



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

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ABSTRACT

Introduction Abiraterone acetate plus prednisone (AAP) and enzalutamide (ENZ) are commonly prescribed for metastatic castration-resistant prostate cancer (mCRPC). Data comparing their effects on patient-reported outcomes (PROs) from routine clinical practice are limited.

Methods AQUARiUS (NCT02813408) is an ongoing, two-cohort, prospective, observational, non-randomised, multicentre, phase IV European study assessing the effects of AAP and ENZ on PROs in 211 patients with mCRPC over 12 months. Patients receive AAP or ENZ per routine clinical practice. Data on cognition, fatigue, pain and health-related quality of life are measured using the Functional Assessment of Cancer Therapy-Cognitive Function, Brief Fatigue Inventory-Short Form, Brief Pain Inventory-Short Form and European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaires, respectively.

Results This 3-month analysis was conducted in 105 patients; 46 received AAP and 59 received ENZ. There were statistically significant differences in mean change from baseline favouring AAP over ENZ at months 1, 2 and 3 for perceived cognitive impairments and cognitive functioning. At each time-point, ENZ-treated patients had a significantly higher risk of experiencing clinically meaningful worsening in perceived cognitive impairments versus those receiving AAP. Statistically significant differences in mean change from baseline favouring AAP over ENZ were seen for usual level of fatigue and fatigue interference at months 2 and 3 and for current fatigue and worse level of fatigue at month 3. Differences favouring AAP versus ENZ were seen for the fatigue scale of the QLQ-C30 questionnaire (months 1 and 3). There was a significantly higher risk of clinically meaningful worsening in usual level of fatigue with ENZ versus AAP at month 3. No significant differences between cohorts were observed for pain (BPI-SF) at any time-point.

Conclusion This analysis suggests more favourable outcomes with AAP versus ENZ for cognition and fatigue in

Key questions

What is already known about this subject?

- Abiraterone acetate plus prednisone (AAP) and enzalutamide (ENZ) have been shown to independently delay radiographic progression and extend survival in patients with metastatic castration-resistant prostate cancer (mCRPC).
- Although limited, clinical data suggest that cognitive and pain outcomes were more favourable in patients treated with AAP versus prednisone and with ENZ versus placebo.

What does this study add?

- This 3-month analysis of AQUARiUS showed significant differences favouring AAP over ENZ in cognitive outcome measures within the first 3 months of treatment initiation and in fatigue from month 2 onwards.
- No significant differences for pain scales were seen during the first 3 months of treatment.

How might this impact on clinical practice?

- AAP and ENZ have both demonstrated improved survival in the treatment of mCRPC.
- Differences in patient-reported outcomes may aid physicians to determine the most appropriate course of treatment in specific patients.

the first 3 months of treatment initiation for mCRPC. These findings require confirmation from future analyses of data from AQUARiUS from a larger number of patients with a longer follow-up period.

INTRODUCTION

Although approximately 90% of patients with metastatic prostate cancer respond to androgen deprivation therapy (ADT),¹ after

2–3 years of remission, virtually all metastatic disease will ultimately progress to castration-resistant prostate cancer (CRPC). Furthermore, of patients diagnosed with CRPC with no metastases, 33% are likely to develop metastases within 2 years¹. Metastatic CRPC (mCRPC) is associated with an expected survival of between 15 and 36 months according to recent studies.² In addition to a poor prognosis, patients with mCRPC are likely to experience deterioration in health-related quality of life (HRQoL) and progressive worsening of pain.³ Docetaxel was the standard of care for mCRPC; however, since 2010, a number of other treatment options have become available, including abiraterone acetate plus prednisone (AAP) and enzalutamide (ENZ), both androgen-targeted therapies that have been shown to delay radiographic progression and increase survival compared with prednisone or placebo, respectively, in clinical trials.^{4–8} Being non-cytotoxic, life-extending therapies, AAP and ENZ have the potential to affect HRQoL and pain positively as compared with chemotherapy, as well as other patient-reported outcomes (PROs), such as fatigue and cognitive function, striking a more favourable balance between cancer control and toxicity than cytotoxic alternatives.³ Indeed, data from phase III trials of AAP and ENZ (COU-AA-302 and PREVAIL, respectively) showed that chemotherapy-naïve patients with mCRPC treated with either agent experienced delayed deterioration in HRQoL, defined as a decrease of at least 10 points in global score on the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale, compared with controls (12.7 months vs 8.3 months for AAP and prednisone alone, respectively; 11.3 months vs 5.6 months for ENZ and placebo, respectively).^{7,8} In addition, results from COU-AA-302 showed that AAP delayed the time to pain progression (26.7 months vs 18.4 months with AAP and prednisone, respectively)⁷ and results from PREVAIL showed that the time to deterioration in FACT-P prostate cancer subscale pain-related score was longer in the ENZ group than in the placebo group (8.3 months vs 2.8 months, respectively).⁹

Recent findings from a phase II trial (NCT02125357) showed more favourable outcomes for quality of life (QoL), depression and cognition with AAP versus ENZ in chemotherapy-naïve patients with mCRPC.^{10,11} Data from a single-centre study indicated that self-reported physical and psychological symptoms (assessed by Edmonton Symptom Assessment System (ESAS) score) were comparable in men with chemotherapy-naïve mCRPC treated with AAP or ENZ in routine clinical practice.¹² Data of this kind, which compare the effects of AAP versus ENZ on PROs in an unselected population in the real-world setting, are limited. Cognitive function in particular is an understudied PRO in patients with mCRPC.

The phase IV AQUARiUS study was designed to explore whether there are differences in PROs (cognitive function, fatigue, pain and HRQoL) and medical resource use between chemotherapy-naïve patients with mCRPC newly initiated on AAP or ENZ in the real-world setting. This initial 3-month analysis focuses on PRO data only.

METHODS

Study design

AQUARiUS (NCT02813408) is an ongoing, two-cohort, prospective, observational, non-randomised, multicentre phase IV study conducted in Denmark, France and the UK. Patients were recruited during routine clinical practice by office-based or hospital-based urology and/or oncology specialists at the point at which treatment with either AAP or ENZ was initiated. The decision to treat the patient with either agent preceded study enrolment and was per routine clinical practice; the treatment and clinical care of patients was not influenced by their participation in the study. All patients meeting the study criteria who visited the study physician were consecutively invited to participate in the study to minimise recruitment bias.

Ahead of site initiation, a national or central independent ethics committee or institutional review board reviewed/received notification of the study, in all countries, as required by local regulations.

Patients and sample size

To be eligible to take part in the study, patients had to meet the following inclusion criteria: males aged ≥ 18 years; histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate; documented metastatic prostate cancer; documented castration resistance with progression of prostate cancer on ADT (surgical or chemical); and were to be initiated on AAP or ENZ for asymptomatic or mildly symptomatic mCRPC after the failure of ADT.

Patients were not eligible if they had received any prior chemotherapy/cytotoxic agent to treat their mCRPC, had received or were currently receiving AAP or ENZ or were receiving an investigational treatment for prostate cancer of any kind before or at the time of initiation of AAP or ENZ treatment.

Prior to data collection, all patients provided informed consent in accordance with local requirements. The study was conducted according to the principles set forth in the Declaration of Helsinki.

Data would be prospectively collected from approximately 211 patients in total, which is the sample size required to detect a difference of ≥ 0.5 SD between the two treatment cohorts, with 85% power at the 5% level of significance. The number of patients in each cohort would be as equal as possible, and recruitment would be closely monitored.

Endpoints and data collection

Data were collected on paper questionnaires and then entered onto electronic case report forms. Patients were asked to provide PRO data on cognition, fatigue, pain and HRQoL via completion of the following questionnaires: the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog),¹³ which comprises four subscales (symptoms of perceived cognitive impairments, perceived cognitive abilities, comments from others and impact of perceived cognitive impairment on QoL); Brief Fatigue

Inventory-Short Form (BFI-SF),¹⁴ which comprises three severity items and six fatigue interference items (disruption to general activity, mood, walking ability, normal work, relations with others and enjoyment of life); Brief Pain Inventory-Short Form (BPI-SF),¹⁵ comprising four pain severity items, seven pain interference items and a question regarding percentage of pain relief from analgesics; and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30),¹⁶ comprising five functional scales (physical, role, cognition, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting), a global health and QoL scale and several single-item symptom measures.

Medical records were used to capture data on prostate cancer diagnosis and history, baseline patient demographics and clinical characteristics and current treatment regimens. Collection of PRO data began before administration of AAP or ENZ (defined as the baseline visit) and would continue until termination of treatment or for approximately 12 months, whichever occurs first. During the observation period, PRO data were collected during a patient's routine visits to the clinic. Study completion was defined as the date of last data collection of the last patient in the study (online supplementary figure 1 and online supplementary table 1).

Data analysis

This current analysis focuses on PROs and was based on enrolment of 50% (n=105) of the planned 211 patients with 3-month follow-up (cut-off date: 16 February 2017). PRO data were analysed at monthly intervals, defined as 28, 56 or 84 days, ± 14 days, following initiation of AAP or ENZ treatment.

Two types of analysis were performed to compare the treatment groups: (1) the mean change from baseline in PRO score, a continuous endpoint, which was analysed using multivariate repeated measures linear models, and (2) the percentage of patients who showed clinically meaningful worsening versus improvements/no change in PROs, a binary endpoint, which was analysed using multivariate repeated measures logistic models. A clinically meaningful change in status was defined as a difference from baseline greater than the minimal important difference (0.5 times the SD of the baseline PRO of all patients). If results could not be obtained from the multivariate repeated measures logistic models due to convergence issues, multivariate logistic models fitted for each time period separately were used instead.

Both analyses were adjusted for the baseline PRO value and for baseline characteristics associated with their corresponding PRO scale. Baseline characteristics considered as covariates in the multivariate models included age, Gleason score at initial diagnosis, Eastern Cooperative Oncology Group performance status, visceral metastases, use of analgesics, use of sedatives, alkaline phosphatase, haemoglobin, prostate-specific antigen and number of comorbidities (lactate dehydrogenase was excluded due to the number of missing values).

The primary analysis is an intention-to-treat analysis; all patients were included regardless of whether they switched treatment during follow-up. Per-protocol and censoring analyses were conducted as sensitivity analyses. In the per-protocol analysis, patients who switched were excluded; in the censoring analysis, patients were censored at the time of switch. The results presented hereafter were based on the intent-to-treat population.

RESULTS

A total of 113 patients were examined for eligibility in the study; however, eight of these patients did not meet the inclusion/exclusion criteria. Therefore, 105 patients were included in this initial analysis—46 patients were treated with AAP (four of whom received dexamethasone instead of prednisone) and 59 were treated with ENZ. Baseline characteristics were reasonably well balanced between the two treatment cohorts, and no statistically significant differences were observed (table 1). As indicated in online supplementary table 2, completion of PRO questionnaires decreased over the 3-month period in the same range in both treatment cohorts.

Patients who switched or discontinued treatment

Within the first 3 months, seven patients (two from the AAP group and five from the ENZ group) switched from one treatment to the other and four patients (two from the AAP group and two from the ENZ group) discontinued treatment. Reasons for discontinuation or switching of treatment are shown in online supplementary table 3.

Analysis 1: mean change from baseline in PRO score

Figure 1 shows the mean difference between treatment groups in the mean change from baseline for each scale evaluated. As shown, all significant differences observed between the two treatment groups favoured AAP over ENZ. Figure 2 shows the mean change from baseline at months 1, 2 and 3 for scales for which a significant difference between treatment groups was seen for at least two consecutive time-points.

Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)

Significant differences favouring AAP over ENZ were consistent across all three time-points for perceived cognitive impairments (4.67, 95% CI 1.20 to 8.13, $p=0.009$; 6.60, 95% CI 2.73 to 10.48, $p=0.001$; and 6.64, 95% CI 0.84 to 12.43, $p=0.025$ at months 1, 2 and 3, respectively) (figure 1 and 2). Significant differences favouring AAP over ENZ were also seen for scale 'impact on QoL' at month 1 and scale 'comments from others' at month 3 (figure 1).

Brief Fatigue Inventory-Short Form (BFI-SF)

At months 2 and 3, significant differences in favour of AAP versus ENZ were seen for usual level of fatigue (-1.17 , 95% CI -2.13 to -0.22 , $p=0.017$; and -1.41 , 95% CI -2.74 to -0.08 , $p=0.038$ at months 2 and 3, respectively) (figure 1 and 2) and for fatigue interference (-0.99 , 95% CI -1.83 to

Table 1 Baseline characteristics of AAP-treated and ENZ-treated patients

	AAP (n=46)	ENZ (n=59)	P values
Age, years, median (range)	n=46 73 (53–90)	n=59 76 (60–92)	0.083
LDH at baseline, IU/L, median (range)	n=21 226.00 (130–1207)	n=20 229.50 (170–837)	0.755
ALP at baseline, IU/L, median (range)	n=37 94.00 (34–2435)	n=46 91.00 (47–4344)	0.781
PSA at baseline, ng/mL, median (range)	n=46 15.56 (1.1–588)	n=59 36.00 (1.3–450)	0.605
Gleason score at initial diagnosis, n (%)			0.944
≤7	24 (52.2)	29 (49.2)	
≥8	18 (39.1)	25 (42.4)	
Missing	4 (8.7)	5 (8.5)	
ECOG performance score, n (%)			0.627
0/1	41 (89.1)	49 (83.1)	
≥2	4 (8.7)	7 (11.9)	
Missing	1 (2.2)	3 (5.1)	
Any visceral metastases, n (%)			0.646
No	40 (87.0)	53 (89.8)	
Yes	6 (13.0)	6 (10.2)	
Anaemia, n (%)			0.810
Grade ≤2	39 (84.8)	51 (86.4)	
Grade ≥3	0 (0.0)	0 (0.0)	
Missing	7 (15.2)	8 (13.6)	
Opioid use at baseline, n (%)			0.694
No	36 (78.3)	48 (81.4)	
Yes	10 (21.7)	11 (18.6)	
Sedative use at baseline, n (%)			0.281
No	39 (84.8)	54 (91.5)	
Yes	7 (15.2)	5 (8.5)	

AAP, abiraterone acetate plus prednisone; ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group.; ENZ, enzalutamide; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

–0.15, $p=0.021$; and -1.20 , 95% CI -2.31 to -0.08 , $p=0.036$ at months 2 and 3, respectively) (figure 1 and 2). Significant differences favouring AAP over ENZ were also observed at month 3 for ‘your fatigue right now’ (-1.41 , 95% CI -2.55 to -0.26 , $p=0.017$) and ‘your worst level of fatigue’ (-1.63 , 95% CI -2.98 to -0.28 , $p=0.019$) (figure 1).

Brief Pain Inventory-Short Form (BPI-SF)

No significant differences between treatment groups were observed for any of the pain PRO scales at any time-point (figure 1).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

Significant differences favouring AAP over ENZ were seen consistently across all time-points for cognitive functioning (6.10, 95% CI 0.92 to 11.28, $p=0.021$; 9.75, 95% CI 3.06 to 16.44, $p=0.005$; and 11.82, 95% CI 0.84 to 22.79,

$p=0.035$ at months, 1, 2 and 3, respectively) (figure 1 and 2). Significant differences favoured AAP over ENZ for the fatigue aspect of the questionnaire at month 1 (-9.85 , 95% CI -18.07 to -1.63 ; $p=0.019$) and month 3 (-16.20 , 95% CI -28.25 to -4.15 , $p=0.009$) and for the pain aspect of the questionnaire at month 3 (-13.59 , 95% CI -24.68 to -2.50 , $p=0.017$) (figure 1). Significant differences also favoured AAP over ENZ for emotional functioning and appetite loss at months 1 and 3, for role functioning at month 1 and for physical functioning at month 3 (figure 1).

Analysis 2: clinically meaningful change in PRO score

The ORs for patients who showed clinically meaningful worsening versus improvement or no change for each PRO scale are presented in figure 3.

PRO scale (min–max range)	Month 1	Month 2	Month 3
FACT-Cog	Difference (95% CI)* p Value	Difference (95% CI)* p Value	Difference (95% CI)* p Value
1. Perceived cognitive impairments (0–72)	4.67 (1.20–8.13) 0.009	6.60 (2.73–10.48) 0.001	6.64 (0.84–12.43) 0.025
2. Comments from others (0–16)	0.66 (–0.08 to 1.39) 0.080	0.76 (–0.05 to 1.57) 0.065	1.53 (0.44–2.62) 0.007
3. Perceived cognitive abilities (0–28)	2.54 (–0.40 to 5.47) 0.090	3.13 (–0.32 to 6.57) 0.074	1.40 (–2.35 to 5.14) 0.460
4. Impact on QoL (0–16)	1.36 (0.00–2.71) 0.050	0.03 (–1.64 to 1.70) 0.974	1.37 (–0.58 to 3.32) 0.164
BFI-SF			
Severity			
1. Your fatigue right now (0–10)	–0.78 (–1.67 to 0.11) 0.084	–1.00 (–2.02 to 0.02) 0.055	–1.41 (–2.55 to –0.26) 0.017
2. Your usual level of fatigue (0–10)	–0.52 (–1.36 to 0.33) 0.230	–1.17 (–2.13 to –0.22) 0.017	–1.41 (–2.74 to –0.08) 0.038
3. Your worst level of fatigue (0–10)	–0.57 (–1.53 to 0.38) 0.235	–1.09 (–2.22 to 0.05) 0.060	–1.63 (–2.98 to –0.28) 0.019
Fatigue interference			
4. Fatigue interference (0–10)	–0.36 (–1.08 to 0.37) 0.330	–0.99 (–1.83 to –0.15) 0.021	–1.20 (–2.31 to –0.08) 0.036
BPI-SF			
Severity			
1. Pain at its worst (0–10)	0.06 (–0.91 to 1.02) 0.910	–0.03 (–1.18 to 1.11) 0.952	–0.59 (–1.84 to 0.66) 0.353
2. Pain at its least (0–10)	–0.28 (–1.02 to 0.46) 0.461	–0.18 (–1.07 to 0.71) 0.688	–0.46 (–1.36 to 0.44) 0.312
3. Pain on the average (0–10)	0.10 (–0.57 to 0.76) 0.775	–0.23 (–1.09 to 0.63) 0.602	–0.59 (–1.61 to 0.42) 0.245
4. Pain right now (0–10)	–0.30 (–1.07 to 0.47) 0.443	–0.05 (–0.98 to 0.88) 0.912	–0.20 (–1.16 to 0.75) 0.675
Pain interference			
5. Pain interference (0–10)	–0.14 (–0.86 to 0.57) 0.689	–0.36 (–1.18 to 0.47) 0.387	–0.71 (–1.89 to 0.47) 0.231
QLQ-C30			
Functional scales			
1. Physical functioning (0–100)	0.60 (–5.05 to 6.24) 0.834	–0.09 (–6.91 to 6.73) 0.980	9.38 (1.08 to 17.68) 0.027
2. Role functioning (0–100)	10.71 (0.08–21.34) 0.048	9.03 (–1.60 to 19.67) 0.095	12.40 (–0.09 to 24.88) 0.052
3. Emotional functioning (0–100)	6.02 (0.04–12.00) 0.048	–0.89 (–8.93 to 7.15) 0.826	5.55 (0.04–11.06) 0.049
4. Cognitive functioning (0–100)	6.10 (0.92–11.28) 0.021	9.75 (3.06–16.44) 0.005	11.82 (0.84–22.79) 0.035
5. Social functioning (0–100)	5.67 (–3.86 to 15.19) 0.241	4.70 (–4.97 to 14.37) 0.336	11.52 (–1.19 to 24.23) 0.075
Symptom scales			
6. Fatigue (0–100)	–9.85 (–18.07 to –1.63) 0.019	–3.94 (–13.31 to 5.42) 0.406	–16.20 (–28.25 to –4.15) 0.009
7. Nausea and vomiting (0–100)	–3.97 (–9.68 to 1.74) 0.170	0.83 (–5.72 to 7.37) 0.802	–5.33 (–12.44 to 1.77) 0.139
8. Pain (0–100)	–1.76 (–11.23 to 7.72) 0.714	–6.43 (–17.39 to 4.53) 0.247	–13.59 (–24.68 to –2.50) 0.017
9. Dyspnoea (0–100)	–1.26 (–9.10 to 6.57) 0.749	–2.81 (–12.41 to 6.79) 0.562	–5.13 (–15.29 to 5.04) 0.318
10. Insomnia (0–100)	–9.75 (–19.83 to 0.33) 0.058	1.06 (–8.54 to 10.66) 0.826	–2.67 (–12.21 to 6.87) 0.578
11. Appetite loss (0–100)	–11.01 (–19.65 to –2.38) 0.013	–7.47 (–17.08 to 2.14) 0.126	–20.25 (–32.73 to –7.77) 0.002
12. Constipation (0–100)	–0.76 (–10.11 to 8.59) 0.872	0.43 (–10.99 to 11.84) 0.941	–3.76 (–16.04 to 8.52) 0.543
13. Diarrhoea (0–100)	–3.30 (–10.84 to 4.24) 0.387	–4.35 (–12.64 to 3.94) 0.299	–6.59 (–14.80 to 1.63) 0.114
14. Financial difficulties (0–100)	0.92 (–4.77 to 6.60) 0.749	–4.53 (–10.86 to 1.81) 0.159	4.45 (–3.03 to 11.93) 0.239
Global health status/QoL			
15. Global health status/QoL (0–100)	4.17 (–2.77 to 11.11) 0.236	7.73 (–2.29 to 17.74) 0.129	7.05 (–4.41 to 18.51) 0.224

■ Signi cant in favour of AAP ■ Trend in favour of AAP ■ Signi cant in favour of ENZ ■ Trend in favour of ENZ

Figure 1 Mean difference between treatment groups in the change from baseline for all PRO scores at months 1, 2 and 3. *Evaluable patients. Interpretation of the PRO scales: for FACT-Cog higher scores are favourable; for EORTC QLQ-C30 functional scales and global health status/QoL higher scores are favourable, for EORTC QLQ-C30 symptom scales lower scores are favourable; for BPI-SF and BFI-SF lower scores are favourable. AAP, abiraterone acetate plus prednisone; BFI-SF, Brief Fatigue Inventory-Short Form; BPI-SF, Brief Pain Inventory-Short Form; ENZ, enzalutamide; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life questionnaire; FACT-Cog, Functional Assessment of Cancer Therapy -Cognitive Function; PRO, patient-reported outcome; QoL, quality of life.

Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)

Patients treated with ENZ had a significantly higher risk of experiencing clinically meaningful worsening versus improvement or no change in perceived cognitive

impairments compared with those treated with AAP at months 1, 2 and 3, with ORs for AAP versus ENZ of 0.13, 95% CI 0.03 to 0.54, p=0.005; 0.06, 95% CI 0.01 to 0.27, p<0.001 and 0.14, 95% CI 0.03 to 0.75, p=0.022 for months 1, 2 and 3, respectively (figure 3 and 4). A significant

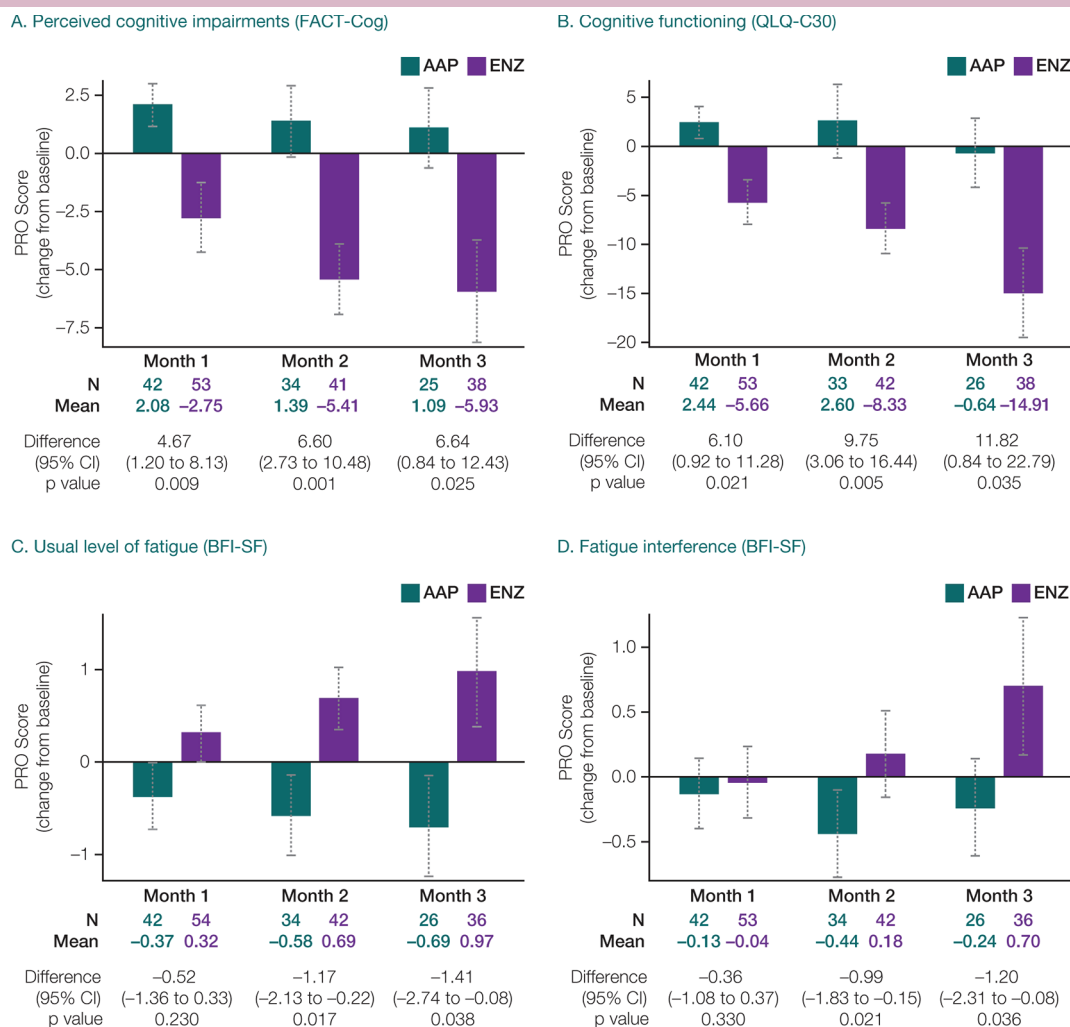


Figure 2 Mean change from baseline for perceived cognitive impairments (A), cognitive functioning (B), usual level of fatigue (C) and fatigue interference (D) at months 1, 2 and 3. For FACT-Cog higher scores are favourable; for EORTC QLQ-C30 functional scales and global health status/QoL higher scores are favourable, for EORTC QLQ-C30 symptom scales lower scores are favourable; for BPI-SF and BFI-SF lower scores are favourable AAP, abiraterone acetate plus prednisone; BFI-SF, Brief Fatigue Inventory-Short Form; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; ENZ, enzalutamide; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life questionnaire; FACT-Cog, Functional Assessment of Cancer Therapy -Cognitive Function; PRO, patient-reported outcome.

difference was also seen for ‘comments from others’ at month 2 (OR for AAP vs ENZ was 0.23, 95% CI 0.06 to 0.94, $p=0.041$, based on the multivariate logistic model fitted for each time period separately; [figure 3](#)).

Brief Fatigue Inventory-Short Form (BFI-SF)

The only significant difference for fatigue was seen at month 3, at which point there was a significant difference favouring AAP over ENZ for usual level of fatigue (the OR for clinically meaningful worsening vs improvement or no change for AAP vs ENZ was 0.33, 95% CI 0.11 to 0.97, $p=0.044$; [figure 3](#)).

Brief Pain Inventory-Short Form (BPI-SF)

There were no significant differences between treatment groups for any of the pain scales at any time-point ([figure 3](#)).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

Significant differences favouring AAP over ENZ were seen for cognitive functioning at month 1 (OR for clinically meaningful worsening vs improvement or no change for AAP vs ENZ was 0.09, 95% CI 0.02 to 0.49, $p=0.006$; [figure 3](#)). A significant difference favouring AAP over ENZ was seen for fatigue at month 1 (OR for AAP vs ENZ was 0.24, 95% CI 0.06 to 0.90, $p=0.034$, based on the multivariate logistic model fitted for each time period separately; [figure 3](#)). Significant differences favouring AAP versus ENZ were also seen for emotional functioning at month 1, global health status/QoL at month 2, physical functioning at month 3 and appetite loss at months 1 and 3 ([figure 3](#)).

PRO scale	Month 1	Month 2	Month 3
FACT-Cog	Odds ratio (95% CI)† p Value	Odds ratio (95% CI)† p Value	Odds ratio (95% CI)† p Value
1. Perceived cognitive impairments	0.13 (0.03–0.54) 0.005	0.06 (0.01–0.27) <0.001	0.14 (0.03–0.75) 0.022
2. Comments from others‡	0.31 (0.09–1.07) 0.065	0.23 (0.06–0.94) 0.041	–
3. Perceived cognitive abilities	0.47 (0.15–1.47) 0.192	0.40 (0.11–1.45) 0.163	0.53 (0.11–2.45) 0.416
4. Impact on QoL	0.62 (0.20–1.89) 0.401	1.33 (0.41–4.27) 0.634	0.49 (0.15–1.60) 0.237
BFI-SF			
Severity			
1. Your fatigue right now	0.85 (0.30–2.40) 0.754	0.80 (0.27–2.37) 0.683	0.38 (0.11–1.29) 0.121
2. Your usual level of fatigue	0.68 (0.25–1.81) 0.437	0.53 (0.17–1.64) 0.272	0.33 (0.11–0.97) 0.044
3. Your worst level of fatigue	1.11 (0.38–3.26) 0.847	0.90 (0.27–3.03) 0.863	0.57 (0.15–2.11) 0.399
Fatigue interference			
4. Fatigue interference	0.59 (0.18–1.93) 0.384	0.76 (0.27–2.15) 0.611	0.53 (0.17–1.62) 0.265
BPI-SF			
Severity			
1. Pain at its worst†	3.50 (0.84–14.61) 0.086	2.82 (0.64–12.47) 0.171	0.94 (0.19–4.69) 0.940
2. Pain at its least	0.74 (0.26–2.10) 0.569	0.70 (0.25–1.95) 0.493	0.62 (0.17–2.26) 0.466
3. Pain on the average‡	–	2.59 (0.44–15.33) 0.293	0.96 (0.20–4.76) 0.964
4. Pain right now	1.25 (0.32–4.79) 0.748	0.87 (0.26–2.91) 0.820	1.34 (0.25–7.14) 0.730
Pain interference			
5. Pain interference	0.43 (0.08–2.28) 0.319	0.36 (0.11–1.18) 0.091	0.77 (0.21–2.91) 0.705
QLQ-C30			
Functional scales			
1. Physical functioning	0.65 (0.24–1.75) 0.396	2.07 (0.63–6.80) 0.230	0.14 (0.03–0.73) 0.019
2. Role functioning	0.45 (0.17–1.24) 0.125	0.84 (0.32–2.18) 0.713	0.45 (0.16–1.27) 0.130
3. Emotional functioning	0.08 (0.01–0.84) 0.036	1.29 (0.32–5.17) 0.716	0.89 (0.21–3.80) 0.879
4. Cognitive functioning	0.09 (0.02–0.49) 0.006	0.22 (0.05–1.06) 0.060	0.45 (0.12–1.75) 0.250
5. Social functioning	1.80 (0.66–4.93) 0.251	1.09 (0.36–3.28) 0.879	0.84 (0.28–2.48) 0.752
Symptom scales			
6. Fatigue	0.24 (0.06–0.90) 0.034	0.61 (0.18–2.09) 0.433	0.37 (0.05–2.72) 0.329
7. Nausea and vomiting	1.59 (0.54–4.73) 0.401	1.92 (0.54–6.83) 0.312	0.59 (0.16–2.19) 0.428
8. Pain	1.12 (0.41–3.06) 0.632	0.71 (0.24–2.12) 0.539	0.46 (0.13–1.68) 0.241
9. Dyspnoea	0.93 (0.30–2.91) 0.900	0.66 (0.21–2.14) 0.492	0.31 (0.05–1.76) 0.186
10. Insomnia	0.50 (0.15–1.64) 0.254	0.57 (0.16–2.00) 0.384	1.19 (0.29–4.92) 0.815
11. Appetite loss	0.20 (0.04–0.99) 0.049	0.31 (0.07–1.34) 0.117	0.12 (0.02–0.63) 0.012
12. Constipation	0.96 (0.29–3.13) 0.940	1.31 (0.35–4.99) 0.691	0.82 (0.22–3.10) 0.769
13. Diarrhoea	0.83 (0.20–3.47) 0.793	0.09 (0.01–1.05) 0.054	0.30 (0.03–2.89) 0.299
14. Financial difficulties‡	0.78 (0.12–4.92) 0.789	0.28 (0.03–2.61) 0.262	–
Global health status/QoL			
15. Global health status/QoL	0.47 (0.16–1.42) 0.183	0.25 (0.07–0.91) 0.036	0.47 (0.11–1.95) 0.300

■ Signi cant in favour of AAP ■ Trend in favour of AAP ■ Signi cant in favour of ENZ ■ Trend in favour of ENZ

Figure 3 Clinically meaningful worsening (versus improvement or no change)* for AAP (n=46) vs ENZ (n=59) for all PRO scales evaluated. *Defined as the difference from baseline \geq minimal important difference (0.5 \times SD of baseline PRO of all patients). †Evaluable patients. ‡Results could not be obtained from the multivariate repeated measures logistic models for these scenarios due to convergence issues. Instead they are taken from multivariate logistic models fitted for each time period separately. (For all scenarios for which both type of models could be fit, results were very much in line.) Empty cells are the results of zero counts and therefore modelling is not possible. Interpretation of the PRO scales: for FACT-Cog higher scores are favourable; for EORTC QLQ-C30 functional scales and global health status/QoL higher scores are favourable, for EORTC QLQ-C30 symptom scales lower scores are favourable; for BPI-SF and BFI-SF lower scores are favourable.

Results of the per-protocol analysis and the censoring analysis remained consistent with those presented for the intent-to treat analysis.

DISCUSSION

Initial results from the AQUARiUS study showed that cognitive outcome measures were consistently more favourable with AAP versus ENZ over the three time-points

assessed. Significant differences favouring AAP over ENZ in mean change from baseline in perceived cognitive impairments, as assessed using the FACT-Cog questionnaire, were observed at months 1, 2 and 3. In addition, the risk of clinically meaningful worsening of perceived cognitive impairments, again assessed via FACT-Cog, was significantly greater with ENZ treatment compared with AAP, at each of the three time-points. These findings

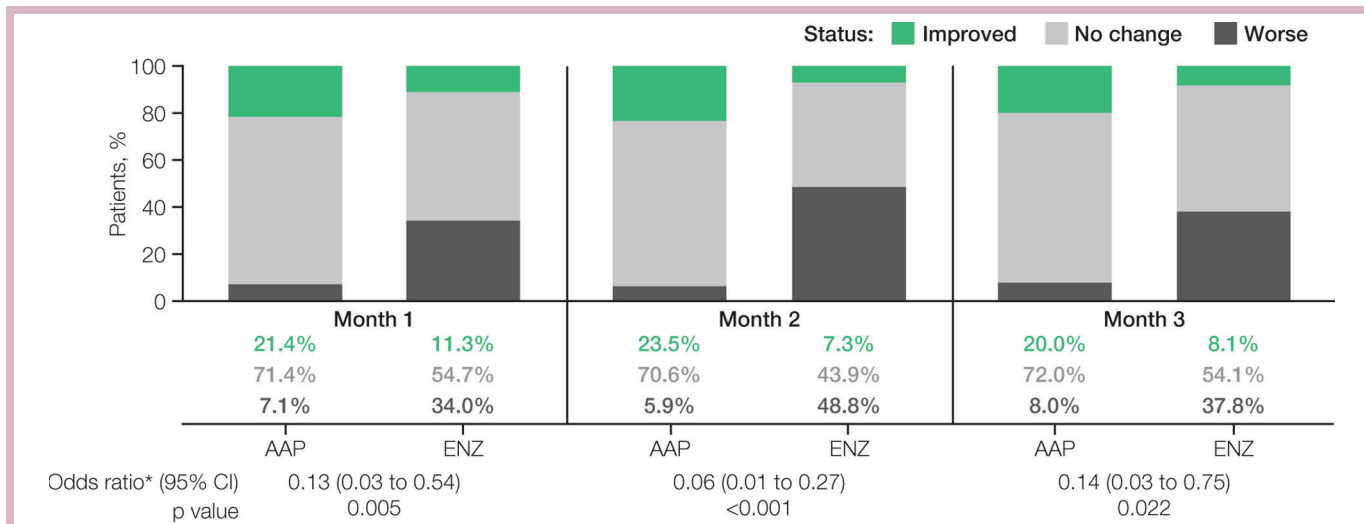


Figure 4 Proportion of patients showing clinically meaningful worsening, improvement or no change in perceived cognitive impairments for AAP versus ENZ at months 1, 2 and 3. *Worsening versus improvement or no change. AAP, abiraterone acetate plus prednisone; CI, confidence interval; ENZ, enzalutamide.

were supported by the cognitive functioning aspect of the QLQ-C30 questionnaire, which showed a significant difference in cognitive functioning at months 1, 2 and 3 in favour of AAP over ENZ.

There were significant differences between treatment groups favouring AAP over ENZ in mean change from baseline in usual level of fatigue and fatigue interference, as assessed using the BFI-SF at months 2 and 3, and for all fatigue scales at month 3. Furthermore, results of the clinically meaningful change from baseline analysis demonstrated that usual level of fatigue was significantly more likely to worsen in those treated with ENZ compared with those treated with AAP at month 3. Significant differences between treatment groups for mean change in baseline were also observed for the fatigue aspect of the EORTC QLC-30 questionnaire at months 1 and 3. No significant differences were observed for pain outcomes measures, as assessed using the BPI-SF, in either of the two analyses at any time-point.

Our finding that the effects of AAP and ENZ on PROs can be observed during the first 3 months of treatment, and in some cases as early as month 1, is not surprising as with daily dosing abiraterone and ENZ reach steady state by days 9 and 28, respectively^{6,17} and have previously been shown to affect patient symptoms such as pain within a similar treatment period (approximately 3 months).^{9,18}

Our study suggests that in order to improve adherence to therapy, particular attention is warranted in the clinical management of patients over the first 3 months of treatment. In the current analysis of AQUARIUS, seven patients from the ENZ cohort switched or discontinued treatment (five of which were due to safety reasons) compared with four from the AAP cohort (one of which was due to safety reasons). Identifying these patients early may improve their management and compliance to further alternative treatment.

Our findings are consistent with those of other recent reports. The effects of AAP and ENZ on PROs have been compared directly in a phase II, randomised, crossover trial (NCT02125357) designed to assess treatment sequence in chemotherapy-naïve patients with mCRPC. Findings showed that after 12 weeks of treatment, median QoL score (total FACT-P score) improved with AAP, whereas there was no change with ENZ; for the physical well-being subscale, there was a higher rate of significant worsening with ENZ versus AAP.¹⁰ More patients receiving ENZ experienced worsening of depression symptoms per Patient Health Questionnaire-9, compared with those taking AAP, and a trend towards worsening in cognitive impairment, as assessed with Montreal Cognitive Association testing, was observed with ENZ compared with AAP.^{10,11} Further follow-up analyses are required to confirm these findings.

The effects of AAP and ENZ on self-reported symptom burden were found to be comparable in a single-centre study in 189 men with chemotherapy-naïve mCRPC in routine clinical practice.¹² Fatigue was considered the most distressing symptom in both groups at baseline and following treatment. Results were similar for AAP-treated and ENZ-treated patients in terms of significant differences from baseline in ESAS score and in the proportion of patients with clinically meaningful symptom improvement or worsening.¹² Of note, the ESAS is designed to assess pain, activity, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath but does not include an evaluation of cognitive function.¹⁹

Deterioration of PROs may be experienced soon after treatment initiation, as demonstrated in the AQUARIUS study, with cognitive deterioration and fatigue progression occurring within the first 3 months. These effects are likely to affect a patient's QoL significantly but may also reduce adherence to medication and therefore result

in suboptimal clinical responses. Several studies suggest that PROs significantly impact clinical outcomes, such as disease progression and mortality. For example, an analysis of data from COU-AA-302 showed that worsening PROs (pain, physical well-being, functional well-being and prostate cancer-specific signs and symptoms) were associated with a greater risk of radiographic progression compared with stable or improved PRO scores.²⁰ In an analysis of data from the PREVAIL and AFFIRM studies—which were conducted in patients treated with ENZ prior to or post chemotherapy, respectively—overall survival was associated with multiple HRQoL measures, including FACT-P total score.²¹ Furthermore, an analysis of three phase III studies in men with CRPC found a significant association between pain interference scores and risk of death.²² These findings highlight the need to consider PROs when managing mCRPC in order to achieve optimal treatment outcomes and ensure that the balance between benefit and harm are acceptable to patients.²³ Results from a discrete choice experiment showed that men with mCRPC take a wide range of factors into consideration when making decisions regarding their treatment.²⁴ They had a strong preference for treatments that could offer better control of bone pain and also valued those that could delay the need for chemotherapy, as well as those that had fewer adverse events such as cognition and memory loss and extreme tiredness.²⁴ Treatment should be tailored to patients based on their individual needs; for example, a treatment associated with fatigue may be something to avoid in those who are still employed or partake in active exercise.

Phase III trials have demonstrated that AAP and ENZ lead to delayed radiographic progression and increased survival compared with prednisone or placebo, respectively.^{7,8} Although extending life expectancy is considered the gold standard for treatment, HRQoL is increasingly being considered an important endpoint.²⁵ AAP-treated and ENZ-treated patients showed more favourable PROs than controls in clinical trials^{7,8}; however, the effect of AAP compared with ENZ in terms of PROs, and cognition in particular, has not been extensively studied. Furthermore, data comparing the effects of these agents on PROs in the real-world setting are limited. Having dedicated PRO data from a study such as AQUARiUS, with ‘real life’ patients, may aid clinicians to treat patients more effectively. PRO data from AQUARiUS may be complemented by those from the Cog-Pro study (NCT02907372), which is designed to prospectively assess the effect of ENZ and AAP on cognitive function in patients with mCRPC and evaluate the effect of cognitive impairments on QoL and adherence.²⁶

One of the major strengths of the AQUARiUS study is its real-world setting. Patients are not limited by strict inclusion and exclusion criteria or treatment regimen, as in a clinical trial; instead, an unselected population is treated as per routine clinical practice. Other strengths of the study include the comprehensive assessment of PROs, which capture patient perspectives on a range of aspects

likely to significantly affect activities of daily living, and the monthly collection of PRO data, starting from within the first month after treatment initiation, allowing very early signals to be identified. A further strength is the use of primary rather than secondary data for all baseline characteristics.

An important limitation of the AQUARiUS study is the lack of randomisation. To help address this issue, a multivariate modelling approach correcting for all relevant baseline characteristics was used to minimise bias. Limitations related to this initial analysis include the small sample size (n=105) and the fact that not all PRO scales were completed by all patients at each time-point. As expected, the proportion of patients who completed PROs decreased over time due to discontinuations and because PRO data were collected at routine clinical visits that did not take place at strict monthly intervals for all patients. Therefore, more mature data from a larger population of patients, which will be available for future analyses of AQUARiUS, are needed to confirm these early findings.

In conclusion, initial results from AQUARiUS indicate significant benefits with AAP versus ENZ for cognitive outcome measures, with differences observed during the first month after treatment initiation and persisting over 3 months. AAP also had a favourable effect on fatigue, with differences showing at month 3 across all fatigue scales evaluated. No significant differences between treatment groups were observed for pain outcomes, as assessed with the BPI-SF, at any time-point. These findings are based on initial data and await confirmation from future analyses, which will include a greater number of patients with a longer follow-up period. This study provides novel and valuable data regarding PRO outcomes with AAP versus ENZ in the real-world setting. Such data are crucial in informing clinical decision making, helping to ensure that patients with mCRPC receive the most appropriate treatment based on their own experiences.

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Competing interests AT-V reports grants and non-financial support from Janssen, personal fees from Astellas, grants from Janssen and Sanofi, grants and personal fees from Ipsen, Roche, BMS and Pfizer. GP serves on the advisory board and has received honoraria from Astellas and Janssen. AB has received personal fees from Janssen, Sanofi Aventis, Astellas and Roche. EP reports personal fees from Astellas, BMS and Clovis Oncology and non-financial support from Astellas, Clovis Oncology and Janssen. RT reports personal fees from Janssen-Cilag Astellas. LA, SVS and GeP are employees of Janssen Pharmaceutica N.V. and hold stock in Johnson & Johnson. ML is an employee of PAREXEL International Czech Republic s.r.o. on behalf of Janssen Pharmaceutica N.V., Beerse, Belgium. AR has received personal fees from Janssen.

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