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Prostate Cancer

Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised, Placebo-controlled, Phase 3 Study

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Abstract

Background: In the ARCHES study in metastatic hormone-sensitive prostate cancer (mHSPC), enzalutamide plus androgen deprivation therapy (ADT) improved radiographic progression-free survival (rPFS) versus ADT alone.
Objective: To evaluate patient-reported outcomes (PROs) to week 73.
Design, setting, and participants: ARCHES (NCT02677896) was a randomised, double-blind, placebo-controlled, phase 3 study in mHSPC patients.
Intervention: Enzalutamide (160 mg/day) plus ADT or placebo plus ADT.
Outcome measurements and statistical analysis: PROs were assessed at baseline, week 13, and every 12 wk until disease progression using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (QLQ-PR25), Functional Assessment of Cancer Therapy-Prostate (FACT-P), Brief Pain Inventory Short Form, and EuroQoL 5-Dimensions, 5-Levels (EQ-5D-5 L) instruments. Endpoints included time to first (TTFD) and first confirmed (TTFCD) clinically meaningful deterioration (using predefined questionnaire thresholds) in health-related quality of life (HRQoL) and pain.
Results and limitations: A total of 1150 patients received ADT plus enzalutamide ($n = 574$) or placebo ($n = 576$). Baseline PRO scores indicated high HRQoL and low pain, which was generally maintained in both groups. There were no statistically significant (nominal $p > 0.05$) between-group differences that occurred in both TTFD and TTFCD together for QLQ-PR25 and FACT-P scores. Enzalutamide significantly delayed TTFD in worst pain (by ~3 mo; nominal $p = 0.032$), pain severity (nominal $p = 0.021$), and EQ-5D-5 L visual analogue scale score (nominal $p = 0.0070$) versus placebo (not significant for confirmed deterioration for pain outcomes). Enzalutamide delays deterioration in several HRQoL subscales and pain severity in high-volume disease.

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Conclusions: Enzalutamide plus ADT enables men with mHSPC to maintain high-functioning HRQoL and low symptom burden.
Patient summary: This study examined the effect on health-related quality of life and pain of adding enzalutamide or placebo to androgen deprivation therapy for patients with metastatic hormone-sensitive prostate cancer. Addition of enzalutamide allowed patients to maintain their health-related quality of life.

1. Introduction

Enzalutamide is an oral androgen receptor inhibitor approved in Europe and the USA for the treatment of metastatic/nonmetastatic castration-resistant prostate cancer (CRPC) [1,2]. Enzalutamide improves overall survival (OS) in metastatic CRPC and metastasis-free survival in nonmetastatic CRPC, and improves health-related quality of life (HRQoL) [3–5]. In phase 3 trials among men with metastatic hormone-sensitive prostate cancer (mHSPC; also sometimes described as metastatic castration-sensitive prostate cancer) receiving androgen deprivation therapy (ADT), enzalutamide significantly prolonged OS in the ENZAMET trial [6] and radiographic progression-free survival (rPFS) in the ARCHES trial [7]. Since treatment may continue for years, it is critical to examine the impact of more intensive therapy on HRQoL, which may be impaired by disease burden and treatment [8]. Here we report patient-reported outcomes (PROs) from ARCHES.

2. Patients and methods

2.1. Study design and participants

ARCHES (NCT02677896) was a multinational, phase 3, randomised, double-blind, placebo-controlled study in 1150 patients with mHSPC [7]. Eligible men (≥18 yr) had histologically or cytologically confirmed adenocarcinoma of the prostate and metastatic disease.

Eligible patients were randomised centrally (1:1) to ADT (luteinising hormone–releasing hormone agonist/previous bilateral orchiectomy) plus enzalutamide 160 mg daily or matching placebo (each as four capsules orally) until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Patients were allowed up to six cycles of prior docetaxel, ≤3 mo of ADT (≤6 mo if they had received prior docetaxel), or prior neoadjuvant/adjuvant ADT for <39 mo (>9 mo before randomisation). Prespecified stratification factors were disease volume (high vs low; Table 1) and prior docetaxel therapy for prostate cancer (0, 1–5, or 6 cycles).

All patients provided written informed consent compliant with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice, and local regulations. Independent ethics committees or institutional review boards reviewed the ethical, scientific, and medical appropriateness before study commencement.

2.2. Procedures

PROs were assessed at baseline, week 13, and every 12 wk until disease progression. PRO analyses are reported up to week 73 to minimise the impact of missing data given that the median rPFS for placebo plus ADT was 20 mo. After treatment discontinuation, patients underwent long-term follow-up, including monitoring for survival, new antineoplastic therapies for prostate cancer, and symptomatic skeletal events. Patients were scanned every 12 wk and PROs were measured (for those continuing with radiological assessments, if seen in clinic) until confirmed radiographic progression (independent central review) or predefined radiographic progression events (≥262) were reached.

2.3. Outcomes

PRO instruments used (Supplementary Table 1) were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) [9]; Functional Assessment of Cancer Therapy-Prostate (FACT-P) [10]; Brief Pain Inventory Short Form (BPI-SF) [11]; and EuroQoL 5-Dimensions, 5-Levels (EQ-5D-5 L) [12].

The primary endpoint in ARCHES was rPFS. Prespecified secondary PRO endpoints reported here are time to first, or first confirmed, clinically meaningful symptom worsening/HRQoL deterioration (Table 1). Generic terms “time to first clinically meaningful deterioration” (TTFD) and “time to first confirmed clinically meaningful deterioration” (TTFCD) were used for symptom worsening/HRQoL deterioration, with their specific meaning depending on the domain analysed; TTFD in modified urinary symptoms was a key secondary endpoint. Clinically meaningful within-patient change thresholds for FACT-P, BPI-SF, and EQ-5D-5 L were based on previously established values [11,13–17]. In the absence of established thresholds, QLQ-PR25 values were derived using distribution-based and anchor-based analyses. Death was not included in the definition of clinically meaningful deterioration; those who died without deterioration were censored at the last completed assessment. Sensitivity analyses were conducted, including death (from any cause) in the definition. Although no fatigue-specific questionnaire was included, data for FACT-P items assessing lack of energy (GP1) and forced to spend time in bed (GP7) were collected and are presented as exploratory analyses.

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Table 1 – Definitions of study endpoints, analyses, and variables.

Endpoint/analysis/ variable	Definition
High-volume disease	High-volume disease consisted of visceral metastases or ≥4 bone lesions (≥1 outside the vertebral column and pelvic bone)
Time to first clinically meaningful deterioration (TTFD)	Time from randomisation to first deterioration in PRO score ≥1 threshold unit that connotes clinically meaningful change to patients vs baseline. Patients with no clinically meaningful deterioration before the end of follow-up, radiographic progression, or death (if not progressed before death) were censored at the last available PRO assessment (date of last non-missing value).
Time to first confirmed clinically meaningful deterioration (TTFCD)	Time from randomisation to first deterioration in PRO score ≥1 threshold unit that connotes clinically meaningful change to patients vs baseline that is confirmed at the next consecutive visit or followed by drop out, resulting in monotone missing data. Patients with no confirmed clinically meaningful deterioration before the end of follow-up, radiographic progression, or death (if not progressed before death) were censored at the last available PRO assessment (date of last non-missing value).
Kaplan-Meier product limit method to estimate distributions of TTFD and TTFCD	TTFD and TTFCD were assessed using Kaplan-Meier estimates. A stratified log-rank test was used to compare these time-to-event variables between treatment groups, adjusting for randomisation stratification factors: volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (yes vs no).
Hazard ratios	Hazard ratios (enzalutamide + ADT/placebo + ADT) and 95% confidence intervals were determined using a stratified Cox proportional-hazards model with treatment as the only covariate and the same randomisation factors (volume of disease score and prior docetaxel therapy for prostate cancer) as strata.
Intent-to-treat population	All patients randomly assigned to study treatment
Observed data	Data collected at each time point without carrying forward previous values
Study size calculation	Study size calculation, based on estimates related to the primary endpoint, was not specifically powered for secondary PRO endpoints; 631 deterioration events would provide 80% power to detect a target hazard ratio of 0.80 based on a two-sided log-rank test and a significance level of 0.05.
Mixed model for repeated measures (MMRM) analyses	An MMRM analysis was used to estimate longitudinal changes in PRO scores from baseline at each scheduled visit.
	MMRM analyses use all available data and assume missing observations are missing at random.
	The dependent variable was change in PRO score from baseline, and the fixed effects were treatment, study visit, and randomisation factors (disease volume and prior docetaxel therapy for prostate cancer) as categorical parameters, baseline PRO score as a continuous parameter, and the interactions between visit and treatment and between baseline PRO score and visit. We used an unstructured variance-covariance matrix to model the covariance structure among each participant's repeated measures. We treated time as a categorical variable so that no restriction is imposed on the trajectory of the means over time. Thus, we estimated and tested the treatment difference in terms of mean change from baseline to a given time point using this MMRM model. The prespecified MMRM analysis was limited to the first 73 weeks after baseline because of the small sample size in both groups beyond this point (<10% of subjects with available data beyond week 73).
Baseline covariates	PRO score, disease volume (low vs high), and prior docetaxel therapy for prostate cancer (yes vs no)
Median follow-up	Median follow-up time in the study for all 1150 patients as determined for the overall survival endpoint. Time is from randomisation up to the date of death or, for those still alive, up to their last known alive date before the analysis cutoff date.

PRO = patient-reported outcome.

2.4. *Statistical analysis*

Study size calculations are shown in Table 1. PRO analyses were performed on the intent-to-treat population and based on observed data (definitions in Table 1). The instrument completion rate (adjusted for study attrition) at each visit was reported for subjects expected to have PRO assessments.

The mean questionnaire score is reported by visit. To estimate longitudinal changes in PRO scores from baseline at each visit, we used a mixed model for repeated measures (MMRM) analysis [18,19] (Table 1). Only patients with baseline and at least one post-baseline score were included in longitudinal change analyses.

The Kaplan-Meier product limit method was used to estimate TTFD and TTFCD distributions, and hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using a stratified Cox proportional-hazards model (Table 1).

For PROs, the proportions of patients with improvement, no change, or deterioration (using the thresholds in Supplementary Table 1) at each visit were compared between groups using a stratified Cochran-Mantel-Haenszel mean score test.

Exploratory subgroup analyses (MMRM, TTFD, and TTFCD) were conducted for prespecified stratification factors and other subgroups. Analyses for disease volume are presented here; other ongoing subgroup analyses will be reported at a later date. Owing to the high volume of data in this paper, we plan to present results for the stratification analysis by prior docetaxel use in a future publication.

We estimated two-sided nominal p values for the PRO analyses (significance testing was set at 0.05) and made no adjustment for multiple testing. Data processing, summarisation, and analyses were performed using SAS v.9.3 (SAS Institute, NC, USA) or higher. The data cutoff date was October 14, 2018.

3. Results

Between March 21, 2016 and January 12, 2018, 1150 patients from 202 centres in 24 countries were randomised to ADT plus either enzalutamide (n = 574) or placebo (n = 576) and included in the intent-to-treat population. At data cutoff (October 14, 2018), the median follow-up (defined in Table 1) for the entire study population was 14.4 mo.

Baseline demographics and PRO scores were well balanced between the groups. The majority of patients had high-volume disease and no prior docetaxel therapy for

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Table 2 – Change in least-squares mean for PRO scores at week 73 (mixed-model for repeated measures).

Instrument[a]	Least-squares mean (SE)		TD at week 73
	ENZA + ADT	PBO + ADT	(95% CI)
EORTC QLQ-PR25 scores[b]			
Modified urinary symptoms	−2.22 (1.84)	−1.18 (2.01)	−1.04 (−6.20, 4.11)
Urinary symptoms	−0.56 (1.30)	−0.02 (1.42)	−0.54 (−4.19, 3.11)
Bowel symptoms/function	0.92 (0.73)	0.59 (0.79)	0.33 (−1.72, 2.38)
Treatment-related symptoms	7.08 (1.00)	4.61 (1.09)	2.46 (−0.35, 5.27)
Incontinence aids[c]	−4.08 (3.22)	3.99 (3.04)	−8.07 (−16.44, 0.30)
Sexual functioning	−3.07 (4.91)	−16.67 (9.30)	13.59 (−7.86, 35.1)
Sexual activity	−2.45 (1.61)	−4.87 (1.74)	2.42 (−2.12, 6.95)
FACT scores[c]			
FACT-P total	−3.17 (1.30)	−1.71 (1.42)	−1.47 (−5.12, 2.18)
Physical wellbeing	−1.42 (0.32)	−0.40 (0.34)	−1.02 (−1.90, −0.13)*
Functional wellbeing	−0.41 (0.40)	−0.15 (0.43)	−0.26 (−1.37, 0.85)
Emotional wellbeing	−0.30 (0.28)	0.06 (0.31)	−0.36 (−1.16, 0.44)
Social wellbeing	0.47 (0.35)	−0.37 (0.38)	0.84 (−0.12, 1.80)
Prostate cancer subscale	−1.01 (0.47)	−0.50 (0.52)	−0.51 (−1.84, 0.81)
Prostate cancer subscale-pain	−1.01 (0.29)	−0.56 (0.32)	−0.45 (−1.29, 0.38)
FACT Advanced Prostate Symptom Index	−0.77 (0.37)	−0.01 (0.40)	−0.76 (−1.79, 0.27)
Trial outcome index	−3.15 (0.98)	−1.28 (1.07)	−1.88 (−4.62, 0.87)
FACT-General	−1.94 (0.95)	−1.08 (1.04)	−0.86 (−3.54, 1.82)
BPI-SF scores[b]			
Worst pain (item 3)	0.54 (0.19)	0.33 (0.20)	0.21 (−0.32, 0.73)
Severity	0.49 (0.15)	0.38 (0.16)	0.11 (−0.30, 0.52)
Interference	0.71 (0.15)	0.58 (0.17)	0.14 (−0.29, 0.57)
EQ-5D-5 L scores[c]			
Visual analogue scale	0.28 (1.16)	0.19 (1.27)	0.10 (−3.14, 3.33)

ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory Short Form; CI = confidence interval; ENZA = enzalutamide; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5 L = EuroQoL 5-Dimensions, 5-Levels; FACT = Functional Assessment of Cancer Therapy; FACT-P = FACT-Prostate; PBO = placebo; PRO = patient-reported outcome; SE = standard error; TD = treatment difference for ENZA versus PBO.

* $p = 0.024$ from the mixed-model repeated measures analyses.

[a] For BPI-SF scores and EORTC QLQ-PR25 bowel symptoms and function, hormonal treatment–related symptoms, and urinary symptoms scores, a positive change from baseline value indicates worsening of symptoms. For FACT-P scores and EQ-VAS, a positive change from baseline value indicates improvement. Therefore, a negative number for the least-squares mean difference at week 73 favours ENZA + ADT over PBO + ADT for BPI-SF scores and bowel symptoms and function, hormonal treatment–related symptoms, and urinary symptoms and problems, whereas a positive number favours ENZA + ADT over PBO + ADT for FACT-P scores and EQ-VAS.

[b] A positive change from baseline indicates worsening of symptoms.

[c] A positive change from baseline indicates improvement of symptoms.

prostate cancer. Baseline PRO scores suggest that patients were generally asymptomatic with good HRQoL, low symptom burden, and minimal functional limitations (Supplementary Table 2).

Pain was low at baseline; approximately half (48%) of patients (similar in both groups) reported a worst pain score of 0 ("no pain"). For PRO outcomes, all questions were completed at baseline by 94–96% of patients on enzalutamide versus 95–96% of patients on placebo. At week 73, completion rates (all questions completed), based on patients remaining on study and available for assessment, ranged from 87% to 88% (Supplementary Fig. 1).

Mean scores by visit indicated that high levels of HRQoL and low levels of pain at baseline were generally maintained during the study in both groups (Supplementary Fig. 2). There were no statistically significant or clinically meaningful differences between the groups in mean change in PRO score from baseline to week 73, except for a statistically significant (nominal $p = 0.024$) difference in FACT-P physical wellbeing score favouring placebo over enzalutamide, although the difference was not clinically meaningful (Table 2). The proportion of patients with clinically meaningful deterioration in modified urinary symptoms, FACT-P total, BPI-SF worst pain, and EQ-5D-5 L visual analogue scale (VAS) scores over time was generally low and similar between the groups (Fig. 1); this also applied to other PRO domains (Supplementary Figs. 3–5). Although higher proportions of patients reported deterioration in sexual functioning over time (Supplementary Fig. 3D), which was higher with placebo versus enzalutamide, patient numbers were very small.

There were no statistically significant (nominal $p > 0.05$) differences in median time to clinically meaningful deterioration (that occurred in both TTFD and TTFCD together) between treatments for QLQ-PR25 (Fig. 2A) or FACT-P (Fig. 2B) domain scores. Enzalutamide plus ADT significantly delayed TTFD in worst pain (14.09 vs 11.10 mo; HR 0.82; nominal $p = 0.032$) and pain severity (19.38 vs 16.76 mo; HR 0.79; nominal $p = 0.021$) versus placebo plus ADT (Fig. 2C). There was no significant between-treatment difference in time to deterioration for pain interference or with TTFCD for worst pain and pain severity. The median time to deterioration on EQ-5D-5 L VAS was significantly delayed with enzalutamide plus ADT versus placebo plus ADT (TTFD 11.14 vs 8.38 mo; HR 0.80, 95% CI 0.67–0.94; nominal $p = 0.0070$). TTFCD for EQ-5D-5 L VAS still showed a

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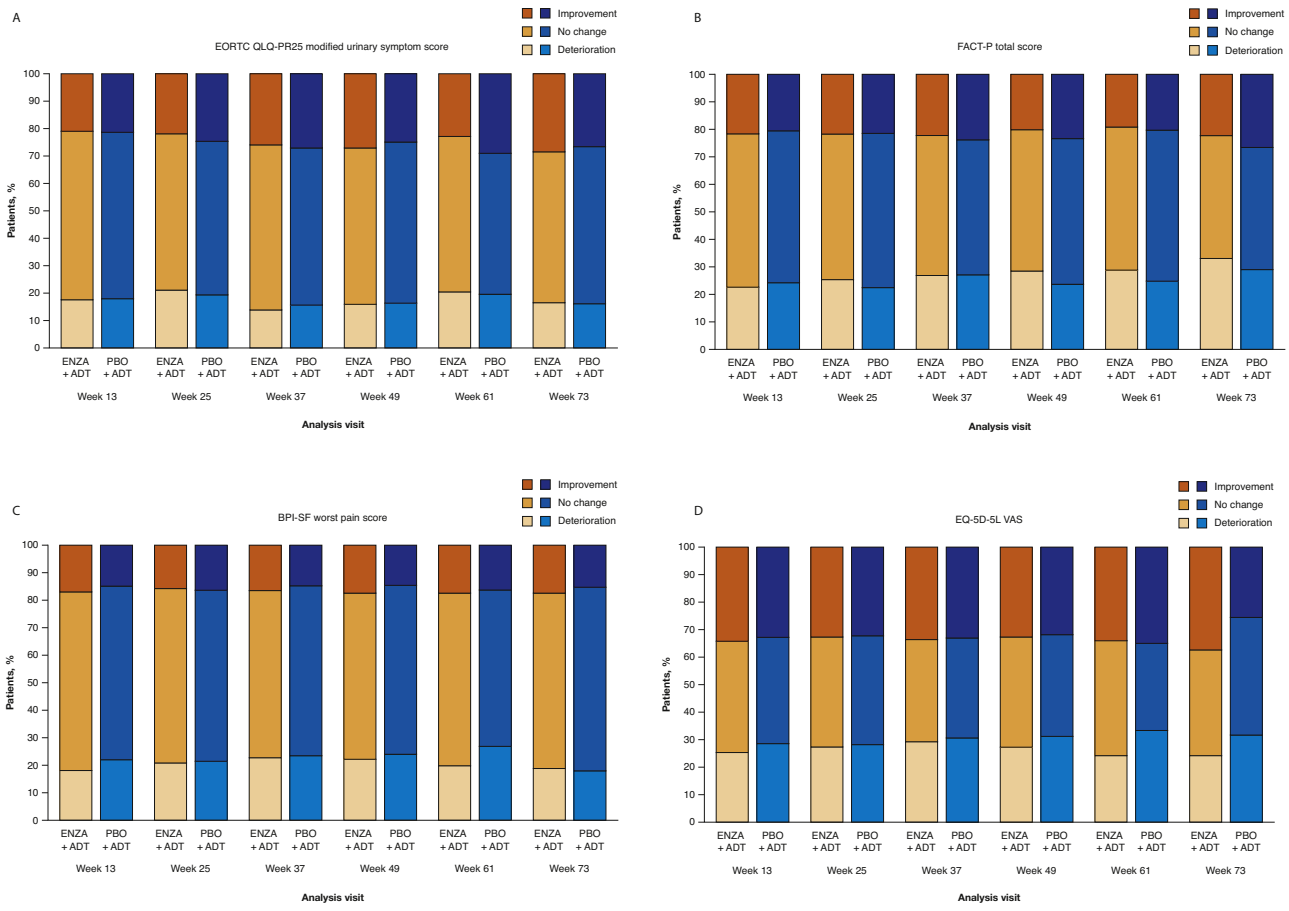

Fig. 1 – Proportion of patients with clinically meaningful improvement, no change, or deterioration from baseline for (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC QLQ-PR25) modified urinary symptom score, (B) Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score, (C) Brief Pain Inventory Short Form (BPI-SF) worst pain score, and (D) EuroQoL 5-Dimensions, 5-Levels (EQ-5D-5 L) visual analogue scale (VAS) over time to week 73. Nominal $p > 0.05$ for enzalutamide versus placebo at each time point. ADT = androgen deprivation therapy; ENZA = enzalutamide; PBO = placebo.

significant between-group difference in favour of enzalutamide. Sensitivity analyses including death in the definition showed similar results (Supplementary Table 3).

PROs were analysed by disease volume at baseline according to criteria from the CHAARTED trial. The median time to deterioration (that occurred in both TTFD and TTFCD together) was significantly delayed with enzalutamide versus placebo for FACT-P total (TTFD HR 0.78; nominal $p = 0.020$; TTFCD HR 0.74; nominal $p = 0.012$), FACT-P social wellbeing (TTFD HR 0.79; nominal $p = 0.035$; TTFCD HR 0.74; nominal $p = 0.025$), and TTFCD only was also delayed for worst pain (TTFCD not yet reached vs 17.22 mo; HR 0.75; nominal $p = 0.030$) in high-volume disease (Fig. 3). Deterioration on EQ-5D-5 L VAS was also significantly delayed with enzalutamide versus placebo (TTFD 11.27 vs 8.34 mo; HR 0.77, 95% CI 0.62–0.94; nominal $p = 0.012$; TTFCD 16.76 vs 13.73 mo; HR 0.72, 95% CI 0.57-0.91; nominal $p = 0.0064$) in high-volume disease. Further subgroup analyses showed no statistically significant or clinically meaningful between-group differences in change in mean PRO scores from baseline to week 73 for low- or high-volume disease, except for a statistically significant (nominal $p = 0.037$) difference in FACT-P physical wellbeing score favouring placebo over enzalutamide in low-volume disease (difference not clinically meaningful at predefined threshold; Supplementary Table 4).

Among men with low-volume mHSPC, there was a delay in time to first deterioration with placebo versus enzalutamide for some measures, but not in confirmed deterioration for FACT-P total (TTFD HR 1.41; nominal $p = 0.020$; TTFCD HR 1.31; nominal $p = 0.11$), prostate cancer subscale (TTFD HR 1.38; nominal $p = 0.013$; TTFCD HR 1.21; nominal $p = 0.2$), and trial outcome index (TTFD HR 1.46; nominal $p = 0.011$; TTFCD HR 1.36; nominal $p = 0.077$; Fig. 3). Only a minority of patients were sexually active; time to deterioration in sexual activity was longer in the placebo group than in the enzalutamide group (TTFD HR 1.50; nominal $p = 0.051$; TTFCD HR 1.58; nominal $p = 0.045$).

The proportions of patients with worsening ($\geq$1 point) lack of energy from baseline to week 73 for enzalutamide and placebo were 39–48% and 26–41% in low-volume disease, and 27–36% and 24–29% in high-volume disease, respectively (Supplementary Table 5). Patients reporting spending a longer time in bed for enzalutamide and placebo were 9.4–15% and 4.3–15% in low-volume disease, and 12–16% and 13–18% in high-volume disease, respectively

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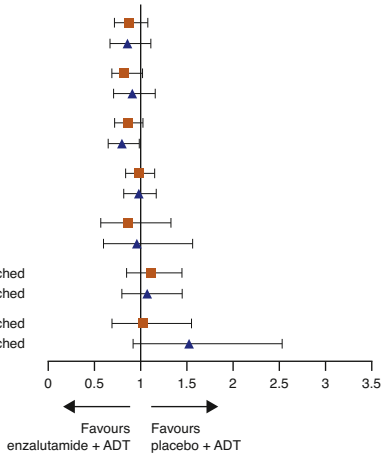
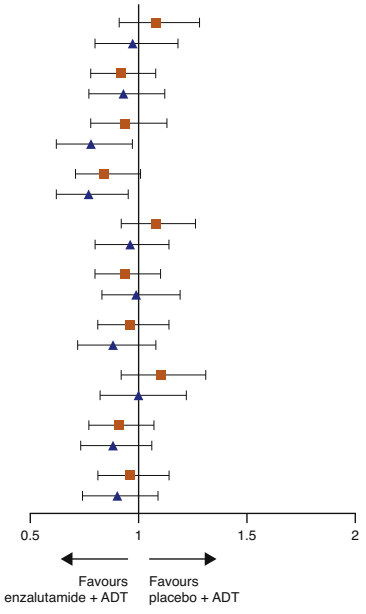
A

EORTC-QLQ-PR25	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	p value
Modified urinary symptoms	184/201	Not yet reached/16.76	0.88 (0.72, 1.08)	0.2
	118/130	Not yet reached/22.11	0.86 (0.67, 1.11)	0.2
Urinary symptoms and problems	193/216	20.47/16.76	0.83 (0.69, 1.02)	0.071
	130/134	Not yet reached/22.11	0.91 (0.71, 1.16)	0.5
Bowel symptoms/function	244/254	13.90/11.10	0.86 (0.72, 1.03)	0.10
	161/175	19.45/16.79	0.80 (0.65, 0.99)	0.044
Treatment-related symptoms	328/318	8.31/8.31	0.98 (0.84, 1.15)	0.8
	251/241	13.86/13.86	0.98 (0.82, 1.17)	0.8
Sexual functioning	56/43	8.31/8.31	0.87 (0.57, 1.33)	0.5
	44/33	13.44/11.27	0.96 (0.60, 1.56)	0.9
Sexual activity	115/102	Not yet reached/not yet reached	1.11 (0.85, 1.45)	0.4
	93/82	Not yet reached/not yet reached	1.07 (0.80, 1.45)	0.6
Incontinence aid	49/48	Not yet reached/not yet reached	1.03 (0.69, 1.55)	0.9
	37/27	Not yet reached/not yet reached	1.52 (0.92, 2.53)	0.10



B

FACT-P	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	p value
Physical wellbeing	281/260	11.10/11.20	1.08 (0.91, 1.28)	0.4
	211/204	16.66/16.66	0.97 (0.80, 1.18)	0.7
Functional wellbeing	307/306	11.01/8.61	0.92 (0.78, 1.08)	0.3
	236/227	16.59/16.49	0.93 (0.77, 1.12)	0.4
Emotional wellbeing	235/233	14.09/13.83	0.94 (0.78, 1.13)	0.5
	145/165	20.47/22.01	0.78 (0.62, 0.97)	0.028
Social/family wellbeing	254/267	13.80/8.54	0.84 (0.71, 1.01)	0.058
	170/193	19.81/17.61	0.77 (0.62, 0.95)	0.014
PCS	344/320	8.31/8.34	1.08 (0.92, 1.26)	0.3
	251/245	13.90/14.06	0.96 (0.80, 1.14)	0.6
PCS pain-related score	321/318	8.51/8.38	0.94 (0.80, 1.10)	0.4
	238/224	13.93/16.59	0.99 (0.83, 1.19)	0.9
FACT Advanced Prostate Symptom Index	271/266	12.25/11.10	0.96 (0.81, 1.14)	0.6
	185/190	20.47/16.82	0.88 (0.72, 1.08)	0.2
Trial outcome index	268/242	11.50/13.86	1.10 (0.92, 1.31)	0.3
	203/191	17.08/16.79	1.00 (0.82, 1.22)	1.0
FACT-General	290/294	11.07/8.51	0.91 (0.77, 1.07)	0.2
	221/227	16.66/14.62	0.88 (0.73, 1.06)	0.2
FACT-P total	280/274	11.30/11.07	0.96 (0.81, 1.14)	0.7
	210/214	16.66/16.76	0.90 (0.74, 1.09)	0.3



C

BPI-SF	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	p value
Item 3 (worst pain)	245/266	14.09/11.10	0.82 (0.69, 0.98)	0.032
	166/179	19.58/22.11	0.82 (0.67, 1.02)	0.075
Pain severity	185/205	19.38/16.76	0.79 (0.65, 0.97)	0.021
	116/123	Not yet reached /22.11	0.85 (0.66, 1.10)	0.2
Pain interference	274/257	11.24/11.14	1.00 (0.84, 1.19)	1.0
	199/186	17.08/22.11	0.95 (0.78, 1.16)	0.6

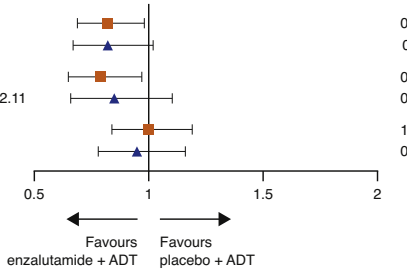


Fig. 2 – Time to first clinically meaningful deterioration and time to first confirmed clinically meaningful deterioration in (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC-QLQ-PR25), (B) Functional Assessment of Cancer Therapy-Prostate (FACT-P), and (C) Brief Pain Inventory Short Form (BPI-SF) scores. Thresholds for minimum clinically meaningful deterioration in scores from baseline were 3 points for physical wellbeing, functional wellbeing, emotional wellbeing, family/social wellbeing, PCS, and FACT Advanced Prostate Symptom Index; 2 points for PCS pain-related score; 9 points for trial outcome index; 7 points for FACT-General; and 10 points for FACT-P. Pain progression was defined as a ≥2-point increase in BPI-SF pain score from baseline (except for pain interference, ≥1). ADT = androgen deprivation therapy; CI = confidence interval; PCS = prostate cancer subscale.

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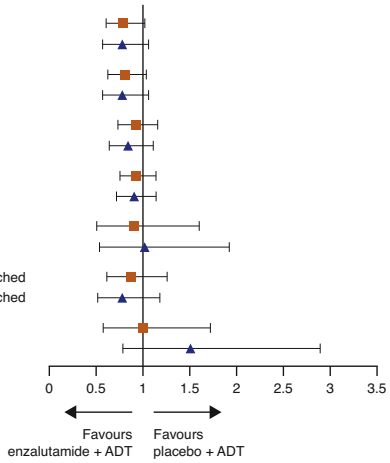
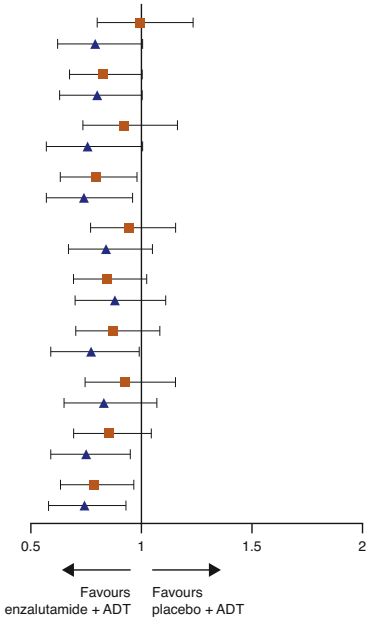
A

EORTC-QLQ-PR25	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Modified urinary symptoms	106/130	Not yet reached/16.76	0.79 (0.61, 1.02)	0.076
	72/88	Not yet reached/19.38	0.78 (0.57, 1.06)	0.12
Urinary symptoms and problems	113/134	20.47/16.79	0.81 (0.63, 1.04)	0.099
	76/92	Not yet reached/22.11	0.78 (0.57, 1.06)	0.11
Bowel symptoms/function	151/151	13.93/11.14	0.93 (0.74, 1.16)	0.5
	102/105	19.45/16.79	0.84 (0.64, 1.11)	0.2
Treatment-related symptoms	196/202	8.31/8.31	0.93 (0.76, 1.14)	0.5
	147/153	16.20/13.80	0.91 (0.72, 1.14)	0.4
Sexual functioning	24/27	8.41/11.07	0.90 (0.51, 1.60)	0.7
	19/21	13.44/13.77	1.02 (0.54, 1.92)	1.0
Sexual activity	57/64	Not yet reached/not yet reached	0.88 (0.62, 1.26)	0.5
	42/51	Not yet reached/not yet reached	0.78 (0.52, 1.18)	0.2
Incontinence aid	26/27	19.38/not yet reached	1.00 (0.58, 1.72)	1.0
	22/16	19.38/not yet reached	1.51 (0.79, 2.89)	0.2



B

FACT-P	No. of events: enzalutamide + ADT /placebo + ADT	Median (months): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	p-value
Physical wellbeing	167/169	11.17/11.20	0.99 (0.80, 1.23)	0.9
	121/139	19.32/16.66	0.79 (0.62, 1.01)	0.061
Functional wellbeing	187/202	11.07/8.38	0.82 (0.67, 1.00)	0.055
	142/154	16.59/11.89	0.80 (0.63, 1.00)	0.053
Emotional wellbeing	142/147	16.59/13.83	0.92 (0.73, 1.16)	0.5
	88/106	20.47/22.11	0.76 (0.57, 1.01)	0.057
Social/family wellbeing	151/174	13.86/8.51	0.79 (0.63, 0.98)	0.035
	103/125	19.81/16.79	0.74 (0.57, 0.96)	0.025
PCS	198/209	10.97/8.34	0.94 (0.77, 1.15)	0.5
	148/125	13.93/13.01	0.84 (0.67, 1.05)	0.12
PCS pain-related score	195/213	11.04/8.31	0.84 (0.69, 1.02)	0.080
	147/155	13.93/13.86	0.88 (0.70, 1.11)	0.3
FACT Advanced Prostate Symptom Index	160/175	13.73/11.07	0.87 (0.70, 1.08)	0.2
	109/130	20.47/16.82	0.77 (0.59, 0.99)	0.042
Trial outcome index	155/162	13.83/11.14	0.92 (0.74, 1.15)	0.5
	123/135	17.18/16.59	0.83 (0.65, 1.07)	0.15
FACT-General	174/190	11.10/8.61	0.85 (0.69, 1.04)	0.12
	130/152	16.76/13.86	0.75 (0.59, 0.95)	0.018
FACT-P total	164/191	11.40/8.48	0.78 (0.63, 0.96)	0.020
	125/152	16.69/13.86	0.74 (0.58, 0.93)	0.012



C

BPI-SF	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Item 3 (worst pain)	159/177	13.86/11.01	0.83 (0.67, 1.03)	0.087
	106/127	Not yet reached/17.22	0.75 (0.58, 0.97)	0.030
Pain severity	118/136	19.32/16.59	0.77 (0.60, 0.98)	0.036
	77/89	Not yet reached /22.11	0.78 (0.58, 1.07)	0.12
Pain interference	170/177	11.30/10.22	0.89 (0.72, 1.11)	0.3
	127/129	16.72/16.62	0.89 (0.69, 1.14)	0.3

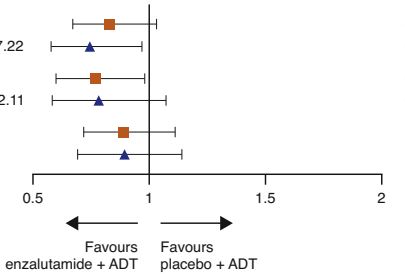


Fig. 3 – Time to first clinically meaningful deterioration and time to first confirmed clinically meaningful deterioration in (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC-QLQ-PR25), (B) Functional Assessment of Cancer Therapy-Prostate (FACT-P), and (C) Brief Pain Inventory Short Form (BPI-SF) scores among patients with high-volume disease, and in (D) EORTC-QLQ-PR25, (E) FACT-P, and (F) BPI-SF scores among patients with low-volume disease. The threshold for minimum clinically meaningful deterioration in score from baseline was 3 points for physical wellbeing, functional wellbeing, emotional wellbeing, family/social wellbeing, PCS, and FACT Advanced Prostate Symptom Index; 2 points for PCS pain-related score; 9 points for trial outcome index; 7 points for FACT-General; and 10 points for FACT-P. Pain progression was defined as a ≥2-point increase in BPI-SF pain score from baseline (except for pain interference, ≥1). ADT = androgen deprivation therapy; CI = confidence interval; PCS = prostate cancer subscale.

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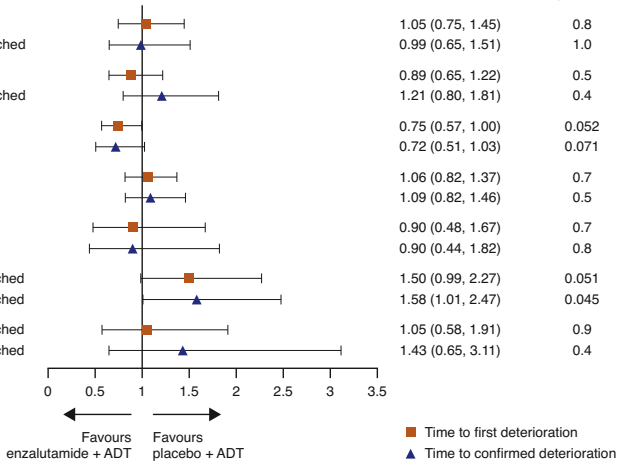
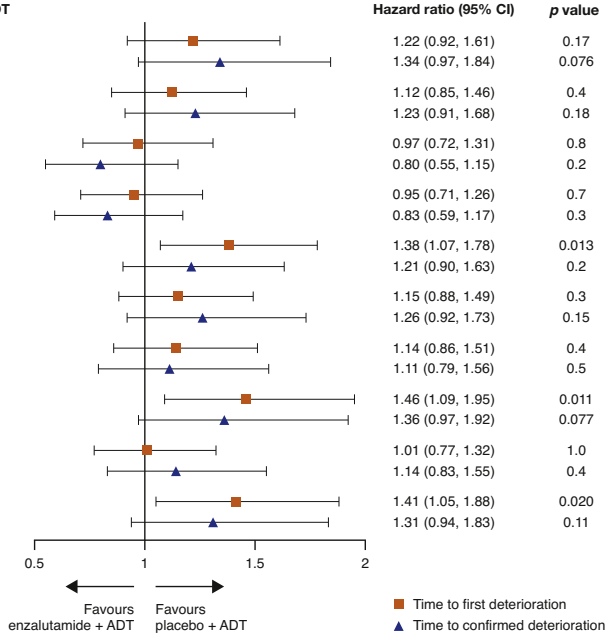
D

EORTC-QLQ-PR25	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Modified urinary symptoms	78/71	Not yet reached/19.25	1.05 (0.75, 1.45)	0.8
	46/42	Not yet reached/Not yet reached	0.99 (0.65, 1.51)	1.0
Urinary symptoms and problems	80/82	19.22/16.69	0.89 (0.65, 1.22)	0.5
	54/42	Not yet reached/Not yet reached	1.21 (0.80, 1.81)	0.4
Bowel symptoms/function	93/103	13.86/10.97	0.75 (0.57, 1.00)	0.052
	59/70	22.31/16.79	0.72 (0.51, 1.03)	0.071
Treatment-related symptoms	132/116	8.18/6.01	1.06 (0.82, 1.37)	0.7
	104/88	13.40/13.93	1.09 (0.82, 1.46)	0.5
Sexual functioning	32/16	5.75/8.31	0.90 (0.48, 1.67)	0.7
	25/12	11.30/11.10	0.90 (0.44, 1.82)	0.8
Sexual activity	58/38	Not yet reached/not yet reached	1.50 (0.99, 2.27)	0.051
	51/31	Not yet reached/not yet reached	1.58 (1.01, 2.47)	0.045
Incontinence aid	23/21	Not yet reached/not yet reached	1.05 (0.58, 1.91)	0.9
	15/11	Not yet reached/not yet reached	1.43 (0.65, 3.11)	0.4



E

FACT-P	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Physical wellbeing	114/91	11.07/13.70	1.22 (0.92, 1.61)	0.17
	90/65	14.09/16.66	1.34 (0.97, 1.84)	0.076
Functional wellbeing	120/104	8.44/11.04	1.12 (0.85, 1.46)	0.4
	94/73	13.90/16.79	1.23 (0.91, 1.68)	0.18
Emotional wellbeing	93/86	13.86/13.83	0.97 (0.72, 1.31)	0.8
	57/59	19.45/22.01	0.80 (0.55, 1.15)	0.2
Social/family wellbeing	103/93	11.17/8.54	0.95 (0.71, 1.26)	0.7
	67/68	22.11/22.11	0.83 (0.59, 1.17)	0.3
PCS	146/111	5.55/8.44	1.38 (1.07, 1.78)	0.013
	103/80	13.86/16.36	1.21 (0.90, 1.63)	0.2
PCS pain-related score	126/105	8.34/11.04	1.15 (0.88, 1.49)	0.3
	91/69	16.59/16.69	1.26 (0.92, 1.73)	0.15
FACT Advanced Prostate Symptom Index	111/91	11.07/13.83	1.14 (0.86, 1.51)	0.4
	76/60	19.22/19.35	1.11 (0.79, 1.56)	0.5
Trial outcome index	113/80	11.07/16.62	1.46 (1.09, 1.95)	0.011
	80/56	16.59/19.35	1.36 (0.97, 1.92)	0.077
FACT-General	116/104	8.84/8.34	1.01 (0.77, 1.32)	1.0
	91/75	16.59/16.69	1.14 (0.83, 1.55)	0.4
FACT-P total	116/83	11.04/16.69	1.41 (1.05, 1.88)	0.020
	85/62	16.59/19.35	1.31 (0.94, 1.83)	0.11



F

BPI-SF	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Item 3 (worst pain)	86/89	16.59/13.86	0.85 (0.63, 1.15)	0.3
	60/52	19.58/not yet reached	1.03 (0.71, 1.49)	0.9
Pain severity	67/69	Not yet reached/19.25	0.84 (0.60, 1.18)	0.3
	39/34	Not yet reached / not yet reached	1.03 (0.65, 1.63)	0.9
Pain interference	104/80	11.24/17.02	1.24 (0.92, 1.66)	0.16
	72/57	19.42/not yet reached	1.09 (0.77, 1.55)	0.6

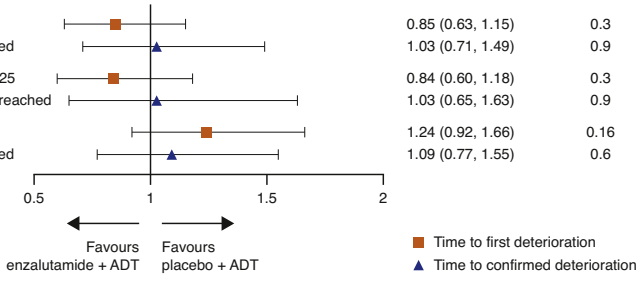


Fig. 3. (*Continued*).

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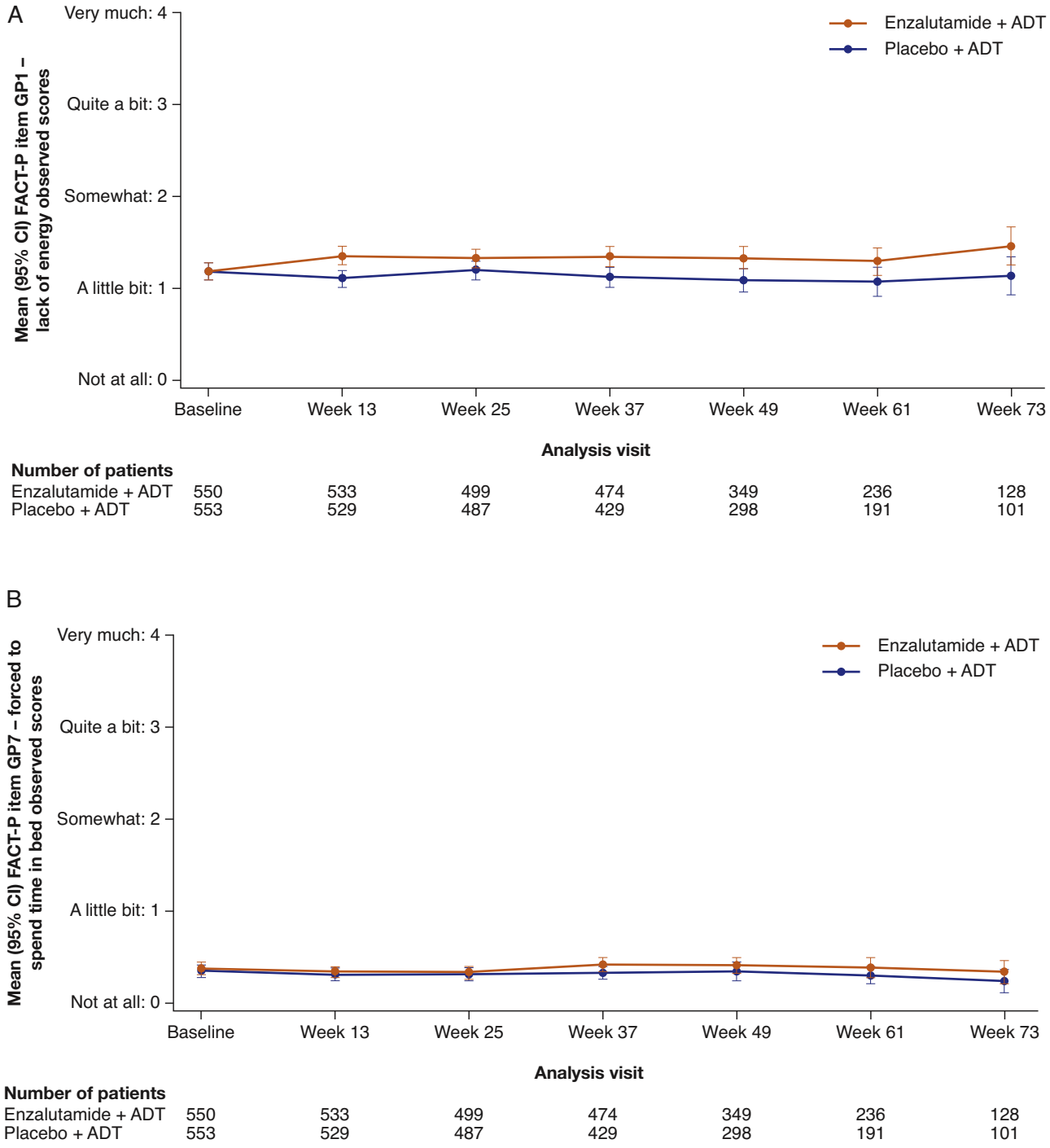

Fig. 4 – Mean scores over time to week 73 for the Functional Assessment of Cancer Therapy-Prostate (FACT-P) items (A) GP1 – lack of energy and (B) GP7 – forced to spend time in bed. ADT = androgen deprivation therapy; CI = confidence interval; PBO = placebo.

(Supplementary Table 6). Mean scores for lack of energy and forced to spend time in bed items (Fig. 4) showed no change over time and were similar between the treatment groups.

4. Discussion

Decisions on the merits of more intensive hormonal therapy in mHSPC should reflect overall net benefits over risks versus ADT alone, including HRQoL. ARCHES demonstrates that high-functioning HRQoL and low symptom burden at baseline are generally maintained post-baseline when enzalutamide is added to ADT. Enzalutamide significantly prolongs time to progression for worst pain and pain severity versus placebo, and significantly delays time to deterioration on EQ-5D-5 L VAS versus placebo for TTFD. There was no difference between treatments in TTFD for other PROs. However, the prespecified confirmed deterioration analysis showed no significant differences between

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treatments for worst pain or pain severity. Thus, the data suggest that adding enzalutamide to ADT does not worsen HRQoL and has a beneficial effect on EQ-5D-5 L VAS, but no statistically significant benefit for deterioration of pain versus placebo. Longer follow-up is needed to understand the impact of enzalutamide plus ADT on HRQoL in subsequent years or beyond disease progression. For FACT-P items measuring patient-reported fatigue (lack of energy/forced to spend time in bed), mean values to week 73 were stable and generally similar between the groups.

Subgroup analyses showed a significant delay in deterioration with enzalutamide versus placebo for several HRQoL subscales and pain severity among men with high-volume mHSPC; conversely, in low-volume disease, there was a modest delay in TTFD with placebo plus ADT versus enzalutamide plus ADT for some FACT-P scales. Since enzalutamide was effective regarding rPFS in both high- and low-volume disease, this may simply reflect that patients with low-volume disease are asymptomatic at baseline and are more impacted by hormone-related symptoms; however, the prespecified confirmed deterioration analysis showed no significant differences between the treatment groups for the low-volume population, except for sexual activity favouring placebo. However, the population in this category was small and the results should be interpreted with caution. The confirmed deterioration analysis may be a more accurate measure, as it ensures that scores are consistently reduced and not fluctuating from a deterioration to a non-deterioration score. This indicates that the clinical benefit in both populations does not come at a significant HRQoL cost, although patients with low-volume disease may experience some numerical decrement.

In ARCHES, enzalutamide plus ADT significantly improved rPFS versus ADT alone, irrespective of disease volume and prior docetaxel [7]. In ENZAMET, enzalutamide plus ADT improved OS versus nonsteroidal antiandrogen therapy plus ADT, irrespective of disease volume, and despite the more common use of concurrent docetaxel for men with mHSPC [6]. In ENZAMET, docetaxel could be given concomitantly with enzalutamide, unlike ARCHES, where docetaxel use was before enzalutamide. Critical to an understanding of the net benefits of more intensive therapy is the impact on HRQoL of enzalutamide plus ADT in patients over time. Importantly, in ARCHES, men commenced ADT before study entry, and thus had low prostate-specific antigen (PSA) and good HRQoL on enrolment [7]. This probably explains why men entering ARCHES were generally asymptomatic with low urinary symptom burden, good HRQoL, and low pain. Indeed, baseline PRO scores in ARCHES are generally similar to those in the PROSPER study [5] (Supplementary Table 7) in nonmetastatic prostate cancer and comparable to those in the general population [20].

HRQoL and pain status before ADT were not captured until study entry. Patients could receive ADT for ≤3 mo (6 mo if treated with docetaxel) before study initiation. Thus, it is likely that the effects of ADT on HRQoL were already evident in most patients at enrolment. Pre-randomisation ADT, while associated with adverse effects, can improve lower urinary tract symptoms in all prostate cancer stages [21] and help reduce bone pain in advanced disease [22].

Maintenance of HRQoL in ARCHES adds to the efficacy benefits of enzalutamide plus ADT in mHSPC, including significantly improved rPFS, time to PSA progression, time to initiation of new antineoplastic therapy, and time to first symptomatic skeletal event versus placebo plus ADT [7]. Improvements in PROs, in addition to survival, also occur with enzalutamide in CRPC [3–5].

Our results are in agreement with those from studies comparing abiraterone acetate and prednisone plus ADT [23], docetaxel plus ADT, and apalutamide plus ADT [24] versus ADT alone [25] in mHSPC. Patients in both the LATITUDE and CHAARTED studies appeared to show good HRQoL at baseline [23,25]. In LATITUDE, comprising patients with newly diagnosed (≤3 mo pre-randomisation) mHSPC, addition of abiraterone acetate and prednisone to ADT significantly prolonged time to worst pain intensity progression and improved health status (measured with EQ-5D-5 L) versus ADT alone [23]. However, differences between populations and study designs make direct comparisons difficult. Unlike ARCHES, LATITUDE comprised a high-risk population, with higher proportions of patients with Eastern Cooperative Oncology Group score ≥1, Gleason score ≥8, and distant metastases. Baseline BPI-SF pain scores also appeared to be generally higher (indicating greater pain) in LATITUDE [23]. Furthermore, in the ARCHES and CHAARTED studies, assessments were conducted every 12 wk versus every 4 wk in LATITUDE for the first 13 mo, followed by every 8 wk. In CHAARTED, FACT-P total scores were significantly lower after 3 mo of docetaxel plus ADT versus ADT alone, and were not improved until 12 mo, perhaps reflecting reversible short-term physical and functional deficits at 3 mo, presumably associated with chemotherapy. Unlike ARCHES, patients were not blinded and knowledge of having received chemotherapy may have influenced HRQoL reporting [25].

We used clinically meaningful HRQoL change thresholds from the literature to interpret FACT-P, BPI-SF, and EQ-5D-5 L scores. Cutoff values of ≥30% or a ≥2-point change in BPI-SF scores have been proposed for detection of clinically important improvements in studies of cancer-related breakthrough pain and chronic pain states [15,16] and in metastatic CRPC [3,26]. However, use of these values in defining pain progression in patients with mHSPC is not yet validated. In view of the very low baseline pain scores in our study, we applied fixed thresholds of ≥1 point (interference) or ≥2 points (worst pain/pain severity), as these are likely to be more meaningful changes from baseline than 30–50% changes, which would have been very small [26]. No threshold values have been established for QLQ-PR25. We therefore derived thresholds using distribution-based and anchor-based analyses; derivation of correlation coefficients between anchors and QLQ-PR25 scores showed that the anchors are adequate.

Study limitations include patient selection using specific criteria, so the results might not be generalisable to other disease-stage prostate cancer populations. There was an absence of HRQoL data before ADT initiation and limited data after treatment discontinuation. This limited our

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ability to document improved HRQoL with initial ADT before enzalutamide, and missing HRQoL data over time is a well-established drawback of studies incorporating PROs as secondary or exploratory endpoints [3]. This pattern of attrition makes data interpretation difficult and can lead to overestimation of HRQoL at later time points. To address this imbalance, MMRM analysis of longitudinal data is limited to 73 weeks. Finally, the follow-up duration in ARCHES is short. Given the positive efficacy results with enzalutamide plus ADT in ARCHES and survival benefits in ENZAMET [6], patients are now being offered access to enzalutamide plus ADT in this setting, which will limit our ability to observe HRQoL differences over time between treatments. Study strengths include the randomised and prospective design, high rates of instrument compliance, and high regional/ethnic diversity of the population.

In conclusion, men with mHSPC are generally asymptomatic, with high levels of HRQoL and low levels of pain at baseline. Notably, the effects of ongoing ADT on HRQoL were already experienced by most patients by study enrolment. Prolongation of rPFS with enzalutamide plus ADT is accompanied by maintenance of HRQoL. Thus, enzalutamide represents a treatment strategy for mHSPC that provides clinical benefits while maintaining HRQoL.

Author contributions: Arnulf Stenzl 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: Ramaswamy, Armstrong.
Acquisition of data: Stenzl, Dunshee, De Giorgi, Alekseev, Iguchi, Flaig, Armstrong.
Analysis and interpretation of data: Stenzl, Alekseev, Iguchi, Szmulewitz, Flaig, Morlock, Ivanescu, Ramaswamy, Saad, Armstrong.
Drafting of the manuscript: Stenzl, Dunshee, De Giorgi, Alekseev, Iguchi, Szmulewitz, Flaig, Tombal, Morlock, Ivanescu, Ramaswamy, Saad, Armstrong.
Critical revision of the manuscript for important intellectual content: Stenzl, Dunshee, De Giorgi, Alekseev, Iguchi, Szmulewitz, Flaig, Tombal, Morlock, Ivanescu, Ramaswamy, Saad, Armstrong.
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Appendix A. Supplementary data

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