses were based on all treated patients (intent-to-treat [ITT] population). Sensitivity analyses were performed using the censored population (ie,



abiraterone patients who switched to enzalutamide were censored at the start of enzalutamide and vice versa).

Repeated measures analyses were used for continuous outcomes (linear models) and binary outcomes (logistic models), adjusting for patient baseline characteristics. All models were adjusted for the baseline PRO value. Additional baseline characteristics considered as covariates in the models included age; Gleason score at initial diagnosis; Eastern Cooperative Oncology Group performance status; visceral metastases; use of analgesics; use of sedatives; levels of alkaline phosphatase, haemoglobin, and prostate-specific antigen (lactate dehydrogenase was excluded due to the number of missing values); and comorbidities. Comparative measures and *p* values at any time point were derived from the repeated measures models.

An exploratory Kaplan-Meier analysis, using PRO data from the overall study period, was performed to determine the time to the first PRO item showing CMW of symptoms. AEs were defined using the *Medical Dictionary for Regulatory Activities* version 19.1.

All statistical analyses were performed using SAS release 9.4 (SAS Institute Inc., Cary, NC, USA).

### **3. Results**

#### **3.1. Patients**

Overall, 226 patients were examined for eligibility and 211 (ITT population) were included (*N* = 105 [abiraterone] and *N* = 106 [enzalutamide]). Patient disposition is shown in Figure 1. Baseline characteristics were well balanced between abiraterone- and enzalutamide-treated patients (Table 1).

Supplementary Table 2 shows the completion rate for the different PRO items during the study. Only the lowest percentage per PRO item (worse-case scenario, all items must be answered to consider a PRO complete) was presented for all patients and for those “still in study”. The overall median completion rate for the 12-mo period was 81% for patients still in the study (this rate was based on all 28 PRO questions and all periods, and for both treatments).

### **3.2. Treatment exposure**

The mean (SD) overall treatment duration was 38.3 (17.2) wk in the abiraterone group and 38.7 (18.2) wk in the enzalutamide group.

The percentages of patients starting on the usual abiraterone dose (1000 mg) and enzalutamide dose (160 mg) were 97% and 95%, respectively. In both cohorts, 5% of patients had at least one dose reduction. Treatment was discontinued during the 12-mo period in 40% of abiraterone patients and 36% of enzalutamide patients. The main reasons for discontinuation were disease progression for 62% versus 53%, toxicity for 12% versus 21%, and others for 26% versus 26% for abiraterone versus enzalutamide (Fig. 1).

### **3.3. Treatment differences in PRO items from baseline to 12 mo**

There were no statistically significant differences between cohorts in baseline PRO scores (absolute values) for each item apart from pain interference (BPI-SF); this difference was not clinically meaningful (Supplementary Table 3). After initiation of treatment, there were statistically significant differences ( $p < 0.05$ ) in favour of abiraterone over enzalutamide for

18 PRO items, as highlighted in Supplementary Table 3. With a more conservative approach (at least three periods [ $\geq 50\%$ ] needed to be significant in consecutive periods), nine of these PRO items were statistically significantly in favour of abiraterone over enzalutamide; these were mainly related to cognition, fatigue, appetite loss, and nausea (Table 2, Supplementary Fig. 1, and Supplementary Table 3). There was also consistency across different questionnaires for items relating to cognition and fatigue. Statistically significant improvements in favour of abiraterone over enzalutamide were observed for “perceived cognitive impairment”, “comments from others” (FACT-Cog), and “cognitive functioning” (QLQ-C30), which were evident at period 1. Similar findings were observed for “worst-level of fatigue”, “usual level of fatigue”, “fatigue right now” (BFI-SF), and “fatigue” (QLQ-C30) (Table 2).

#### **3.4. CMW in PRO items over 12 mo**

We checked whether the nine significant items detailed above were also clinically meaningful—with cumulative CMW analysis over 12 mo. Only those with statistically significant results in consecutive periods in the “mean change from baseline” analysis were reported. Overall, significantly fewer patients receiving abiraterone versus enzalutamide experienced at least one episode of CMW in “perceived cognitive impairments” (49% vs 76% [OR = 0.31; 95% CI: 0.14; 0.70;  $p = 0.005$ ]), “comments from others” (32% vs 62% [OR = 0.14; 95% CI: 0.05; 0.39;  $p < 0.001$ ]; FACT-Cog), “worst level of fatigue” (53% vs 79% [OR = 0.33; 95% CI: 0.15; 0.75;  $p = 0.008$ ]; BFI-SF), “fatigue” (45% vs 74% [OR = 0.29; 95% CI: 0.14; 0.62;  $p = 0.001$ ]), and “appetite loss” (36% vs 60% [OR = 0.38; 95% CI: 0.17; 0.88;  $p = 0.023$ ]; QLQ-C30; Fig. 2). These differences could be observed early within the 1st month of treatment

(see Supplementary Table 4). There were four other items with statistically significant CMW in favour of abiraterone (none for enzalutamide); these were “emotional functioning”, “social functioning”, “physical functioning”, and “pain right now”. These were not reported based on the conservative approach used.

### **3.5. Time to the first measured PRO item showing CMW of symptoms**

Exploratory Kaplan-Meier analyses of the time to the first measured PRO item showing CMW suggested that early and sustained numerical differences favouring abiraterone over enzalutamide were observed for “perceived cognitive impairments” and “comments from others” (FACT-Cog), “worst level of fatigue” (BFI-SF), “fatigue”, and “appetite loss” (QLQ-C30; Supplementary Fig. 2).

### **3.6. Sensitivity analyses**

Results from the censoring analysis remained consistent with those presented for the ITT analyses (Supplementary Table 5). A model with a random centre effect was tested, and it gave very similar results (model not shown).

### **3.7. Safety outcomes**

The percentages of patients with at least one AE over 12 mo were 69% (abiraterone) and 77% (enzalutamide; Supplementary Table 6). Both fatigue and asthenia were lower with abiraterone than with enzalutamide (5% vs 15% and 10% vs 11%, respectively). The percentages of patients with at least one serious AE were 23% (abiraterone) and 26%

(enzalutamide), and with AEs leading to treatment or study termination were 5% (abiraterone) and 11% (enzalutamide). The most common serious AEs were infections and infestations (7% [abiraterone] and 9% [enzalutamide]), and renal and urinary disorders (5% [abiraterone] and 7% [enzalutamide]). The percentages of patients with AEs leading to hospitalisation were 22% (abiraterone) and 24% (enzalutamide). There were five deaths in the abiraterone group and seven in the enzalutamide group, but none were treatment related.

#### **4. Discussion**

AQUARiUS evaluated the impact of abiraterone and enzalutamide on self-reported PROs in patients with mCRPC over 12 mo in a real-world setting. The study showed that abiraterone was consistently associated with less cognitive impairments and fatigue than enzalutamide over the 12-mo period, and these differences were observed early after treatment initiation. The proportion of patients with CMW in cognitive impairments and fatigue was also statistically significantly lower with abiraterone than with enzalutamide over the 12-mo study period. The findings were consistent across specific (FACT-Cog and BFI-SF) and general (QLQ-C30) instruments. Findings relating to pain (BPI-SF), however, were inconclusive, as results were not consistent over consecutive periods and not confirmed by different analyses. Overall, these findings confirm those reported in the 3- and 6-mo analyses of AQUARiUS [9,10]. The AQUARiUS outcomes are also comparable with those observed in randomised studies [17–19]. Results of a randomised phase II study also showed that total Functional Assessment of Cancer Therapy—Prostate scores favoured abiraterone over enzalutamide [20].

The importance of determining the impact of treatment on PROs was shown in post hoc analyses of the pivotal studies for abiraterone and enzalutamide [18,19]. PRO improvements (eg, pain, functional well-being, and physical well-being) with abiraterone or enzalutamide were significantly associated with longer overall survival and radiographic progression-free survival. Worsening in PROs was also associated with a higher likelihood of radiographic progression compared with improvement/no change for patients treated with abiraterone. However, AQUARiUS was not designed to assess this association.

This is the first study to report safety outcomes for abiraterone and enzalutamide in the same study according to a real-world setting. Rate of comorbidities, old age of patients, and opioid and sedative consumption are closer to routine practice than to registration trials [6,7]. However, the safety profiles were consistent with those reported in randomised studies [21]. Abiraterone was associated with less asthenia and fatigue than enzalutamide, which is comparable with the findings from meta-analyses of randomised studies (COU-AA-301, COU-AA-302, AFFIRM, and PREVAIL) [21]. The number of neurological AEs was higher in the enzalutamide cohort. The incidence of cardiac and vascular disorders was low and comparable between groups. However, it is important to note that there was potential for under-reporting of safety data due to the observational design.

Other limitations of AQUARiUS include lack of randomisation, although baseline characteristics were well balanced and a modelling approach correcting for all relevant baseline characteristics was used to minimise the confounding bias. There was no formal correction for multiple testing, but significant results were interpreted with extreme caution. Kaplan-Meier plots of the time to the first measured PRO item showing CMW should also be interpreted with caution as these were post hoc; limitations of this analysis are listed in Supplementary Figure 2.

The study also has several strengths; it has a large sample size, despite a decline in questionnaire response over 12 mo. Data are based on validated questionnaires, with consistency across cognitive and fatigue items (FACT-Cog, BFI-SF, and QLQ-C30). The findings are confirmed by several different analyses (mean change from baseline, CMW [overall and at individual periods], and time to worsening of symptoms). The results are also supported by sensitivity analyses. The treatment periods were preplanned with monthly intervals at the beginning of the study to capture early treatment differences.

## **5. Conclusions**

This 12-mo study showed that patients with mCRPC who were treated with abiraterone experienced significantly less fatigue and cognitive impairments than enzalutamide-treated patients. This difference occurred early after treatment initiation. In a real-world setting, it suggests an advantage of abiraterone over enzalutamide in reducing fatigue and cognitive function. This difference should be considered when choosing treatment. These results are also in line with other published data [20]. The safety outcomes were consistent with the known safety profile of each drug, but abiraterone was associated with fewer fatigue, asthenia, and neurological AEs than enzalutamide. Overall, these data confirm previously published interim analyses from this study [9,10], and support the positive impact of abiraterone and enzalutamide treatment on HRQoL under real-world conditions. AQUARIUS also shows that the results achieved in the pivotal studies for each drug can be translated into clinical practice.

**Author contributions:** Antoine Thiery-Vuillemin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Acquisition of data:* Thiery-Vuillemin, Poulsen, Lagneau, Ploussard, Birtle, Dourthe, Beal-Ardisson, Pintus, Trepikakas, Reid.

*Analysis and interpretation of data:* Thiery-Vuillemin, Reid, Lefresne, Lukac, Van Sanden, Pissart.

*Drafting of the manuscript:* Thiery-Vuillemin, Poulsen, Lagneau, Ploussard, Birtle, Dourthe, Beal-Ardisson, Pintus, Trepikakas, Lefresne, Lukac, Van Sanden, Pissart, Reid.

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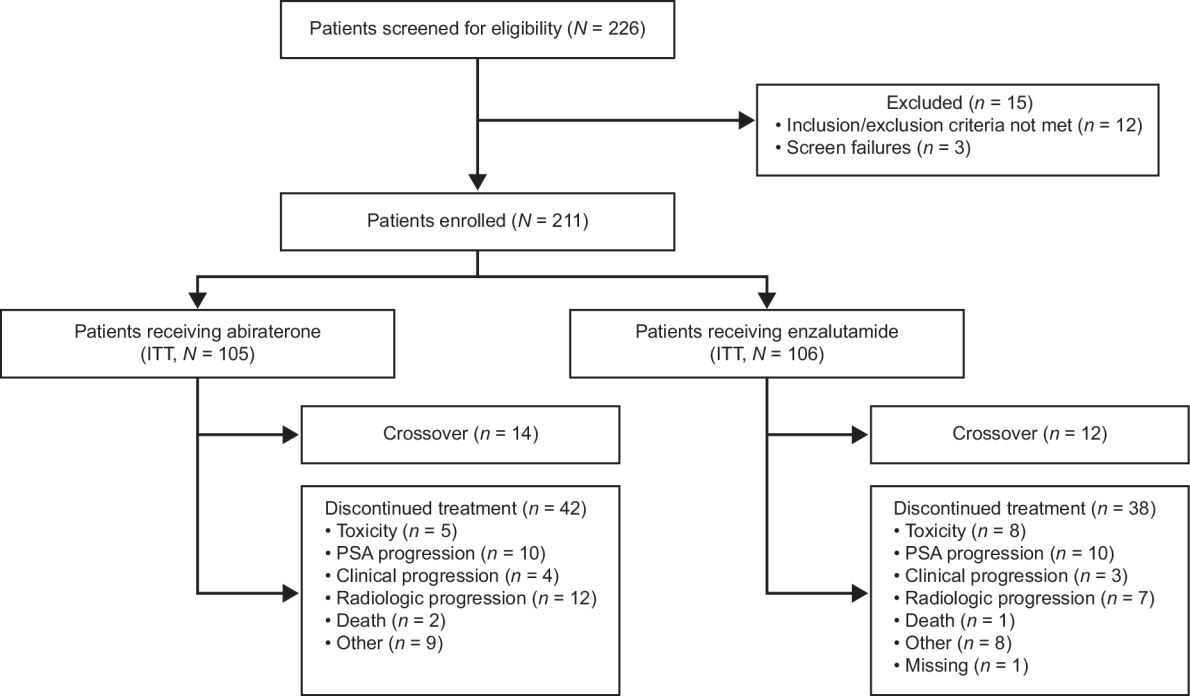
## References

- [1] Dueregger A, Heidegger I, Ofer P, et al. The use of dietary supplements to alleviate androgen deprivation therapy side effects during prostate cancer treatment. *Nutrients* 2014;6:4491–519.
- [2] Crawford ED, Petrylak D, Sartor O. Navigating the evolving therapeutic landscape in advanced prostate cancer. *Urol Oncol* 2017;35S:S1–13.
- [3] American Society of Clinical Oncology. Prostate cancer: statistics 2018. <https://www.cancer.net/cancer-types/prostate-cancer/statistics>
- [4] Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011;65:1180–92.
- [5] Nussbaum N, George DJ, Abernethy AP, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. *Prostate Cancer Prostatic Dis* 2016;19:111–21.
- [6] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;368:138–48.
- [7] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–33.
- [8] Lortot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol* 2015;16:509–21.

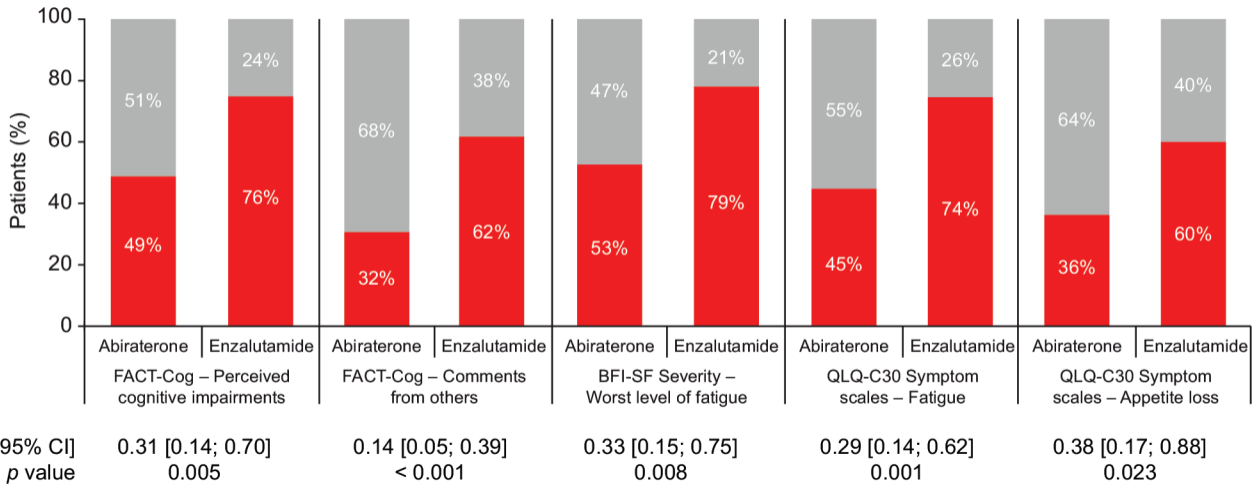
- [9] Thiery-Vuillemin A, Poulsen MH, Lagneau E, et al. Impact of abiraterone acetate plus prednisone or enzalutamide on fatigue and cognition in patients with metastatic castration-resistant prostate cancer: initial results from the observational AQUARiUS study. *ESMO Open* 2018;3:e000397.
- [10] Thiery-Vuillemin A, Poulsen MH, Dourthe LM. Six-month patient-reported outcome (PRO) results from AQUARiUS, a prospective, observational, multicenter phase 4 study in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) receiving abiraterone acetate + prednisone (AAP) or enzalutamide (ENZ). *J Clin Oncol* 2018;36:5058.
- [11] Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–9.
- [12] Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999;85:1186–96.
- [13] Cleeland CS. The brief pain inventory user guide 2009. [https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI\\_UserGuide.pdf](https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf)
- [14] European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 scoring manual. ed. 3. 2001. <https://www.eortc.be/qol/files/SCManualQLQ-C30.pdf>
- [15] Wong K, Zeng L, Zhang L, et al. Minimal clinically important differences in the brief pain inventory in patients with bone metastases. *Support Care Cancer* 2013;21:1893–9.
- [16] Cheung YT, Foo YL, Shwe M, et al. Minimal clinically important difference (MCID) for the functional assessment of cancer therapy: cognitive function (FACT-Cog) in breast cancer patients. *J Clin Epidemiol* 2014;67:811–20.
- [17] Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol* 2013;14:1193–9.
- [18] Cella D, Traina S, Li T, et al. Relationship between patient-reported outcomes and clinical outcomes in metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-301 and COU-AA-302. *Ann Oncol* 2018;29:392–7.
- [19] Beer TM, Miller K, Tombal B, et al. The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: Exploratory analyses of AFFIRM and PREVAIL studies. *Eur J Cancer* 2017;87:21–9.
- [20] Khalaf DJ, Sunderland K, Eigl BJ, et al. Health-related quality of life for abiraterone plus prednisone versus enzalutamide in patients with metastatic castration-resistant prostate cancer: results from a phase II randomized trial. *Eur Urol* 2019;75:940–7.
- [21] Moreira RB, Debiasi M, Francini E, et al. Differential side effects profile in patients with mCRPC treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials. *Oncotarget* 2017;8:84572–8.

**Fig. 1 – Patient flow chart during the study.** Abiraterone = abiraterone acetate plus prednisone; ITT = intention to treat; PSA = prostate-specific antigen.

**Fig. 2 – Proportion of patients (%) with one or more episodes of clinically meaningful worsening in patient-reported outcomes over 12 mo.** Abiraterone = abiraterone acetate plus prednisone; BFI-SF = Brief Fatigue Inventory—Short Form; CI = confidence interval; FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; QLQ-C30 = European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire.



■ Worsening ■ Improvement/no change



**Table 1 – Baseline characteristics of abiraterone- and enzalutamide-treated patients**

	Abiraterone (N = 105)	Enzalutamide (N = 106)
Age (yr), median (IQR)	76.0 (10.0)	76.0 (11.0)
Time since mCRPC diagnosis (mo), median (IQR)	1.4 (3.1)	1.7 (5.7)
	(n = 95)	(n = 102)
Time since prostate cancer diagnosis (mo), median (IQR)	51.9 (98.1)	59.6 (85.0)
	(n = 93)	(n = 99)
Lactate dehydrogenase at baseline (IU/l), median (IQR)	213.0 (79.0)	228.0 (66.0)
	(n = 55)	(n = 33)
Alkaline phosphatase at baseline (IU/l), median (IQR)	93.5 (67.0)	92.0 (84.0)
	(n = 86)	(n = 82)
PSA at baseline (ng/ml), median (IQR)	22.0 (66.6)	34.0 (70.4)
De novo metastases at initial diagnosis, n (%)		
MX	5 (5)	10 (9)
M0	38 (36)	38 (36)
M1	44 (42)	42 (40)
Missing	18 (17)	16 (15)
Gleason score at initial diagnosis, n (%)		
≤7	52 (50)	46 (43)
≥8	45 (43)	49 (46)
Missing	8 (8)	11 (10)
ECOG performance score, n (%)		
0/1	90 (86)	92 (87)
≥2	8 (8)	11 (10)
Missing	7 (7)	3 (3)
Any visceral metastases, n (%)	12 (11)	13 (12)
Anaemia, n (%)		
Grade ≤2	90 (86)	90 (85)
Grade ≥3	0 (0)	0 (0)
Missing	15 (14)	16 (15)
Opioid use at baseline, n (%)	23 (22)	28 (26)
Sedative use at baseline, n (%)	4 (4)	4 (4)
Bone medication use at baseline, n (%)	19 (18)	12 (11)
Cardiovascular abnormalities, n (%)	50 (48)	51 (48)
Musculoskeletal abnormalities, n (%)	24 (23)	23 (22)
Endocrine or metabolic abnormalities, n (%)	29 (28)	36 (34)
Neurological abnormalities, n (%)	11 (11)	8 (8)

Abiraterone = abiraterone acetate plus prednisone; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.

**Table 2 – Mean difference (95% CI) between treatment groups in the change from baseline for significant PRO item scores over 12 mo**

PRO	Period 1 (14–41 d)		Period 2 (42–69 d)		Period 3 (70–97 d)		Period 4–6 (98–181 d)		Period 7–9 (182–265 d)		Period 10–12 (266–456 d)	
	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value
Cognitive functioning <sup>a</sup>	4.38 (0.66; 8.10)	0.021	7.47 (2.72; 12.21)	0.002	8.04 (1.55; 14.52)	0.016	2.75 (-1.92; 7.41)	0.2	6.24 (0.79; 11.70)	0.025	5.14 (-1.11; 11.40)	0.1
Fatigue <sup>a</sup>	-10.53 [(-15.87; -5.18)]	<0.001	-7.99 (-13.93; -2.06)	0.009	-15.24 (-22.56; -7.92)	<0.001	-8.02 (-14.65; -1.40)	0.018	-11.15 (-19.51; -2.79)	0.009	-6.91 (-14.16; 0.34)	0.1
Nausea and vomiting <sup>a</sup>	-2.91 (-6.89; 1.08)	0.2	-0.37 (-4.52; 3.78)	0.9	-5.77 (-9.74; -1.80)	0.005	-4.45 (-8.54; -0.36)	0.033	-6.74 (-10.90; -2.58)	0.002	-1.67 (-5.42; 2.08)	0.4
Appetite loss <sup>a</sup>	-9.28 (-15.17; -3.40)	0.002	-5.09 (-12.15; 1.97)	0.2	-12.94 (-19.93; -5.96)	<0.001	-8.63 (-15.21; -2.05)	0.011	-11.86 (-20.83; -2.89)	0.010	-1.29 (-8.66; 6.08)	0.7
Fatigue right now <sup>b</sup>	-0.78 (-1.39; -0.18)	0.012	-1.01 (-1.68; -0.34)	0.003	-1.04 (-1.82; -0.26)	0.009	-0.16 (-0.87; 0.55)	0.7	-0.80 (-1.58; -0.02)	0.042	-0.49 (-1.28; 0.31)	0.2
Usual level of fatigue <sup>b</sup>	-0.81 (-1.41; -0.20)	0.009	-1.23 (-1.89; -0.57)	<0.001	-1.31 (-2.10; -0.52)	0.001	-0.43 (-1.06; 0.20)	0.2	-0.97 (-1.70; -0.24)	0.010	-0.63 (-1.40; 0.15)	0.1
Worst level of fatigue <sup>b</sup>	-0.98 (-1.61; -0.35)	0.002	-1.19 (-1.93; -0.45)	0.002	-1.43 (-2.23; -0.62)	0.001	-0.28 (-1.00; 0.45)	0.5	-0.78 (-1.65; 0.09)	0.078	-0.65 (-1.52; 0.23)	0.1
Perceived cognitive impairments <sup>c</sup>	3.32 (1.16; 5.48)	0.003	4.62 (2.12; 7.12)	<0.001	5.56 (2.61; 8.51)	<0.001	4.70 (1.98; 7.42)	0.001	4.12 (1.25; 7.00)	0.005	2.15 (-0.46; 4.75)	0.1
Comments from others <sup>c</sup>	0.65 (0.14; 1.16)	0.012	0.63 (0.09; 1.17)	0.022	1.04 (0.39; 1.69)	0.002	0.55 (0.05; 1.04)	0.030	0.96 (0.07; 1.86)	0.036	0.78 (0.02; 1.54)	0.044

Abiraterone = abiraterone acetate plus prednisone; CI = confidence interval; PRO = patient-reported outcome.

Different colours used in the table indicate the following: light green = trend in favour of abiraterone; dark green = significant in favour of abiraterone; light blue = trend in favour of enzalutamide; and dark blue = significant in favour of enzalutamide.

<sup>a</sup> European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire.

<sup>b</sup> Brief Fatigue Inventory—Short Form.

<sup>c</sup> Functional Assessment of Cancer Therapy—Cognitive Function.