Prostate Cancer

Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis

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Abstract

Background: The degree of antitumour activity of enzalutamide following disease progression on docetaxel and abiraterone remains controversial.

Objective: To examine the effect of enzalutamide in patients progressing following taxane-based chemotherapy and abiraterone.

Design, setting, and participants: Metastatic castration-resistant prostate cancer patients entering one of four European compassionate use programmes of enzalutamide.

Outcome measurements and statistical analysis: The primary end point was overall survival (OS). Secondary end points were association between OS and posttreatment prostate-specific antigen (PSA) kinetics, patient characteristics, and progression-free survival, respectively. Kaplan-Meier survival analysis and Cox proportional hazard analysis were performed.

Results and limitations: We identified 137 patients who prior to enzalutamide had progressed following a median of eight cycles of docetaxel and seven courses of abiraterone. The median time on enzalutamide was 3.2 mo; median OS from the time patients started enzalutamide was 8.3 mo (95% confidence interval, 6.8–9.8). Only 45 (38%) and 22 (18%) patients had PSA declines (unconfirmed) >30% and 50%, respectively. Patients who had more than 30% or 50% falls in PSA had improved survival compared with patients who had no such PSA fall (11.4 mo vs 7.1 mo; p = 0.001 and 12.6 vs 7.4 mo; p = 0.007, respectively). Poor performance status and low haemoglobin was negatively associated with OS.

Conclusions: Median OS on enzalutamide following disease progression on taxane-based chemotherapy and abiraterone was modest, but patients who experience a PSA decline >30% or 50%, respectively, with enzalutamide in this setting had longer survival.

Patient summary: Enzalutamide produces modest prostate-specific antigen (PSA) responses in patients progressing following chemotherapy and abiraterone. Despite a modest PSA response, survival may still be improved.

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1. Introduction

The introduction of new treatment options for patients who have metastatic castration-resistant prostate cancer (mCRPC) during the past decade has provided several effective new therapeutic strategies, including two different taxanes, a systemic alpha particle–emitting radionuclide, as well as two novel endocrine drugs and a vaccine [1–8]. Because docetaxel had been shown to prolong survival [1,2], first cabazitaxel [3] and more recently two new drugs—blocking androgen synthesis through CYP17 inhibition and the androgen receptor (AR), respectively—have been shown to further improve survival in mCRPC patients both before and after chemotherapy [5–8]. Abiraterone acetate, a selective CYP17A1 inhibitor, blocks the synthesis of androgenic steroids, causing effective systemic and intratumoural suppression of androgen production [9]. Enzalutamide is a second-generation antiandrogen that binds to and blocks the AR with higher affinity than previously available antiandrogens. Enzalutamide is also reported to inhibit AR nuclear translocation and binding of the AR complex to DNA [10]. Abiraterone and enzalutamide can prolong survival by 4.6 mo and 4.8 mo, respectively, and produce significant prostate-specific antigen (PSA) and objective responses in mCRPC patients progressing after docetaxel [6,11].

This increasing number of new therapies has resulted in a multiple unresolved issues regarding optimal timing, sequencing, possible combinations, drug-resistance mechanisms, and cost. Recently, PSA response and survival have been reported both in patients managed with abiraterone following progression on docetaxel and enzalutamide [12,13] and in patients managed with enzalutamide following docetaxel and abiraterone [14–17]. All publications involve small patient numbers and retrospective case series, and the all demonstrate modest PSA responses and median survival compared with the randomised, placebo-controlled COU-AA-301 and AFFIRM trials [6,11].

In this report, we present a pooled analysis of PSA response and survival from four independent European compassionate access programmes that provided enzalutamide as third-line treatment to patients with mCRPC following progression after docetaxel and abiraterone treatment.

2. Materials and methods

The US Food and Drug Administration (FDA) approved enzalutamide for postdocetaxel mCRPC patients who experienced disease progression following publication of the AFFIRM trial [6]. In Europe, compassionate use programmes were initiated to bridge the time between FDA and European Medicines Agency approval. All programmes, from which we derived the patients presented in this study, have been described in details elsewhere [14–17]. Patients and clinical information included is presented in the Consolidated Standards of Reporting Trials diagram (Fig. 1). In brief, mCRPC patients progressing following chemotherapy and subsequent abiraterone and prednisone were treated with 160 mg enzalutamide daily in two German [14,15], one British [16], and one Danish [17] compassionate use programme if considered candidates for further therapy. All patients continued castration-based therapy during enzalutamide.

Follow-up consisted of regular outpatient clinic visits with biochemical and clinical evaluations. Between trials, there were minor differences in the imaging follow-up, and evaluation of progression based on radiographic assessment or bone scans was not mandatory. For all patients, the following pretreatment information was recorded, if available: Gleason score at diagnosis; time from primary endocrine treatment to CRPC; number of docetaxel cycles; time on and PSA response to abiraterone; Eastern Cooperative Oncology Group (ECOG) performance score; PSA; haemoglobin; albumin; lactate dehydrogenase (LDH); and alkaline phosphatase (ALP). The primary end point was overall survival (OS) calculated from initiation of enzalutamidine; the secondary end point was PSA response. Radiographic response and radiographic progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [18] were available only in a subgroup of patients.

2.1. Statistics

Continuous variables are presented as median and range. The best PSA response was defined as percentage of change from baseline (start of abiraterone or enzalutamide) to nadir. The first PSA measurement was used in patients who had an increase in PSA. Patients were dichotomised according to their best PSA response as nonresponders (continued PSA progression) or responders (decrease or stabilised PSA). Furthermore, patients responding were categorised according to the best PSA fall reported: >30% and >50% falls (unconfirmed), respectively.

Survival was calculated from the date enzalutamide was initiated using Kaplan–Meier survival analysis and presented with a 95% confidence interval (CI). Log-rank analysis was used to compare survival among subgroups. We used Cox proportional hazards to estimate the effect of clinical pre-enzalutamide parameters as well as absolute and percentage PSA response to enzalutamide on survival. No patient was lost to follow-up. Two-sided p value <0.05 was considered significant. Statistical analysis was performed with R (R Development Core Team, Vienna, Austria, www.R-project.org).
3. Results

Prior to initiation of 160 mg/d of enzalutamide, the 137 patients included in this study had received a median of eight courses of docetaxel and had subsequently received abiraterone plus prednisone for a median of 7 mo (Table 1; Supplemental Table 1). Of the 137 patients, information about PSA response with prior abiraterone was available in 94 patients, of whom 32 had PSA progression and 62 were categorised as PSA nonprogression.

The median duration of enzalutamide treatment until clinical progression was 3.2 mo (range: 0.03–21.9). At the time of these analyses, 14 patients were still being treated with enzalutamide. PSA information following enzalutamide initiation was available in 122 patients (Fig. 1). Among these 122 patients, 44 (36%) had PSA progression (nonresponders), and the remaining 78 (64%) patients had decreased or stabilised PSA (nonprogression, described here as responders; Fig. 2). Forty-five (36.9%) patients had a PSA fall (unconfirmed) $>30\%$ and 22 (18.0%) patients $>50\%$, respectively.

![Waterfall plot of best percentage change in prostate-specific antigen (PSA) from baseline. Twelve patients who had an increase in PSA were excluded because of unknown first PSA measurement.](image-url)

PSA = prostate-specific antigen.
Table 2 – Univariate Cox proportional hazard analysis between pre-enzalutamide parameters and survival

| Age*       | 137 | 0.98 | 0.95–1.01 | 0.13 |
| ECOG       | 96  | 1 (ref) | 0.07 |
| 0           |     |       |       |
| 1           | 3.00 | 0.92–9.80 |       |
| 2           | 3.41 | 1.01–11.5 |       |
| PSA**       | 135 | 1.10 | 0.99–1.22 | 0.08 |
| Diagnostic Gleason score | 104 |       |       |
| 6           | 1 (ref) | 0.77 |
| 7           | 0.71 | 0.29–1.72 |       |
| 8           | 0.85 | 0.33–2.20 |       |
| 9           | 0.89 | 0.38–2.06 |       |
| 10          | 1.55 | 0.40–6.03 |       |
| Time from primary endocrine treatment to CRPC | 58 | 0.91 | 0.76–1.09 | 0.29 |
| No. of docetaxel series*** | 99 | 1.02 | 0.98–1.07 | 0.36 |
| Time on abiraterone acetate† | 135 | 0.99 | 0.97–1.02 | 0.66 |
| PSA response to abiraterone acetate | 93 |       |       |
| Increase in PSA | 1 (ref) |       |       |
| Stable or decrease in PSA | 63 | 0.88 | 0.50–1.56 | 0.67 |
| Haemoglobin| 63 | 1.50 | 1.05–2.12 | 0.02 |
| Albumin††   | 57  | 0.74 | 0.38–1.43 | 0.37 |
| LDH††       | 47  | 0.99 | 0.98–1.02 | 0.68 |
| ALP††       | 63  | 1.01 | 1.00–1.01 | 0.02 |

ALP = alkaline phosphatase; CI = confidence interval; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDH = lactate dehydrogenase; PSA = prostate-specific antigen.

* 1-yr increase.
** A 2-fold increase.
*** 1 series increase.
† 1-mo increase.
†† 1-mmol/l decrease.
††† 10-unit increase.

Overall, the estimated median survival was 8.3 mo (95% CI, 6.8–9.8) for the 137 patients. On univariate analysis, pretreatment clinical characteristics had little or no influence on survival (Table 2). Patients who had an ECOG score of 2 had a higher mortality than patients who had ECOG 0 (hazard ratio [HR]: 3.41; 95% CI, 1.01–11.5), but there was no survival difference between patients with ECOG score 1 and ECOG score 2. A 1 mmol/l decrease in haemoglobin was associated with an increased mortality (HR: 1.50; 95% CI, 1.05–2.12). A 10-unit increase in ALP concentration at enzalutamide initiation had a statistically significant association with increased mortality (HR: 1.01;
Fig. 4 – (a) Kaplan-Meier survival curve for the 122 patients who had a prostate-specific antigen (PSA) response to enzalutamide treatment, dichotomised according to a continued PSA progression (orange line) and decline or stabilised PSA (blue line). (b) Kaplan-Meier survival curve for the 122 patients who had a PSA response to enzalutamide treatment, dichotomised according to a PSA response greater than (blue line) or lower than (orange line) 30%. (c) Kaplan-Meier survival curve for the 122 patients who had a PSA response to enzalutamide treatment, dichotomised according to a PSA response greater than (blue line) or lower than (orange line) 50%.

PSA = prostate-specific antigen.
95% CI, 1.00–1.01), although this finding is of limited clinical relevance. A borderline significant association between PSA at enzalutamide initiation and survival was found (HR: 1.10; 95% CI, 0.99–1.22), although again, the clinical relevance of this finding is uncertain. Survival was not associated with age (p = 0.13), albumin (p = 0.37); LDH (p = 0.68) at enzalutamide initiation; Gleason score at diagnosis (p = 0.77); time from primary endocrine treatment to CRPC (p = 0.29); number of docetaxel courses (p = 0.36); or time on or PSA response to abiraterone (p = 0.66 and p = 0.67, respectively). Assessment by RECIST criteria was not performed in all compassionate use programmes.

Responses according to RECIST criteria were reported in 59 patients [14,16]. Overall, only seven of these patients had a radiographic response to enzalutamide resulting in a partial remission according to the RECIST criteria. No patients experienced complete remissions. The median duration of radiographic PFS in the 34 patients who underwent regular radiographic follow-up was 3.1 mo (95% CI, 2.3–3.9) [15,16].

In univariate analysis, a 10% lower PSA response was associated with an increased risk of death (HR: 1.07; 95% CI, 1.03–1.10; p < 0.001). Kaplan-Meier survival curves stratified into quartiles according to the best PSA response are depicted in Figure 3. No association between the absolute PSA decline and survival was found in univariate analysis (HR: 1.003; 95% CI, 0.996–1.01; p = 0.37). Patients presenting with stable or declining PSA following enzalutamide had a median survival of 9.4 mo (95% CI, 7.5–11.3) compared with 6.7 mo (95% CI, 5.5–7.9) in patients who had PSA progression (p = 0.047; Fig. 4a). Patients who had a PSA fall >30% had a median survival of 11.4 mo (95% CI, 8.0–14.8) compared with 7.1 mo (95% CI, 5.9–8.2) in patients who had a PSA decline <30% (p = 0.002; Fig. 4b). Patients who had a ≥50% fall in PSA had a median survival of 12.6 mo (undefined 95% CI) compared with 7.4 mo (95% CI, 6.1–8.6) for patients who had a PSA response <50% (p = 0.007; Fig. 4c). Finally, there were no major differences in pre-enzalutamide characteristics among patients who had a PSA response >30% compared with those patients who had a lower response (Supplemental Table 2).

4. Discussion

Since the introduction of docetaxel, mCRPC has been artificially divided into a prechemotherapy and a postchemotherapy disease state for regulatory reasons. AR signalling remains a key driver of progression during mCRPC, despite testosterone at castration levels in both of these disease states [19]. New therapeutic modalities targeting the AR have been successfully developed and are currently being introduced for both pre- and postchemotherapy mCRPC. With the introduction of these new treatment options, the questions of optimal timing, patient selection, sequencing, and the development of drug resistance have been heavily debated.

In vitro experiments have also demonstrated impaired antitumour activity of taxanes in cell lines resistant to next-generation AR-targeting drugs [20]. This finding may reflect the taxane mode of action, which involves the AR pathway through the role of microtubules on AR nuclear-cytoplasmic shuttling or may be the result of up-regulation of other antiapoptotic mechanisms [21,22]. The response to enzalutamide has also been reported to be affected by glucocorticoid receptor signalling in preclinical studies, although limited clinical data are available to support this hypothesis to date [23]. Arora et al. indicate that exposure to enzalutamide in a preclinical model of prostate cancer induces glucocorticoid receptor up-regulation leading to the development of enzalutamide resistance.

Compared with the AFFIRM trial [6], the data from the compassionate use programmes pooled in this study indicate more modest antitumour activity for enzalutamide in postchemotherapy mCRPC patients previously treated with abiraterone [14–17]. The antitumour activity of abiraterone following both docetaxel and enzalutamide has similarly been reported to be modest compared with COU-301 [11–13]. Mezynski et al. have also shown a lower antitumour activity for docetaxel in patients previously managed with abiraterone [24]. Nevertheless, our results indicate that a subset of patients previously managed with docetaxel and abiraterone who responded with nonincreasing or decreasing PSA following enzalutamide may have improved OS. In univariate analysis, PSA declines were associated with improved survival; further analysis stratifying by response in patients who had no PSA increase, a 30% decrease, and a 50% decrease in PSA following initiation of enzalutamide, respectively, demonstrated longer survival compared with patients who experienced increasing PSA, <30% decrease, or a 50% decrease, respectively. Studies applying the Prostate Cancer Working Group 2 guidelines and implementing regular imagining should be performed to confirm these findings. Patients benefiting from enzalutamide may therefore be those who have a PSA response to this agent, while patients who have a poorer PSA response could benefit from other treatment options. Overall, the biochemical activity of enzalutamide after abiraterone and docetaxel may be higher than that of abiraterone following progression on docetaxel and enzalutamide [12,13]. Randomised clinical trials are, however, now required to address the optimal sequences or combinations for the administration of these novel agents.

Lower haemoglobin and ECOG score 2 were both associated with poorer prognosis in univariate analysis. Patients who had a PSA >30% had significantly higher baseline haemoglobin and a trend towards better ECOG scores (Supplemental Table 2). These differences in baseline parameters may partly explain the survival benefit seen in patients who have a better PSA response. Survival following initiation of enzalutamide was not associated with evaluated pretreatment characteristics—time to CRPC, the PSA response, and duration of prior chemotherapy and abiraterone or age.

This preliminary report of PSA response to enzalutamide treatment in mCRPC patients progressing after postchemotherapy abiraterone has obvious limitations. First, it is a
retrospective study; baseline characteristics are incompletely recorded, with differences among the four centres; and the patients have not been followed systematically by protocol. The number of patients is limited, and the study lacks information about PSA kinetics and parameters other than PSA to monitor the response of enzalutamide treatment. Bone scans and radiographic evaluation was performed only if clinically indicated; radiographic response in accordance with the RECIST criteria was recorded only in a subset of patients [18]. Of the patients included in the present study, only 36.9% and 18.0% responded with a PSA decline of 30% and 50%, respectively. However, the combined analyses demonstrate that despite a modest PSA response, with only a limited number of patients reaching a PSA response >30%, a survival benefit was demonstrated in patients who did not have a rising PSA following the introduction of enzalutamide.

5. Conclusions

This study presents data from four European studies on compassionate-access enzalutamide for mCRPC patients progressing following docetaxel and abiraterone. We demonstrate that enzalutamide, when administered as a third-line treatment, has more modest antitumour activity than that reported in the AFFIRM trial. Nonetheless, patients who had a PSA decline >30% and 50% have superior survival and may benefit from this agent. With the increasing number of treatment options available for patients who have mCRPC, well-conducted studies determining the optimal treatment sequence or combination of these drugs are urgently needed to base future treatment algorithms on solid evidence.

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Acquisition of data: Brasso, Thomsen, Schrader, Schmid, Lorente, Retz, Merseburger, von Klot, Boegemann, de Bono.

Analysis and interpretation of data: Brasso, Thomsen, Schrader, Schmid, Lorente, Retz, Merseburger, von Klot, Boegemann, de Bono.

Drafting of the manuscript: Brasso, Thomsen.

Critical revision of the manuscript for important intellectual content: Schrader, Schmid, Lorente, Retz, Merseburger, von Klot, Boegemann, de Bono.

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Appendix B. Supplementary data

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