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A Prospective Randomised Trial to Determine the Effect of a Reduced Versus Standard Dose of Enzalutamide on Side Effects in Frail Patients with Prostate Cancer

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Abstract

Background and objective: Enzalutamide is a potent androgen receptor signalling inhibitor, effectively used for the treatment of different stages of prostate cancer. Side effects occur frequently at the registered dose, whilst a lower dose might be equally effective. Therefore, the aim of this study is to determine the effect of a reduced dose of enzalutamide on side effects in frail patients with prostate cancer.

Methods: This multicentre randomised trial compared the standard enzalutamide dose of 160 mg once daily (OD) with a reduced dose of 120 mg OD in frail patients with prostate cancer. Fatigue, cognitive side effects, and depressive symptoms were measured by the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-Fatigue) questionnaire, Functional Assessment of Cancer Therapy—Cognitive Function (FACT-Cog) questionnaire, and Geriatric Depression Scale—15 (GDS-15). Linear mixed-effect models were used to study differences in side effects over time between both groups.

Key findings and limitations: In total, 52 patients were included in the analysis (25 reduced dose and 27 standard dose). Patients treated with the reduced dose had significantly lower fatigue after 24 wk than those with the standard dose (difference FACIT-Fatigue 6.2; 95% confidence interval 1.4–11.0; p = 0.01). Patients treated with the reduced dose showed stable fatigue, cognitive side effects, and depressive symptoms over time, whilst patients with the standard dose showed significantly worse side effects after 24 wk than at baseline.

Conclusions and clinical implications: A reduced dose of enzalutamide results in less fatigue, cognitive side effects, and depressive symptoms in frail patients with prostate cancer than the standard dose, without any indication of interference with efficacy endpoints.

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Patient summary: In this report, we looked at the side effects of enzalutamide at two dose levels. We found that, in frail patients, three tablets a day result in less fatigue than four tablets a day. Patients treated with four tablets a day showed an increase in fatigue, cognitive side effects, and depression. We conclude that a lower dose of three tablets can be used to alleviate side effects without indications for less efficacy.

1. Introduction

The availability of androgen receptor (AR) signalling inhibitors (ARSIs) has dramatically improved progression-free survival (PFS) of patients with prostate cancer. Enzalutamide is an ARSI and is registered for patients with metastatic and nonmetastatic castration-resistant prostate cancer (CRPC) and metastatic hormone-sensitive prostate cancer (mHSPC) [1–5].

Although enzalutamide is generally well tolerated, there are several frequently observed side effects that may significantly impact patients' quality of life [6–8]. The most notorious side effects are associated with the central nervous system, including fatigue, cognitive impairment, and depressive symptoms [8–11]. Fatigue is the most frequently observed side effect, reported by around 35% of patients in pivotal trials [2,12]. Particularly the elderly treated with enzalutamide showed deterioration in physical and functional well-being. Among the elderly, 23% require a dose reduction due to fatigue, cognitive dysfunction, or falls [8,13].

Fatigue is considered to be a dose-dependent side effect of enzalutamide. In the dose escalation study, increasing proportions of patients required dose reductions due to grade 3 fatigue at doses of ≥240 mg. Consequently, the registered dose of enzalutamide is 160 mg once daily (OD) [14]. However, this dose resulted only in marginally higher prostate-specific antigen (PSA) responses compared with the lower dose of 60 mg OD. Furthermore, the AR was already saturated at plasma concentrations of >5.0 mg/l, which is presumed to be reached at doses >80 mg [14]. Moreover, no exposure-response relationship for enzalutamide has been observed in patients treated with 160 mg OD, suggesting that a lower dose could achieve comparable efficacy [15].

Taking into account that AR saturation is already reached at dosages above 80 mg and that fatigue is a dose-dependent side effect, the efficacy-safety balance of enzalutamide might be improved by using a reduced dose, especially in frail patients.

The aim of this randomised controlled trial was to examine the differences in fatigue, cognitive side effects, and depressive symptoms between a lower dose of enzalutamide (120 mg OD) and the standard dose of enzalutamide (160 mg OD) in frail patients with prostate cancer.

2. Patients and methods

2.1. Study design

This was an open-label, randomised clinical trial (NCT03927391) comparing a reduced dose of enzalutamide (120 mg OD) with its standard dose (160 mg OD) in frail patients with prostate cancer. Patients who started with enzalutamide according to the drug label were eligible for inclusion. Frail was defined as ≤14 points on the comprehensive Geriatric 8 (G8) assessment scale and one or more adverse event of the central nervous disorders according to the Common Toxicity Criteria Adverse Events criteria, version 4.0 [16,17].

Patients were randomised 1:1 between the reduced and standard doses, stratified according to age (<75 and ≥75 yr). Written informed consent was obtained prior to study enrolment. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and approved by the medical ethical committee.

During the 6-mo study period, patients visited the clinic four times: at baseline before start of enzalutamide treatment, and after 6, 12, and 24 wk of treatment. Patients who dropped out before the first on-treatment evaluation after 6 wk were ineligible for the analysis of the primary endpoint and were replaced. After study termination, patients continued therapy according to standard patient care. Further study details are included in the Supplementary material.

2.2. Endpoints and assessments

The primary endpoint was the difference in fatigue between both dose groups, as measured by the Functional Assessment of Chronic Illness Therapy—Fatigue Scale (FACIT-Fatigue) version 4 [18]. The secondary endpoints included changes in fatigue over time within patients, differences between both dose groups, and changes over time in experienced cognitive side effects and depressive symptoms in patients, as measured by the Functional Assessment of Cancer Therapy—Cognitive Function (FACT-Cog) version 3 and Geriatric Depression Scale—Short Form (GDS-15) [19,20]. Higher scores represent fewer symptoms for the FACIT-Fatigue and FACT-Cog, whilst they represent more symptoms for the GDS-15. The minimum clinically important difference (MCID) was set at 3.0 for the FACIT-Fatigue, 7.0 for the FACT-Cog, and 2.0 for the GDS-15, based on previous studies [21–26].

The sum C_{trough} level of enzalutamide and NDME was measured with a validated bioanalytical method [15,27]. If patients in either dose group had an enzalutamide exposure below the minimal exposure to reach AR saturation of 5.0 mg/l, the dose was increased to reach therapeutic exposure [14].

Exploratory endpoints for treatment efficacy included PSA response (≥50% decrease from baseline), PFS, and over-

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all survival (OS). PFS and OS were defined as the time from randomisation to disease progression or death from any cause, and to death from any cause, respectively. Disease progression was defined as radiographic, scintigraphic, clinical, and/or biochemical progression, as assessed by the treating physician.

2.3. Statistical analysis

Analyses were performed based on the allocated dose group, regardless of dose modifications during treatment.

Linear mixed-effect model analyses were performed to study the differences in side effects over time. Regression coefficients (β) and corresponding 95% confidence intervals (CIs) were presented, indicating the difference in side effects between and within dose groups over time.

Proportions of patients with a decrease in the FACIT-Fatigue, FACT-Cog, or GDS-15 score larger than the MCID were compared.

Linear mixed-effect model analyses were also performed to study the association between exposure and side effects. Treatment efficacy was explored with an intention-to-treat analysis for CRPC and mHSPC patients separately.

All analyses were performed in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) with the package lme4 [28]. Alpha was set at 0.05.

3. Results

3.1. Patients

Between July 2019 and February 2023, 57 patients were enrolled in the study (Fig. 1). Twenty-eight patients were randomised to the standard dose, of whom 27 completed the first follow-up after 6 wk and were included in the primary analysis. One patient had progressive disease within 6 wk. Twenty-nine patients were randomised to the reduced dose, of whom 25 completed the first follow-up. One patient withdrew consent, one patient died due to progressive disease, one patient quit enzalutamide after a fall, and one patient quit due to severe fatigue. Baseline characteristics for the primary analysis are summarised in Table 1. Baseline characteristics for the intention-to-treat analysis are summarised in Supplementary Table 2. Forty-eight patients received enzalutamide for metastatic castration-resistant prostate cancer (mCRPC) versus four patients for mHSPC. The completion rates for the questionnaires were high throughout the study (median 96% and range 84–100%; Supplementary Table 3).

3.2. Side effects

3.2.1. Fatigue

Patients treated with the reduced dose of enzalutamide experienced less fatigue after 24 wk than patients with the standard dose (β, 6.2; 95% CI 1.4, 11.0; $p = 0.01$; Table 2 and Fig. 2A). This difference is larger than the MCID of 3.0.

Within the standard dose group, fatigue worsened significantly from baseline to 24 wk (β, –4.9; 95% CI –8.1, –1.7; $p = 0.004$), whilst no significant changes over time were found in the reduced dose group (after 24 wk β, 1.3; 95% CI –2.3, 5.0; $p = 0.48$; Table 3).

Twenty-one (78%) patients with the standard dose experienced a clinically relevant worsening of fatigue, compared with 14 (56%) patients with the reduced dose ($p = 0.09$; Supplementary Fig. 1A).

3.2.2. Cognitive side effects

Patients treated with the reduced dose reported fewer cognitive side effects than patients with the standard dose, although these differences were not statistically significant (β, 7.3; 95% CI –2.0, 17.0; $p = 0.13$; Table 2 and Fig. 2B).

Cognitive side effects increased significantly from baseline to 24 wk in the standard dose group (β, –10.0; 95% CI –16.0, –3.8; $p < 0.01$), whilst there was no change in the reduced dose group (after 24 wk: β, –2.9; 95% CI –9.6, 3.9; $p = 0.41$; Table 3).

Sixteen (64%) patients with the standard dose experienced a clinically relevant increase in cognitive side effects, compared with 13 (52%) patients with the reduced dose ($p = 0.39$; Supplementary Fig. 1B).

3.2.3. Depressive symptoms

No significant differences in depressive symptoms were observed between the dose groups (Table 2 and Fig. 2C).

Patients treated with the standard dose had more depressive symptoms at 24 wk than at baseline (β, 1.0; 95% CI 0.22, 1.8; $p = 0.01$), whilst depressive symptoms remained stable in patients with the reduced dose (after 24 wk: β, 0.3; 95% CI –0.6, 1.3; $p = 0.48$; Table 3).

Eleven (42%) patients with the standard dose experienced a clinically relevant increase in depressive symptoms, compared with nine (41%) patients with the reduced dose ($p = 0.92$; Supplementary Fig. 1C).

3.2.4. Exposure toxicity

During the study period, two patients with the standard dose and two with the reduced dose had a dose reduction to 120 and 80 mg, respectively, due to severe fatigue. All patients had enzalutamide exposures ≥5.0 mg/l; therefore, no dose increments were required.

The mean enzalutamide C_{trough} levels were 11 mg/l (range 7–17) for the standard dose and 8 mg/l (range 5–19) for the reduced dose. The mean sum C_{trough} levels of enzalutamide and NDME were 23 mg/l (range 16–31) for the standard dose and 17 mg/l (range 10–31) for the reduced dose. Higher sum C_{trough} levels were related with more fatigue, though this difference was not statistically significant ($p = 0.11$). No association was seen between the sum C_{trough} levels and FACT-Cog or GDS-15 (Supplementary Table 4).

3.3. Treatment efficacy

The proportion of mCRPC patients with a PSA response within 24 wk was 75% for the standard versus 78% for the reduced dose ($p = 0.82$; Supplementary Fig. 2A). All four mHSPC patients had a PSA response (Supplementary Fig. 2B).

The median duration of follow-up was 17.7 mo (range 5.2–43.4). At the time of the survival analysis, 37 (65%)

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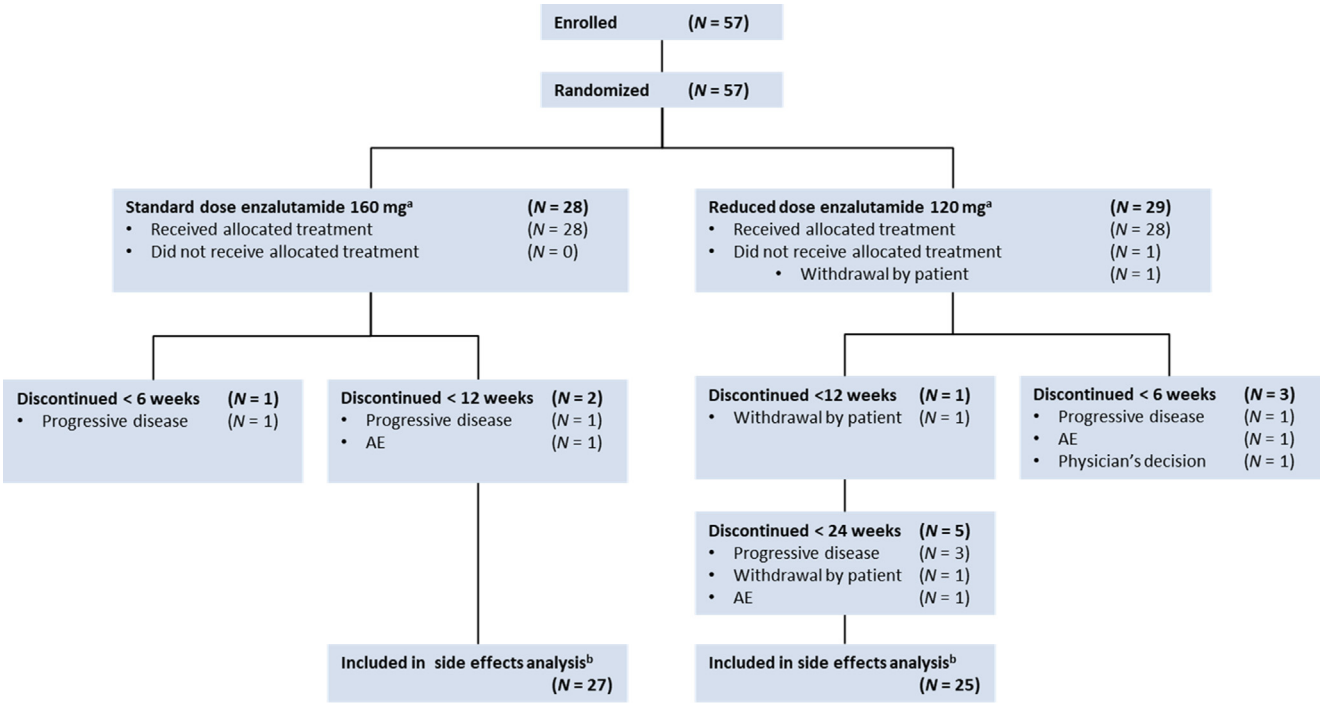

Fig. 1 – CONSORT diagram for patients enrolled in the study. AE = adverse event. [a] Patients included in the exploratory intention-to-treat analysis for efficacy. [b] Patients were excluded from the primary side effect analysis if they discontinued within <6 wk.

patients had progressive disease and 23 (40%) had died. The median PFS for patients with mCRPC was 22.8 mo (95% CI 9.5–not reached [NR]) for the standard dose versus 8.8 mo (95% CI 7.3–26.3) for the reduced dose (p = 0.14; Supplementary Fig. 3A). The median OS for patients with mCRPC was 31.4 mo (95% CI 17.9–NR) for the standard dose versus 34.0 mo (95% CI 16.0–NR) for the reduced dose (p = 0.97; Supplementary Fig. 3B).

4. Discussion

This study demonstrates that initiating enzalutamide treatment with a reduced dose of 120 mg OD results in less fatigue and fewer cognitive side effects in frail patients with prostate cancer. In contrast to patients treated with the reduced dose, patients with the standard dose experienced worsening of fatigue, reported more cognitive side effects, and experienced more depressive symptoms over time. Notably, although the study was not designed to assess noninferiority, no major differences were observed in PSA response rates or survival rates between both groups. These findings strongly suggest that lowering the starting dose of enzalutamide is a promising strategy to limit side effects in frail prostate cancer patients.

This study is the first prospective, randomised controlled trial showing that a reduced dose of enzalutamide can result in less fatigue and fewer cognitive side effects. In support of our findings, a retrospective study by Terada et al [29] showed a lower incidence of toxicities with a reduced dose versus the standard dose of enzalutamide. Our prospective study further strengthens the evidence that lower doses are associated with a reduced incidence of side effects.

In our study, patients treated with the standard dose showed worsening of fatigue over time, which was significant and clinically relevant after 24 wk of treatment. Many studies have shown that enzalutamide increases fatigue at the standard dose, which is consistent with our results [7,8,10,11]. Ternov et al [10] also found a similar decrease in the FACIT-Fatigue score after 12 wk of treatment, corresponding to more fatigue with the standard dose. This estimated difference was significant in contrast to our observation, potentially due to a larger sample size.

In patients treated with the standard dose, deterioration in self-reported cognitive side effects was seen. This is in line with the AQUARiUS study, which found worse self-reported cognitive functioning in patients treated with enzalutamide [11]. In contrast, Khalaf et al [8] and Alibhai et al [30] did not find changes in objective cognitive performance in patients treated with enzalutamide. Both trials used the Montreal Cognitive Assessment (MoCA) test to measure cognitive performance, whilst the AQUARiUS and our study used the FACT-Cog [11]. The FACT-Cog focuses on perceived cognitive function rather than cognitive performance as such. Moreover, the FACT-Cog questionnaire is designed for cancer patients, possibly making it more sensitive for our population than the MoCA that was developed to diagnose mild cognitive impairment due to neurodegenerative disease in elderly.

Several studies have established that abiraterone acetate outperforms enzalutamide in terms of fatigue, cognitive function, and quality of life [8,10,11]. The large majority of patients in these studies was treated with the standard dose

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Table 1 – Baseline characteristics[a]

	Standard dose (*N* = 27)	Reduced dose (*N* = 25)
Age (yr)	80 (68–88)	80 (69–90)
BMI (kg/m^2)	26.2 (20.0–36.3)	28.4 (22.7–37.9)
PSA (ng/ml)	39.0 (0.4–750)	73.7 (4.3–323)
Alkaline phosphatase (U/l)	94 (55–679)	99 (49–538)
Haemoglobin (mmol/l)	8.1 (5.8–9.2)	8.0 (6.7–9.0)
Haemoglobin (g/l)	13.1 (9.4–14.8)	12.9 (10.8–14.5)
Albumin (g/l)	38 (32–50)	42 (33–46)
ECOG performance status		
0–1	21 (78)	22 (88)
2	5 (18)	2 (8)
Missing	1 (4)	1 (4)
Gleason score at diagnosis		
≤7	10 (37)	11 (44)
≥8	15 (56)	12 (48)
Missing	2 (7)	2 (8)
Disease status		
CRPC	24 (89)	24 (96)
HSPC	3 (11)	1 (4)
Metastatic spread at baseline		
Bone	18 (67)	18 (72)
Lymph node	14 (52)	12 (48)
Visceral	4 (15)	2 (8)
Previous lines of systemic therapy		
0	11 (41)	17 (68)
1	13 (48)	7 (28)
≥2	3 (11)	1 (4)
Pain score at baseline		
0 (asymptomatic)	14 (52)	15 (60)
≥1 (symptomatic)	6 (22)	8 (32)
Missing	7 (26)	2 (8)

BMI = body mass index; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; HSPC = hormone-sensitive prostate cancer; PSA = prostate specific antigen.

[a] Data are presented as median (range) for continuous data or *n* (%) for categorical data.

of enzalutamide [8,10,11]. Our findings suggest that a lower dose of enzalutamide reduces side effects, and may consequently alter the outcome of a comparison between abiraterone acetate and enzalutamide in terms of quality of life, which needs to be confirmed.

In our study, we did not observe any indication of reduced treatment efficacy when comparing a lower dose of enzalutamide with the standard dose. All patients reached a therapeutic exposure of >5.0 mg/l enzalutamide throughout the study, which is related to complete AR saturation [14]. Although the study was not powered to establish noninferiority in terms of efficacy, the results are promising. Similar findings were reported by Vinh-Hung et al [31,32] in their retrospective evaluation of lower enzalutamide doses (≤80 mg OD). They found no significant differences in response rates, duration of response, PFS, and OS between the dosing groups. Furthermore, a retrospective analysis compared the efficacy and tolerability of abiraterone acetate versus enzalutamide in elderly patients with mCRPC [13]. Enzalutamide was associated with higher PSA response rates and longer PFS than abiraterone acetate, despite more dose reductions and a higher treatment discontinuation rate. In conclusion, our results and previous studies indicate that a reduced dose of enzalutamide does not interfere with efficacy [13,31].

Our study has some limitations. The open-label design might cause a bias. Since patients are aware of the dose, this could interfere with the outcomes of the questionnaires. Moreover, the FACIT-Fatigue, FACT-Cog, and GDS-15 are self-report questionnaires where the outcomes can be influenced by several aspects such as comorbidities, comedication, and pain. However, these questionnaires have been validated for use in clinical trials. In addition, the exclusion criteria of our study minimise the influence of these aspects since patients with neurological conditions or medication that affect cognition or fatigue were excluded.

The outcomes of this study are highly relevant for a number of reasons. Enzalutamide is a widely prescribed drug for one of the most diagnosed cancers worldwide. The use of a reduced dose can therefore reduce the financial toxicity of this treatment. Moreover, patients with prostate cancer are generally older and have multiple comorbidities, whilst frail patients are under-represented in pivotal trials [33]. These frail patients are at a higher risk for side effects and are suspected to have less or slower recovery from side effects [6]. Preventing side effects by starting with a reduced dose is therefore preferred over reducing the dose once side effects have occurred.

Finally, side effects of anticancer drugs are one of the biggest concerns of patients diagnosed with cancer, as these side effects can greatly impact the well-being and overall quality of life [34,35]. Our analysis shows that a reduced dose can decrease fatigue, self-reported cognitive side effects, and depressive symptoms, and thereby might enhance the quality of life for frail patients with prostate cancer.

Table 2 – Estimated difference in side effect score between the reduced dose group and the standard dose group per time point[a]

Time on therapy	6 wk		12 wk		24 wk	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
FACIT-Fatigue	2.2 (−2.3, 6.6)	0.356	3.3 (−1.3, 7.9)	0.171	6.2 (1.4, 11.0)	0.015 *
FACT-Cog	4.2 (−4.5, 13.0)	0.356	3.4 (−5.4, 12.0)	0.458	7.3 (−2.0, 17.0)	0.132
GDS-15	−0.2 (−1.3, 0.9)	0.779	0.20 (−0.9, 1.3)	0.735	−0.7 (−1.9, 0.5)	0.285

FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy—Fatigue; FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; GDS-15 = Geriatric Depression Scale–15.

[a] Higher scores represent less fatigue and fewer cognitive side effects for FACIT-Fatigue and FACT-Cog, whilst these represent more depressive symptoms for GDS-15.

* $p < 0.05$.

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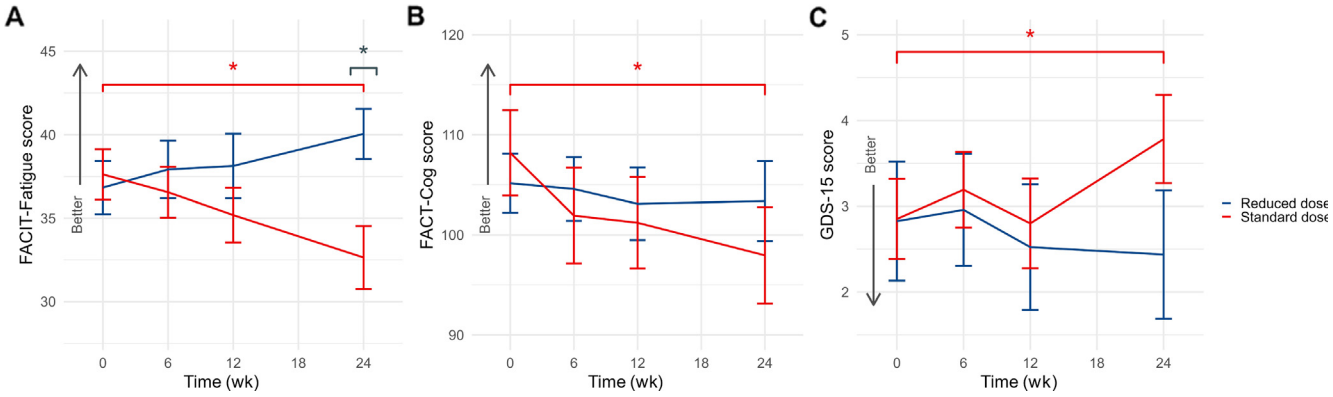

Fig. 2 – Estimated side effect score for (A) fatigue measured by the FACIT-Fatigue, (B) self-reported cognitive side effects measured by the FACT-Cog, and (C) depressive symptoms measured by the GDS-15. Data are expressed as estimated mean ± standard error. Black * represents significant ($p < 0.05$) difference between dose groups. Red * represents significant change ($p < 0.05$) within the standard dose group after 24 wk compared with baseline. FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy—Fatigue; FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; GDS-15 = Geriatric Depression Scale—15.

Table 3 – Estimated change in side effect score compared with baseline per time point within each dosing group[a]

Time on therapy		6 wk		12 wk		24 wk	
		β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
FACIT-Fatigue	Standard dose	−1.1 (−4.2, 2.0)	0.51	−2.3 (−5.5, 0.9)	0.17	−4.9 (−8.1, −1.7)	<0.01 *
	Reduced dose	1.1 (−2.2, 4.3)	0.52	1.0 (−2.3, 4.3)	0.57	1.3 (−2.3, 5.0)	0.48
FACT-Cog	Standard dose	−5.8 (−12.0, 0.3)	0.07	−5.8 (−12.0, 0.4)	0.08	−10.0 (−16.0, −3.8)	<0.01 *
	Reduced dose	−1.6 (−7.8, 4.7)	0.63	−2.4 (−8.7, 3.9)	0.47	−2.9 (−9.6, 3.9)	0.41
GDS-15	Standard dose	0.3 (−0.4, 1.1)	0.42	0.0 (−0.8, 0.8)	0.98	1.0 (0.2, 1.8)	0.01 *
	Reduced dose	0.2 (−0.7, 1.0)	0.71	0.2 (−0.7, 1.0)	0.66	0.3 (−0.6, 1.3)	0.48

FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy—Fatigue; FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; GDS-15 = Geriatric Depression Scale–15.

[a] Increasing scores represent less fatigue and fewer cognitive side effects for FACIT-Fatigue and FACT-Cog, whilst these represent more depressive symptoms with GDS-15.

* $p < 0.05$.

5. Conclusions

A reduced dose of enzalutamide results in less fatigue in frail patients with prostate cancer than the standard dose. Cognitive side effects and depressive symptoms increase in patients treated with the standard dose, whilst these remain stable in patients treated with the reduced dose. Starting with a reduced dose of enzalutamide in frail patients with prostate cancer is associated with fewer side effects, without any indication of interference with efficacy endpoints, and should therefore be considered for frail patients.

***Author contributions*:** Nielka P. van Erp 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: Boerrigter, Benoist, Kessels, Mehra, van Oort, van Erp.
Acquisition of data: Somford, Hamberg, Tol, Scholtes, Willemsen, Mehra, van Oort.
Analysis and interpretation of data: Boerrigter, Overbeek, Buffart.
Drafting of the manuscript: Boerrigter, Overbeek.
Critical revision of the manuscript for important intellectual content: Benoist, Somford, Hamberg, Tol, Scholtes, Willemsen, Buffart, Kessels, Mehra, van Oort, van Erp.
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Appendix A. Supplementary data

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