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Long-term Safety and Antitumor Activity in the Phase 1–2 Study of Enzalutamide in Pre- and Post-docetaxel Castration-Resistant Prostate Cancer

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Abstract

Background: Given that some patients with castration-resistant prostate cancer (CRPC) have shown extended responses to the androgen receptor inhibitor enzalutamide, long-term safety of this drug is of interest.
Objective: To evaluate the long-term safety and antitumor activity of enzalutamide in CRPC patients.
Design, setting, and participants: This phase 1–2 study evaluated enzalutamide in 140 CRPC patients with and without prior chemotherapy. Initial findings were published in 2010. We report updated results from an additional 17-mo follow-up for antitumor activity and >4 yr for safety.
Intervention: Patients received 30–600 mg/d oral enzalutamide. During long-term dosing, all patients were switched first to the maximum tolerated dose of 240 mg/d and then to the phase 3 dose of 160 mg/d.
Outcome measurements and statistical analysis: Safety was assessed regularly. The Kaplan-Meier method was used to estimate the distributions of time to prostate-specific antigen (PSA) progression and time to radiographic progression.
Results and limitations: The safety profile of enzalutamide was consistent over time, with little change in the rates of commonly reported adverse events (AEs) or the incidence of grade 3/4 AEs. Fatigue of any grade was the most common dose-dependent AE, experienced by 70% of patients, with 14% of patients reporting grade 3/4 fatigue. The median time to PSA progression was not reached for chemotherapy-naive patients and was 45 wk for postchemotherapy patients; the corresponding median time to radiographic progression was 56 wk and 25 wk.
Conclusions: Enzalutamide showed durable antitumor activity in chemotherapy-naive and postchemotherapy patients, and was well tolerated, even in patients treated for 4 yr.
Patient summary: Enzalutamide was active against prostate cancer and was well tolerated, even for up to 4 yr of treatment, supporting its potential for long-term use in men with prostate cancer. Fatigue was the most common side effect, occurring at varying degrees of severity in most patients.

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1. Introduction

Prostate cancer growth is dependent on androgen receptor (AR) signaling. Initial hormonal treatment strategies include depletion of testosterone and inhibition of AR signaling [1]. The response can be dramatic, but virtually all patients progress to a castration-resistant prostate cancer (CRPC) state over time [2]. It is now recognized that tumor growth and progression in the CRPC state remain dependent on AR signaling [3]. Enzalutamide (formerly MDV3100) is an orally administered AR inhibitor that acts on multiple steps in the AR signaling pathway [4]. In phase 3 trials, enzalutamide had overall survival and radiographic progression-free survival benefits in patients with metastatic CRPC both before and after docetaxel treatment [5,6].

The first clinical trial of enzalutamide was an open-label, phase 1–2 dose-escalation study (NCT00510718) assessing the safety, pharmacokinetics (PK), and antitumor activity of enzalutamide in CRPC patients, both with and without prior exposure to chemotherapy [7]. The doses tested ranged from 30 to 600 mg/d. The maximum tolerated dose (MTD) of enzalutamide was identified as 240 mg/d. Full evaluation of the antitumor activity and safety data led to selection of 160 mg/d as the dose for evaluation in phase 3 registration studies, and this is now the approved dose. The most common grade 3/4 adverse event (AE) in the phase 1–2 trial was fatigue, which was more common at doses ≥240 mg/d and generally resolved after dose reduction. Antitumor effects, including prostate-specific antigen (PSA) declines, regression of soft-tissue disease, stabilization of bone disease, and conversion from unfavorable to favorable circulating tumor cell counts, were found at all doses studied [7].

Here we present the results of the final efficacy analysis conducted in September 2010, 17 mo after the initial data cutoff date, and of a long-term safety analysis conducted in September 2013, nearly 4.5 yr after the cutoff date for the initial study report [7].

2. Patients and methods

The complete study design and methods were published previously [7]. Patients had histologically confirmed prostate cancer, castrate levels of testosterone (<1.7 nmol/l), and increasing PSA levels (minimum of three measurements more than 2 wk apart showing ≥50% increase, with the last value >2 ng/ml). Institutional review board approval and written informed consent from patients were obtained before commencement of any study-related activities. The study was conducted in compliance with the Declaration of Helsinki and its later revisions and all International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice Guidelines. Patients were enrolled from July 2007 to December 2008.

Patients received oral enzalutamide starting at 30 mg/d, with sequential escalations in cohorts of three to six patients to the following dose levels: 60, 150, 240, 360, 480, and 600 mg/d. After confirming dose tolerability, 24 patients were included per dose level (12 chemotherapy-naive and 12 postchemotherapy) at doses ≥60 mg/d, except for 480 and 600 mg/d, for which only postchemotherapy (docetaxel) patients were enrolled.

The study consisted of four periods: single-dose, multiple-dose, long-term dosing, and safety follow-up periods. All patients received a single dose of enzalutamide and were then followed for 6 d (single-dose period). Those not experiencing dose-limiting toxicity (DLT) then entered the multiple-dose period, in which they received the same dose as previously, once daily for 84 d. Patients completing the multiple-dose period entered the long-term dosing period and continued to receive the same dose taken in the multiple-dose period. When patients discontinued treatment for any reason, they entered the 30-d safety follow-up period.

All patients in the long-term dosing period were switched to the 240-mg/d dose in January 2009 after it was determined to be the MTD, and to 160 mg/d in September 2009 after 160 mg/d was determined to be the dose for phase 3 investigation based on the updated risk-benefit analysis [7]. During the long-term dosing period, safety was assessed every 28 d for the first 3 mo and every 12 wk thereafter via a physical examination and evaluation of vital signs, AEs, 12-lead electrocardiogram, and clinical laboratory tests. PSA levels were evaluated every 28 d for the first 3 mo and then every 12 wk thereafter; bone scans and imaging studies (computerized tomography or magnetic resonance imaging) were evaluated every 12 wk. Overall survival was not assessed as a study endpoint.

2.1. Statistical analyses

All analyses were based on the total study population ($n = 140$); complete statistical methods were published previously [7]. Safety data were analyzed using descriptive statistics. The Kaplan-Meier method was used to estimate distributions of time to PSA progression and time to radiographic progression. PSA progression was defined in the protocol as a ≥25% increase in PSA level from baseline that represented a ≥5 ng/ml increase. An exploratory analysis of PSA progression was undertaken for patients stratified by prior ketoconazole use and chemotherapy exposure.

The initial analysis of this study used a data cutoff of April 1, 2009 [7]. The final analysis of antitumor activity reported here was conducted in September 2010 with the exception of the time to radiographic progression, which was based on data collected up to December 2010. Safety data for patients still receiving the study drug at the September 2010 cutoff were collected through September 2013 and contributed to the long-term safety analysis.

3. Results

3.1. Patients

A total of 140 patients were enrolled: 65 chemotherapy-naive and 75 postchemotherapy patients. Demographic and other baseline disease characteristics are presented in Table 1. The median age was 68 yr (range 44–93 yr). At initial screening, 15% of chemotherapy-naive patients and 24% of postchemotherapy patients had disease progression according to Response Evaluation Criteria for Solid Tumors (RECIST), while approximately 90% of both groups had PSA progression.

At the time of the final analysis of antitumor activity in September 2010, 19 of 140 patients (14%)—including 17 of the 65 patients (26%) in the chemotherapy-naive subgroup—remained on treatment. The remaining 121 patients (86%) discontinued the trial for the following reasons in the chemotherapy-naive and postchemotherapy subgroups, respectively: radiographic progression, 29 (45%) and 25 (33%) patients; PSA progression, 6 (9%) and 14 (19%) patients; clinical progression, 4 (6%) and 12 (16%) patients;

Table 1 – Demographic and other baseline patient characteristics

Characteristic	Chemotherapy-naive (*n* = 65)	Postchemotherapy (*n* = 75)	Total (*n* = 140)
Median age, yr (range)	68 (44–93)	68 (51–85)	68 (44–93)
Median PSA, ng/ml (range)	35 (1.7–334.7)	64 (1.9–2158.8)	49 (1.7–2158.8)
Disease progression at screening, *n* (%)			
Disease progression by RECIST	10 (15)	18 (24)	28 (20)
PSA progression	61 (94)	68 (90)	129 (92)
Number of hormonal medications, *n* (%)			
1	2 (3.1)	5 (6.7)	7 (5.0)
2	13 (20)	20 (27)	33 (24)
≥3	50 (77)	50 (67)	100 (71)
Number of previous chemotherapy regimens, *n* (%)			
0	60 (92)	0	60 (43)
1	4 (6.2) [a]	59 (79)	63 (45)
2	1 (1.5) [a]	16 (21)	17 (12)
Bone disease at screening, *n* (%)	31 (48)	42 (56)	73 (52)
Soft-tissue disease at screening, *n* (%)	37 (57)	55 (73)	92 (66)
Lymph node only	0	1 (1.3)	1 (0.7)
Lymph node and bone	1 (1.5)	11 (15)	12 (8.6)
Visceral only	18 (28)	3 (4.0)	21 (15)
Visceral and bone	17 (26)	36 (48)	53 (38)
Other only	0	3 (4.0)	3 (2.1)
Other and bone	1 (1.5)	1 (1.3)	2 (1.4)

PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria for Solid Tumors.
[a] Includes patients who were not on chemotherapy long enough to become resistant.

Table 2 – Treatment-emergent adverse events

	Patients reporting AE, *n* (%)		
	Chemotherapy-naive (*n* = 65)	Postchemotherapy (*n* = 75)	Total (*n* = 140)
Any treatment-emergent AE	64 (99)	74 (99)	138 (99)
Common treatment-emergent AEs [a]			
Fatigue	47 (72)	51 (68)	98 (70)
Nausea	20 (31)	36 (48)	56 (40)
Constipation	18 (28)	27 (36)	45 (32)
Back pain	16 (25)	26 (35)	42 (30)
Arthralgia	22 (34)	19 (25)	41 (29)
Dyspnea	22 (34)	14 (19)	36 (26)
Diarrhea	15 (23)	19 (25)	34 (24)
Pain in extremity	14 (22)	19 (25)	33 (24)
Anorexia	15 (23)	17 (23)	32 (23)
Dizziness	15 (23)	15 (20)	30 (21)
Peripheral edema	18 (28)	11 (15)	29 (21)

AE = adverse event.
[a] Reported in at least 20% of patients in the total population at the time of the final study analysis conducted in September 2010; events are sorted by decreasing frequency in the Total column.

AE, 4 (6%) and 11 (15%) patients; and other reasons, including withdrawn consent, 5 (8%) and 11 (15%) patients.

At the updated analysis of antitumor activity in September 2010, the median time on study treatment for the full population was 51.3 wk (interquartile range [IQR] 16.1–111.3 wk) in the chemotherapy-naive subgroup and 16.5 wk (IQR 9.1–30.9 wk) in the postchemotherapy subgroup. An additional long-term safety analysis was performed with a cutoff date of September 2013 to collect AE data for the 19 patients with extended dosing.

3.2. Safety

At least one treatment-emergent AE was reported by 138 (99%) of the 140 patients (Table 2) according to the assessment in September 2010. The most common AEs included fatigue (70%), nausea (40%), constipation (32%), back pain (30%), arthralgia (29%), dyspnea (26%), diarrhea (24%), pain in an extremity (24%), anorexia (23%), dizziness (21%), and peripheral edema (21%). Some differences were noted in the AE profiles for chemotherapy-naive and postchemotherapy patients, with nausea, constipation, and back pain more common in the postchemotherapy setting.

At least one grade 3/4 AE was reported by 70 patients (50%) at a similar frequency in the chemotherapy-naive and postchemotherapy subgroups (Table 3). Fatigue was the most common grade 3/4 AE (19 patients, 14%), and occurred at an increasing frequency as the administered dose was increased: no patients at 30 or 60 mg/d, 2% of patients at

Table 3 – Grade 3/4 adverse events and adverse events resulting in discontinuation of the study drug

	Patients reporting an AE, *n* (%)			
	Final study analysis [a]			Long-term safety [b]
	Chemotherapy-naive (*n* = 65)	Postchemotherapy (*n* = 75)	Total (*n* = 140)	(*n* = 140)
Any grade 3/4 AE [c]	29 (45)	41 (55)	70 (50)	73 (52)
Fatigue	10 (15)	9 (12)	19 (14)	19 (14)
Anemia	1 (1.5)	6 (8.0)	7 (5.0)	7 (5.0)
Back pain	1 (1.5)	6 (8.0)	7 (5.0)	7 (5.0)
Spinal cord compression	1 (1.5)	2 (2.7)	3 (2.1)	5 (3.6)
Arthralgia	2 (3.1)	1 (1.3)	3 (2.1)	3 (2.1)
Asthenia	1 (1.5)	2 (2.7)	3 (2.1)	3 (2.1)
Constipation	2 (3.1)	1 (1.3)	3 (2.1)	3 (2.1)
Convulsion (seizure)	0	3 (4.0)	3 (2.1)	3 (2.1)
Dizziness	2 (3.1)	1 (1.3)	3 (2.1)	3 (2.1)
Prolonged QT corrected interval on ECG	2 (3.1)	1 (1.3)	3 (2.1)	3 (2.1)
Syncope	0	0	0	3 (2.1)
Any AE resulting in discontinuation [c]	6 (9.2)	16 (21)	22 (16)	23 (16)
Fatigue	2 (3.1)	2 (2.7)	4 (2.9)	4 (2.9)
Convulsion (seizure)	0	3 (4.0)	3 (2.1)	3 (2.1)
Spinal cord compression	1 (1.5)	2 (2.7)	3 (2.1)	3 (2.1)

AE = adverse event; ECG = electrocardiogram.
[a] Based on the final study analysis conducted in September 2010.
[b] Based on the long-term safety analysis conducted in September 2013 that included AE data collected for the 19 patients still being treated at the September 2010 analysis.
[c] AEs were graded according to National Cancer Institute Common Terminology Criteria for AEs, version 3.0. Events listed are those reported by more than two patients in the total population.

150 or 160 mg/d, 10% at 240 mg/d, and approximately 20% of patients at 360 and 480 mg/d. Reports of any grade 3/4 AEs were more common among postchemotherapy patients, as were reports of anemia, back pain, and seizure.

At the time of the September 2010 analysis, no deaths had been reported. Serious treatment-emergent AEs were reported by 36 patients (26%). Twenty-two patients (16%) reported AEs leading to study drug discontinuation; those that occurred in more than one patient included fatigue (*n* = 4), convulsion/seizure (*n* = 3, all in the postchemotherapy subgroup at doses ≥360 mg/d), spinal cord compression (*n* = 3), nerve root compression (*n* = 2), and rash (*n* = 2). As previously reported [7], seizure and rash were DLTs identified during the initial dose escalation and expansion phase of the trial. Hypertension was reported as any grade in 10 (7%) patients and as grade 3 in 1 (0.7%) patient. No falls were reported.

3.2.1. *Safety with extended dosing*

There was little change in the overall safety profile with the additional 3 yr of safety follow-up compared with what was previously reported (Table 3). Three patients who had not previously reported grade 3/4 AEs did so during the safety follow-up period; this included two cases of spinal cord compression. Syncope, which had not been previously reported as a grade 3/4 AE, was reported by three patients during the safety follow-up period. None of the events of syncope led to study drug discontinuation. No seizures, grade 3/4 hypertension, or falls were reported during the safety follow-up period, and only one patient reported an AE (lacunar infarction) resulting in study drug discontinuation during this time.

3.2.2. *Safety by duration of treatment*

AEs judged as related to the study drug were evaluated at three time points: within 2, 3, and 4 yr of the patient's first dose (Table 4). A total of 24, 15, and 12 patients remained on treatment at each of these landmark time points, contributing additional safety data during this period.

There was little or no change in the frequency of the most common AEs considered to be related to the study drug during the additional safety follow-up (Table 4). New study drug–related AEs (ie, new terms not previously reported in the study and judged by the investigator as possibly related to the study drug that were captured by extending the analysis window to include 3 and 4 yr of dosing) included dental discomfort, diverticular intestinal hemorrhage, heart rate irregularity, muscle atrophy, clumsiness, incontinence, night sweats, and Schamberg's disease. Of these, only night sweats (*n* = 2) were reported by more than one patient.

3.3. *Anti-tumor activity*

The majority of patients, irrespective of prior chemotherapy exposure, showed substantial decreases in PSA as assessed by the maximum decline in PSA at any point during treatment (Table 5). Overall, 79 patients (57%), comprising 40 (63%) chemotherapy-naive and 39 (53%) postchemotherapy patients, had a ≥50% decrease in PSA levels relative to baseline, while 31 patients (23%), comprising 22 (34%) chemotherapy-naive and 9 (12%) postchemotherapy patients, had a PSA decrease ≥90%.

At the time of the final antitumor activity analysis, a total of 42 patients (30%), comprising 16 (25%) chemotherapy-naive and 26 (35%) postchemotherapy patients, had

Table 4 – Adverse events related to the study drug reported within 2, 3, and 4 yr of the patient's first dose

	Patients reporting drug-related AEs, *n* (%)		
	Within 2 yr of first dose [a]	Within 3 yr of first dose [b]	Within 4 yr of first dose [c]
Any drug-related AE [d]	120 (86)	121 (86)	121 (86)
Fatigue	80 (57)	82 (59)	82 (59)
Nausea	45 (32)	46 (33)	46 (33)
Anorexia	21 (15)	21 (15)	21 (15)
Dysgeusia	19 (14)	19 (14)	19 (14)
Hot flush	19 (14)	20 (14)	20 (14)
Dizziness	18 (13)	19 (14)	19 (14)
Diarrhea	12 (8.6)	13 (9.3)	15 (11)

AE = adverse event.
[a] 24 patients remaining in the study.
[b] 15 patients remaining in the study.
[c] 12 patients remaining in the study.
[d] Events listed are those reported by ≥10% of patients for at least one time point.

Table 5 – Prostate-specific antigen (PSA) response, time to PSA progression, and time to radiographic progression

Efficacy endpoint [a]	Chemotherapy-naive (*n* = 65)	Postchemotherapy (*n* = 75)	Total (*n* = 140)
PSA at baseline and at least one further time point (*n*)	64	74	138
Reduction in PSA response from baseline, *n* (%)[b]			
≥50% reduction	40 (63)	39 (53)	79 (57)
≥90% reduction	22 (34)	9 (12)	31 (23)
Time to PSA progression (wk) [c]			
Median	Not reached	45.1	106.1
95% confidence interval	106–NA	33–85	82–NA
Time to radiographic progression (wk)			
Median	56	25	36
95% confidence interval	25–95	12–46	23–59

NA = not applicable.
[a] PSA response and time to PSA progression were based on the final study analysis conducted in September 2010; time to radiographic progression was based on data collected up to December 2010.
[b] Percentages were based on patients with PSA values at baseline and at least one further time point.
[c] PSA progression was defined as a ≥25% increase in PSA level from baseline that represented a ≥5-ng/ml increase. A second confirmatory PSA measurement meeting the above criterion was also required.

experienced PSA progression, defined in the protocol as an increase in PSA of ≥25% over the baseline value, provided that the 25% rise also represented an absolute PSA increase of ≥5 ng/ml. The median time to PSA progression had not been reached in the chemotherapy-naive subgroup and was 45.1 wk in the postchemotherapy subgroup (Fig. 1A). The median time to radiographic progression was 56.3 wk for chemotherapy-naive patients and 24.7 wk for postchemotherapy patients (Fig. 1B).

3.3.1. *Ketoconazole exposure*

An exploratory analysis of time to PSA progression according to prior ketoconazole exposure was also undertaken at the final antitumor activity assessment in September 2010. A similar proportion of chemotherapy-naive patients (31 patients; 48%) and postchemotherapy patients (35 patients; 47%) had received previous ketoconazole therapy. In this analysis, the median time to PSA progression was substantially longer for ketoconazole-naive patients than for those with prior ketoconazole exposure in both the chemotherapy-naive (not reached vs 97 wk) and postchemotherapy subgroups (78 vs 20 wk).

4. Discussion

This report provides an additional 17-mo follow-up for antitumor activity and >4 yr for safety for the initial phase 1–2 trial [7] that evaluated the safety, tolerability, PK, and antitumor activity of enzalutamide in men with CRPC. Our results show that enzalutamide continued to demonstrate durable antitumor activity and a favorable tolerability profile for the men who remained in the study. No new safety signals were detected with extended dosing. The results provide a unique insight into the long-term outcomes with enzalutamide because the follow-up periods exceed that of the completed phase 3 AFFIRM [5] and PREVAIL trials [6], although these trials enrolled a significantly greater number of patients. It is noteworthy that 31% of the chemotherapy-naive patients remained on enzalutamide therapy for >2 yr and 17% for >4 yr. This contrasts with the 2-yr on-treatment rate of 5% for postchemotherapy patients.

In further support of the durable antitumor activity of enzalutamide, 70% of patients had not experienced PSA progression at 2 yr, and for chemotherapy-naive patients

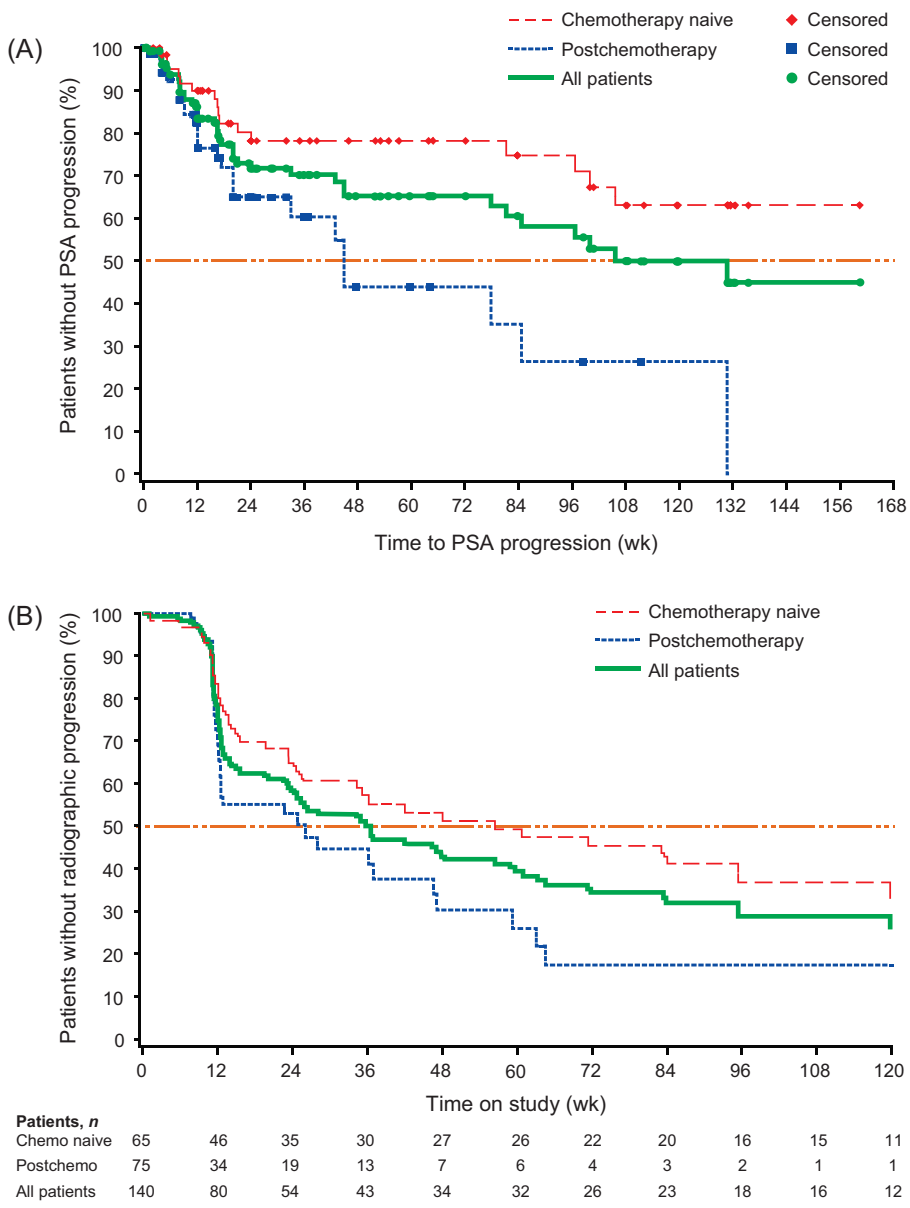

Fig. 1 – Time to (A) PSA progression and (B) radiographic progression. The dashed horizontal lines indicate median values. PSA = prostate-specific antigen.

the median time to PSA progression had not been reached and the median time to radiographic progression was more than 1 yr (56 wk). Importantly, patients who were both ketoconazole- and chemotherapy-naive experienced a longer duration of PSA response (median 1.9 yr to PSA progression). These results illustrate the possibility of extended disease control with enzalutamide treatment for a subset of patients, yet to be further characterized with any specific biomarker.

The most common AEs during extended dosing (all grades and grade 3/4) were similar to those previously reported [7]. Fatigue remained the most common dose-dependent AE, reported as any grade by 70% of patients and as grade 3/4 by 14% of patients across the 30–600-mg/d range. Fatigue was also the most common AE in the AFFIRM and PREVAIL trials, phase 3 studies conducted with the approved dose of 160 mg/d. These larger, randomized, double-blind, placebo-controlled studies provide a more thorough evaluation of the safety and tolerability of enzalutamide [5,6]. In particular, the rate of fatigue was 34% with enzalutamide and 29% with placebo in AFFIRM, and 36% with enzalutamide and 26% with placebo in PREVAIL.

The safety analyses described here provides evidence that enzalutamide remains well tolerated over extended use. During long-term follow-up, there was no meaningful change in the overall incidence of common AEs or grade 3/4 AEs, and only one of the 19 patients still being treated at the time of the final efficacy analysis in 2010 subsequently discontinued enzalutamide because of an AE. A safety analysis summarizing AEs occurring within 2, 3, or 4 yr after the patient's first dose showed little to no change in

frequency of the most common drug-related AEs over time, with few new AEs reported after 2 yr of treatment.

Limitations of the findings reported reflect both the study design, the heterogeneity of this early-phase study population, and the bias inherent in any long-term analysis. First, patients initially received a wide range of doses and were switched to a common dose at several time points during the study. Of particular note is that many patients received enzalutamide at a higher dose (up to 600 mg/d) than the currently approved dose (160 mg/d). Second, patients who remained on treatment at the time of the final analysis had already benefitted from and tolerated enzalutamide for at least 20 mo. Thus, the paucity of new events reported during long-term treatment is within a population of patients who had already demonstrated tolerability and prolonged benefit from enzalutamide. Even though no new safety signal was detected during long-term treatment in this study, clinicians should be mindful of the potential for late-occurring, initially subtle AEs such as bone loss and metabolic syndrome, which have been observed with other hormonal therapies.

5. Conclusions

Given that up to 26% of patients who have not previously been treated with chemotherapy may have very prolonged responses to enzalutamide, our results demonstrate that long-term exposure is feasible and is not associated with additional safety concerns.

Author contributions: Celestia S. Higano 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: Higano, Beer, Hirmand, Scher.
Acquisition of data: Higano, Beer, Taplin, Efstathiou, Scher.
Analysis and interpretation of data: Higano, Beer, Taplin, Efstathiou, Hirmand, Forer, Scher.
Drafting of the manuscript: Higano, Beer, Taplin, Efstathiou, Hirmand, Forer, Scher.
Critical revision of the manuscript for important intellectual content: Higano, Beer, Scher.
Statistical analysis: Forer.
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