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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

Daniel J. Khalaf[a], *Katherine Sunderland*[b], *Bernhard J. Eigl*[a], *Christian K. Kollmannsberger*[a], *Nikita Ivanov*[a], *Daygen L. Finch*[c], *Conrad Oja*[d], *Joanna Vergidis*[e], *Muhammad Zulfiqar*[f], *Martin E. Gleave*[g], *Kim N. Chi*[a,g,*]

[a] *Department of Medical Oncology, BC Cancer Vancouver Centre, Vancouver, BC, Canada;* [b] *Department of Biostatistics, BC Cancer Vancouver Centre, Vancouver, BC, Canada;* [c] *Department of Medical Oncology, BC Cancer Southern Interior, Kelowna, BC, Canada;* [d] *Department of Medical Oncology, BC Cancer Fraser Valley, Surrey, BC, Canada;* [e] *Department of Medical Oncology, BC Cancer Island Centre, Victoria, BC, Canada;* [f] *Department of Medical Oncology, BC Cancer Abbotsford Centre, Abbotsford, BC, Canada;* [g] *Department of Urological Sciences, The Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada*

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Abstract

Background: Abiraterone and enzalutamide are associated with side effects that may impair health-related quality of life (HRQoL).
Objective: To assess patient-reported HRQoL, depression symptoms, and cognitive function for abiraterone versus enzalutamide.
Design, setting, and participants: We randomized 202 patients in a phase II study of abiraterone versus enzalutamide for first-line treatment of metastatic castration-resistant prostate cancer (ClinicalTrials.gov: NCT02125357).
Intervention: Patients completed Functional Assessment of Cancer Therapy—Prostate (FACT-P) and Patient Health Questionnaire-9 (PHQ-9) questionnaires, and Montreal Cognitive Assessment (MoCA) cognitive assessments at baseline and on treatment.
Outcome measurements and statistical analysis: To compare the change in FACT-P scores over time between treatment arms, we used a mixed model for repeated measures (MMRM). For FACT-P domains where there was an interaction between the treatment arm and age, we constructed separate models for patients aged <75 and ≥ 75 yr. We compared the proportion of patients with clinically meaningful change from baseline for FACT-P, and the proportion of patients with an abnormal score and median change from baseline for PHQ-9 and MoCA using Fisher's exact test and Mann-Whitney *U* test.
Results and limitations: In the MMRM analysis, there was a positive test for interaction in the treatment arm by age for total FACT-P ($p = 0.048$). FACT-P change from baseline over time was better for abiraterone than for enzalutamide in the ≥ 75-yr model ($p = 0.003$), with no difference in the <75-yr model ($p > 0.9$). A higher proportion of patients experienced clinically meaningful worsening with enzalutamide for the physi-

* Corresponding author. Department of Medical Oncology, BC Cancer Vancouver Centre, 600 West 10th Avenue, Vancouver, BC, Canada, V5Z 4E6. Tel. +1 604 877 6000; Fax: +1 604 877 0585.
E-mail address: kchi@bccancer.bc.ca (K.N. Chi).

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cal and functional well-being domains (37% vs 21%, $p = 0.013$; 39% vs 23%, $p = 0.015$). The distribution of change in PHQ-9 scores from baseline favored abiraterone at weeks 4, 8, and 12. These analyses were not prespecified, and results should be considered to be hypothesis generating.
Conclusions: Patient-reported outcomes favored abiraterone compared with enzalutamide with differences in FACT-P HRQoL and PHQ-9 depression scores. Differences in the total FACT-P scores were seen only in the elderly patient subgroup.
Patient summary: In this report, we examined the change in patient-reported quality-of-life scores from the start of treatment over time for patients treated with abiraterone versus enzalutamide for metastatic castration-resistant prostate cancer. We found that elderly patients treated with abiraterone had better quality of life over time, with no difference between treatments for the younger subgroup of patients.

1. Introduction

Patients with metastatic castration-resistant prostate cancer (mCRPC) may experience an array of distressing symptoms, including pain due to bone metastasis, constitutional symptoms, and urinary dysfunction [1]. The disease incidence is highest in men over the age of 70 yr and the median survival from diagnosis is <3 yr [2–4]. Improving well-being and maintaining adequate quality of life are crucial treatment goals in this patient population.

Abiraterone acetate (henceforth abiraterone) and enzalutamide are both androgen receptor (AR) pathway–targeting agents. Both agents have been shown to improve outcomes considerably in the treatment of mCRPC and are widely used first-line treatments [3,4]. Furthermore, treatment efficacy has translated into better health-related quality-of-life (HRQoL) outcomes: across five randomized controlled trials, both abiraterone and enzalutamide improved time to HRQoL deterioration and resulted in higher rates of improvement in most quality-of-life domains [5–9]. Longitudinal analysis of the HRQoL data using mixed models for repeat measures (MMRMs) showed durable and clinically significant benefits with abiraterone and enzalutamide [9–11].

The toxicity profile for abiraterone and enzalutamide is generally safe with low rates of grade 3 and 4 treatment-related adverse events [3,4]. Although there is overlapping toxicity between both treatments, a higher incidence of increased liver function tests, peripheral edema, and cardiac toxicity is associated with abiraterone [4,12], and a higher incidence of fatigue as well as memory impairment and seizures is associated with enzalutamide [3,12]. Moreover, the frequency of toxicity has been shown to be higher in patients of ≥75 yr of age for both treatments [13,14]. The impact of these toxicities on HRQoL is poorly understood.

We conducted a phase II randomized trial of abiraterone plus prednisone versus enzalutamide with a secondary objective of assessing patient-reported HRQoL, depression, and cognitive function. Both treatments showed similar efficacy with a time to prostate-specific antigen (PSA), radiographic, or clinical progression, which we have previously reported [15]. Herein, we report the results from patient-completed Functional Assessment of Cancer Therapy—Prostate (FACT-P) quality-of-life questionnaires, Patient Health Questionnaire-9 (PHQ-9) depression symptom questionnaires, and Montreal Cognitive Assessment (MoCA) tests.

2. Patients and methods

2.1. Trial design

Details of trial design and patient inclusion criteria have previously been reported [15]. In brief, this was a multicenter, randomized phase II trial of abiraterone 1000 mg and prednisone 5 mg given daily versus enzalutamide 160 mg daily for first-line treatment of mCRPC with cross-over at PSA progression. Evaluation of HRQoL, depression, and cognitive function was a secondary objective. Institutional ethics board approval was obtained and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

2.2. Patients

Key eligibility criteria included requirements for histological confirmation of prostatic adenocarcinoma, demonstrable metastatic disease on computed tomography scan or bone scan, as well as confirmed PSA or radiographic progression with a castrate level of testosterone. Patients were required to have adequate organ function, Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and absence of contraindication to abiraterone or enzalutamide. Visceral metastatic disease and presence of pain requiring opioid analgesia were allowed.

2.3. HRQoL, mood symptom, and cognitive assessments

The FACT-P is a validated patient self-administered questionnaire comprising 39 questions, each worth a maximum of 4 points [16]. It consists of four quality-of-life domains (physical [PWB], functional [FWB], emotional [EWB], and social [SWB] well-being), which comprise the Functional Assessment of Cancer Therapy—General (FACT-G) score, in addition to a 12-item prostate cancer score (PCS) that includes four pain-related questions (PCS pain score). For all questions, higher scores indicate better HRQoL. The PHQ-9 is a self-administered questionnaire consisting of the nine diagnostic criteria for depressive episode from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV); each criterion was scored from 0 to 3, with a higher score indicating worse symptoms. It has been validated and shown to perform well in patients with a diagnosis of cancer [17,18]. The Montreal Cognitive assessment (MoCA) is a validated test designed to screen for mild cognitive impairment and includes questions evaluating the domains of attention, short-term memory, executive function, working memory, abstraction, and language [19].

Both FACT-P and PHQ-9 questionnaires were patient self-administered at baseline, every 4 wk while on treatment, as well as at the time of

discontinuation of first-line therapy. MoCA tests were performed by a trained research nurse at baseline, at 12 wk of treatment, and at treatment discontinuation. We included questionnaires completed before January 1, 2017, and up until week 24 of treatment after which <50% of patients in both arms were assessable.

2.4. Statistical analysis

We used a mixed-effect model for repeated measures (MMRM) for the longitudinal analysis of FACT-P change from baseline score and to determine whether there was a difference according to the treatment arm. The MMRM has been shown to provide accurate modeling of treatment outcome in the presence of missing data under the assumption that data are missing at random (MAR) [10]. For each quality-of-life domain, a model, hereby known as the all-patients model, was constructed, controlling for baseline score, treatment assignment, age group <75 versus ≥75 yr, treatment week, baseline ECOG score (0–1 vs 2), and treatment by age group interaction. An initial analysis of our data showed improved FACT-P scores for abiraterone versus enzalutamide at week 12 [20], and further analysis suggested that the difference between arms was most pronounced for elderly patients with a chosen cut-point of ≥75 yr, which was the median age of the study population (unpublished data). Therefore, where a significant treatment by age group interaction was observed in the all-patients model, separate MMRMs were constructed for each age group (<75 and ≥75 yr), controlling for baseline score, treatment assignment, treatment week, and baseline ECOG score. Patients with an assessable baseline questionnaire and at least one subsequent assessable questionnaire were considered for this analysis. In order to investigate the assumption that data are MAR, we compared the treatment arms with respect to the number of nonmissing responses over time for each FACT-P measure using the log-rank test, where nonmissing response count was treated as the time to event for each patient.

The minimal clinically important difference (MCID) for the FACT-P score and individual HRQoL domains have previously been determined (Supplementary Table 1) [21]. For each FACT-P domain, we compared the proportion of patients with a clinically meaningful change from baseline in at least one questionnaire, based on the highest MCID values determined previously, using Fisher's exact test. With 101 patients per arm, our study would have 84% power to detect a 20% difference between the treatment groups in the proportion of patients with a clinically meaningful decrease in FACT-P score, under the assumption that the treatment groups have 20% and 40% clinically meaningful decreases, respectively, in the population.

For the PHQ-9 and MoCA tests, we compared the proportion of patients with a positive test meeting the previously determined diagnostic threshold (≥10 and <26, respectively) at each cycle. We compared the distribution of score change from baseline for the MoCA and PHQ-9 using the Wilcoxon Mann-Whitney U test. For all comparisons, we used a significance α level of $p \leq 0.05$ without correction for multiple testing, as our statistical analyses were not prespecified and are considered exploratory.

3. Results

3.1. Baseline data

A total of 101 patients were randomized to each arm. Baseline characteristics were well balanced between study arms except for age (Table 1). The overall FACT-P and PHQ-9 questionnaire response rates were above 90% (Supplementary Table 2). One center did not conduct routine study visits at week 20, and thus completion rates were lower at that time point. The median baseline FACT-P and MoCA scores were similar in both arms (Table 1). The median baseline PHQ-9 score was higher in the enzalutamide arm than in the abiraterone arm (Table 1); however, the proportion of patients with a score of ≥10 at baseline was similar in both arms.

Table 1 – Baseline characteristics

Characteristic	Abiraterone + Prednisone	Enzalutamide
Median age (IQR)	72.9 (67.4–79.05)	77.6 (69.1–83.4)
<75 yr, *n* (%)	58 (57)	42 (42)
≥75 yr, *n* (%)	43 (43)	59 (58)
ECOG PS, *n* (%)		
0–1	89 (88)	79 (78)
2	12 (12)	22 (22)
Median PSA, μg/l (IQR)	35.0 (8.5–106.6)	37.0 (13.3–105.6)
Median hemoglobin, g/l (IQR)	130 (122–137)	130 (119–138)
Alkaline phosphatase > ULN, *n* (%)	34 (34)	35 (35)
LDH > ULN, *n* (%)	17 (17)	22 (22)
Site of metastases, *n* (%)		
Lymph node	38 (38)	44 (44)
Bone	86 (85)	83 (82)
Visceral (lung or liver)	12 (12)	15 (15)
Baseline score, median (IQR)		
FACT-P	116 (105.67–130.09)	114 (100.0–128.0)
PWB	25 (22–26)	24 (21–26)
FWB	21 (16–25)	20 (15–24)
SWB	22 (20–27)	23 (19–26.83)
EWB	18 (16–21)	19 (16–21)
PCS	32 (28–38)	33 (27–37)
Pain score	11 (7–14)	10 (7–13)
PHQ-9	2 (1–5)	4 (1–7)
MoCA	25 (23–27)	25 (23–27)

ECOG = Eastern Cooperative Oncology Group; EWB = emotional well-being; FACT-P = Functional Assessment of Cancer Therapy—Prostate; FWB = functional well-being; IQR = interquartile range; LDH = lactate dehydrogenase; MoCA = Montreal Cognitive Assessment; PCS = prostate cancer score; PHQ-9 = Patient Health Questionnaire-9; PSA = prostate-specific antigen; PWB = physical well-being; SWB = social well-being; ULN = upper limit of normal.

3.2. Mixed model for repeated measures

The test for interaction between age group (≥75 vs <75 yr) and treatment arm for change from baseline was significant for total FACT-P ($p = 0.048$), Trials Outcome Index (TOI; $p = 0.039$), and PCS ($p = 0.009$), and near significant for EWB ($p = 0.054$).

Owing to the interaction, age groups were modeled separately for total FACT-P, TOI, PCS, and EWB (Fig. 1 and Table 2). For total FACT-P, adjusted mean change from baseline over time was superior in the abiraterone arm in the ≥75-yr model ($p = 0.003$), with no difference between arms in the <75-yr model ($p > 0.9$). Similar results were observed for the TOI and PCS where change over time was superior for abiraterone only for patients aged ≥75 yr, while for EWB, there was no difference between the treatment arms for patients in either group (Fig. 1 and Table 2). Scatter plots of change from baseline FACT-P scores by age for both arms are shown in Supplementary Figure 1. There is a distinct divergence in score change between both arms that occurs between 70 and 75 yr for total FACT-P and most FACT-P domains that increased with age.

For all FACT-P domains where there was no interaction between age group and treatment arm, MMRM results for the all-patients model are shown in Table 2 and Supplementary Figure 2. The adjusted mean change from baseline over time was superior in the abiraterone arm for PWB and PCS pain score, while no significant differences were observed between the treatment arms for FWB or SWB or FACT-G.

Results of the MAR assumption investigation supported the conclusion that the patterns of intermittent missing data and dropouts were random across the treatment arms. To further exclude the possibility of an effect of differential patient dropout between treatment arms on the results from our model, we performed the same analysis truncated at 12 wk, given that data are more complete during that time period. We found the pattern of results to be consistent between the truncated and full models with similar mean estimates and standard errors for the FACT-P domains at each time point.

3.3. Analysis of MCID change from baseline

The proportion of patients with a clinically meaningful change from baseline for at least one postbaseline FACT-P assessment is shown in Supplementary Table 3. A high proportion of patients had clinically significant improvement for most HRQoL domains, and this was similar between both arms. However, the proportion of patients with clinically significant worsening was higher in the enzalutamide arm for the PWB domain (37% vs 21%, 95% confidence interval [CI] for difference: [3.6–28.1%], $p = 0.013$) and the FWB domain (39% vs 23%, 95% CI for difference: [3.3–28.4%], $p = 0.015$; Fig. 2).

The proportion of patients with an abnormal PHQ-9 score was significantly higher in the enzalutamide arm at weeks 4–16 (Supplementary Figure 3). The distribution of PHQ-9 score change from baseline differed significantly between study arms for weeks 4–12, with a skew toward the right (higherscores) in the enzalutamide arm (Fig. 3). The proportion of patients with a MoCA score of <26 was similar between arms at week 12 (47% vs 54%, 95% CI for difference: [−8.6% to 23.8%], $p = 0.4$; Supplementary Figure 3), and the distribution of score change from baseline was also similar ($p = 0.11$; data not shown).

4. Discussion

Abiraterone and enzalutamide are both standard first-line treatment options for mCRPC with similar efficacy but different side-effect profiles. Our study was the first to perform a randomized head-to-head comparison of abiraterone and enzalutamide and included assessments of patient-reported HRQoL, depression, and cognitive function. The importance of systematically assessing patient-reported outcomes (PROs) in clinical trials is well recognized; the yield of toxicity information is increased compared with the assessment of clinician-reported adverse events alone, and the assessment of the underlying health and functional status of patients is improved [22,23]. In our study, questionnaires were completed at every visit and completion rates were high, allowing for longitudinal analysis of PROs and correction for confounding variables. Owing to the pragmatic inclusion criteria, the study cohort was representative of the real-world mCRPC patient population, which is elderly and generally frail relative to patients participating in randomized phase III trials [24].

We showed that abiraterone was associated with superior HRQoL over time compared with enzalutamide. Importantly, there was a significant interaction with age, and the difference in FACT-P HRQoL between arms was present only in the elderly subgroup, increasing with age. The difference between arms was seen across many HRQoL domains and was of clinically significant magnitude for patients aged ≥75 yr. The difference between arms was also consistent throughout the studied timeframe from the start of therapy to week 24, which is important given that both agents are often taken for protracted periods of time. This may prove to be even more important as AR-targeting agents move earlier in the disease course to the castration-sensitive/hormone-naïve and nonmetastatic castration-resistant settings [25,26].

The adverse events that we reported were consistent with those reported in previous studies; however, the proportion of patients with grade ≥2 fatigue was higher with enzalutamide (39% vs 20%). In addition, 12% of patients in the enzalutamide arm required a dose reduction due to fatigue [20]. In a meta-analysis of individual patient data from phase III trials of abiraterone and enzalutamide, only enzalutamide was associated with increased fatigue [12]. It is possible that the higher incidence of fatigue with enzalutamide may have accounted for the inferior HRQoL outcomes, particularly with regard to the PWB, FWB, and PHQ-9 scores. Indeed, cancer-related and drug-induced fatigue may lead to considerable impairment in daily functioning and HRQoL, as well as increased depression and anxiety [27,28]. In addition, the elderly patient population is

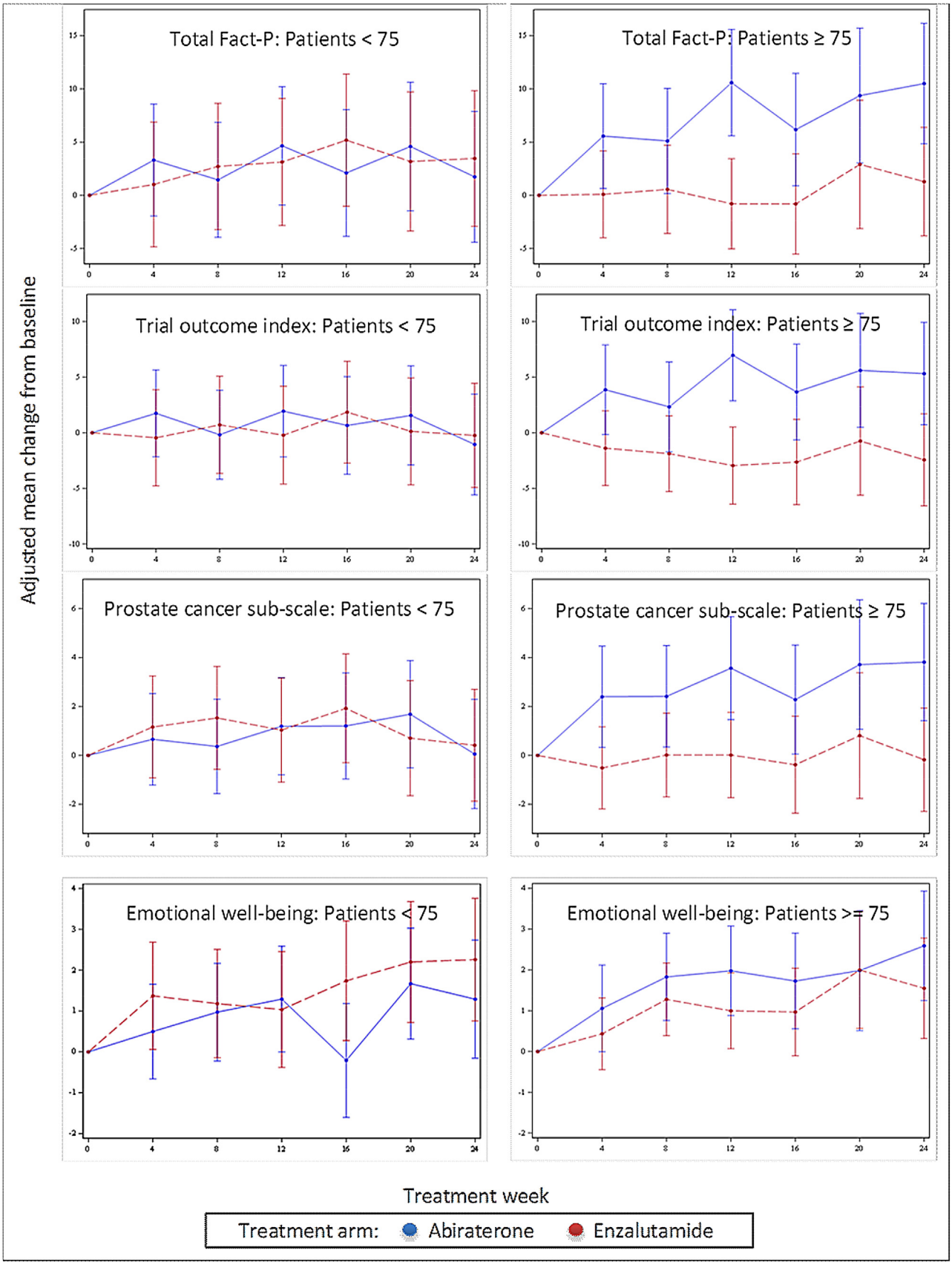

Fig. 1 – Mixed model for repeated measures analysis by age group (<75 vs ≥75 yr) for FACT-P domains and subscales for which there was an interaction between treatment arm and age. FACT-P = Functional Assessment of Cancer Therapy—prostate.

Table 2 – Results for the mixed model for repeated measures

	AMS Abiraterone	AMS Enzalutamide	Difference in AMS	95% Confidence interval	*p* value
Total FACT-P					
<75 yr	2.97	3.11	−0.14	(−5.27 to 4.98)	>0.9
≥75 yr	7.89	0.54	7.35	(2.59–12.11)	0.003
TOI					
<75 yr	0.78	0.29	0.48	(−3.25 to 4.21)	0.80
≥75 yr	4.62	−2.01	6.63	(2.73–10.53)	0.001
PCS					
<75 yr	0.86	1.13	−0.27	(−2.03 to 1.50)	0.8
≥75 yr	3.03	−0.04	3.07	(1.12–5.01)	0.002
EWB					
<75 yr	0.92	1.63	0.71	(−1.87 to 0.44)	0.22
≥75 yr	1.86	1.20	0.66	(−0.20 to 1.51)	0.13
PWB					
All patients	0.29	−0.97	1.25	(0.38–2.14)	0.007
PCS pain					
All patients	1.26	0.33	0.93	(0.18–0.68)	0.017
FWB					
All patients	0.32	−0.41	0.73	(−0.33 to 1.79)	0.2
SWB					
All patients	1.19	1.04	0.15	(−0.81 to 1.11)	0.8
FACT-G					
All patients	3.14	0.84	2.31	(−0.23 to 4.85)	0.089

AMS = adjusted mean score (reference is enzalutamide); EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy—General; FACT-P = Functional Assessment of Cancer Therapy—Prostate; FWB = functional well-being; PCS = prostate cancer score; PWB = physical well-being; SWB = social well-being; TOI = Trials Outcome Index.
Separate models for patients aged <75 and ≥75 yr were constructed for domains where a significant age by treatment arm interaction was detected. For all other domains, all patients were included in a single model.

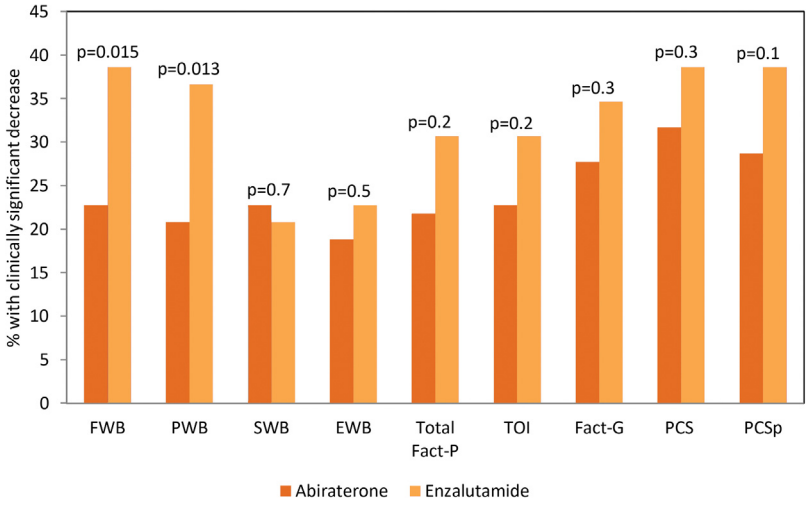

Fig. 2 – Percentage of patients with a clinically significant decrease in one or more on-treatment questionnaires compared with baseline for FACT-P and FACT-P domains and subscales. EWB = emotional well-being; FACT-G: Functional Assessment of Cancer Therapy—General; FACT-P: Functional Assessment of Cancer Therapy—Prostate; FWB = functional well-being; PCS = prostate cancer score; PCSp: prostate cancer pain score; PWB = physical well-being; SWB = social well-being; TOI = Trials Outcome Index.

more vulnerable to drug-induced fatigue, as greater pharmacodynamic sensitivity and increased blood-brain barrier permeability with advancing age confer an increased risk of central nervous system toxicity [29].

Prednisone as a single agent is known to improve pain and may improve HRQoL in mCRPC [30]. It could be hypothesized that prednisone used in combination with abiraterone might have helped improve patient HRQoL, although it is currently unknown to what degree prednisone increases symptomatic benefit when used in combination with abiraterone. Abiraterone must be administered with prednisone to substitute the decreased physiological cortisol production and to counteract the effect of increased mineralocorticoid activity.

The limitations of our study included the relatively small number of patients, which resulted in large confidence intervals at individual time points for FACT-P assessments, as well as the open-label design. Our findings should be

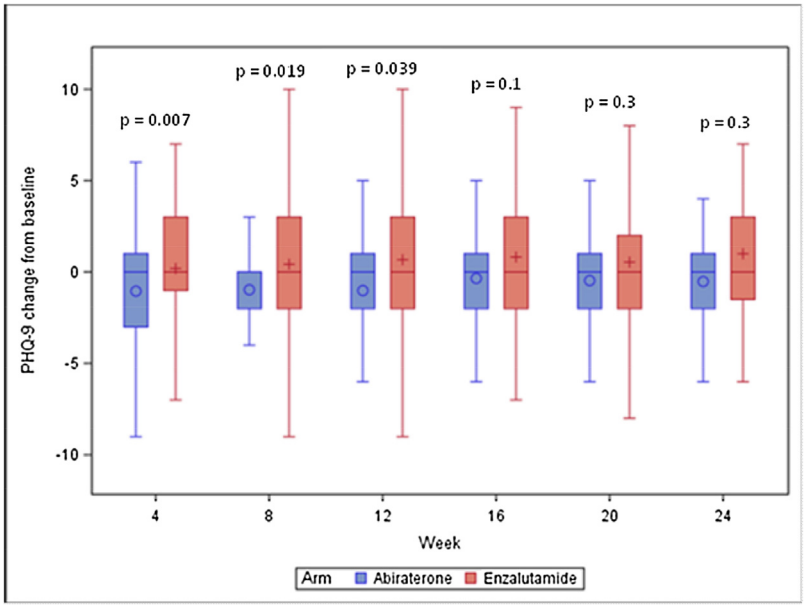

Fig. 3 – Boxplots of PHQ-9 change from baseline. PHQ-9 = Patient Health Questionnaire-9.

considered exploratory as our statistical analyses were not prespecified and we did not correct for multiple comparisons. Our assessment of depression symptoms was likely confounded by increased rates of fatigue and decreased HRQoL in the enzalutamide arm, and no preplanned formal psychiatric assessments were mandated to validate PHQ-9 results. In addition, the MoCA cognitive assessment has not been validated in this clinical setting, and a more rigorous neuropsychiatric evaluation would be necessary to fully characterize and quantify any cognitive effects observed with therapy.

5. Conclusions

Our study demonstrated improved PROs in patients with mCRPC treated with first-line abiraterone compared with those treated with enzalutamide, based on FACT-P HRQoL scores and PHQ-9 depression scores. Differences between arms in the total FACT-P score were present only in the elderly subgroup. There was minimal change in MoCA cognitive test scores, with no difference between both arms. Additional studies are required to further define the relationship between increasing age and HRQoL in men receiving AR-targeting agents for mCRPC.

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Author contributions: Kim N. Chi 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.

Study concept and design: Chi, Eigl.
Acquisition of data: Khalaf, Chi, Ivanov, Kollmannsberger, Eigl, Gleave, Finch, Oja, Vergidis, Zulfiqar.
Analysis and interpretation of data: Khalaf, Sunderland, Chi.
Drafting of the manuscript: Khalaf, Sunderland, Chi.
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Appendix A. Supplementary data

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