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Antitumour Activity and Safety of Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer Previously Treated with Abiraterone Acetate Plus Prednisone for ≥24 weeks in Europe

Johann S. de Bono[a,*], *Simon Chowdhury*[b,c,d], *Susan Feyerabend*[e], *Tony Elliott*[f], *Enrique Grande*[g], *Amal Melhem-Bertrandt*[h], *Benoit Baron*[i], *Mohammad Hirmand*[j,†], *Patrick Werbrouck*[k], *Karim Fizazi*[l]

[a] *The Institute of Cancer Research, London, UK;* [b] *Guy's Hospital, London, UK;* [c] *King's Hospital, London, UK;* [d] *St Thomas' Hospital, London, UK;* [e] *Studienpraxis Urologie, Nürtingen, Germany;* [f] *The Christie Hospital, Manchester, UK;* [g] *Hospital Universitario Ramon y Cajal, Madrid, Spain;* [h] *Astellas Pharma, Inc, Northbrook, IL, USA;* [i] *Astellas Pharma, Inc, Leiden, the Netherlands;* [j] *Medivation, Inc, which was acquired by Pfizer, Inc in September 2016, San Francisco, CA, USA;* [k] *AZ Groeninge, Kortrijk, Belgium;* [l] *Institut Gustave Roussy, Paris-Sud University, Villejuif, France*

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Abstract

Background: Enzalutamide and abiraterone acetate plus prednisone, which target the androgen receptor axis, have expanded the treatment of advanced prostate cancer. Retrospective analyses suggest some cross-resistance between these two drugs when used sequentially, but robust, prospective studies have not yet been reported.
Objective: To fulfil a regulatory postregistration commitment by evaluating the efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed following abiraterone acetate plus prednisone treatment.
Design, setting, and participants: Multicentre, single-arm, open-label study, enrolled patients with progressing mCRPC after ≥24 wk of abiraterone acetate plus prednisone treatment. All patients maintained castration therapy during the trial. Prior chemotherapy was allowed but not required.
Intervention: Patients received enzalutamide 160 mg/d orally.
Outcome measurements and statistical analysis: The primary endpoint was radiographic progression-free survival. Secondary endpoints were overall survival, prostate-specific antigen (PSA) response, and time-to-PSA progression. Safety data were also assessed. Kaplan-Meier methods were used to descriptively analyse time-to-event endpoints.
Results and limitations: Overall, 214 patients received enzalutamide treatment, 145 of whom were chemotherapy-naïve. Median radiographic progression-free survival was 8.1 mo (95% confidence interval: 6.1–8.3); median overall survival had not been reached. Unconfirmed PSA response rate was 27% (48 of 181). Median time-to-PSA progression was 5.7 mo (95% confidence interval: 5.6–5.8). The most common treatment-emergent adverse events were fatigue (32%), decreased appetite (25%), asthenia (18%), back pain (17%), and arthralgia (16%). No seizures were reported.

† An employee of Medivation, Inc at the initiation of this work.
* Corresponding author. The Institute of Cancer Research, Royal Marsden NHS Foundation Trust, Sycamore House, Downs Road, Sutton, Surrey SM2 5PT, UK. Tel. +44 208 722 4029; Fax: +44 208 642 7979.
E-mail address: johann.de-bono@icr.ac.uk (J.S. de Bono).

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Conclusions: Enzalutamide showed antitumour activity in some patients with mCRPC who had previously progressed following ≥24 wk of abiraterone acetate plus prednisone treatment.

Patient summary: Patients with mCRPC who progressed on previous abiraterone acetate plus prednisone treatment, with or without prior chemotherapy, received enzalutamide. Although cross-resistance between the two agents was observed in a majority of patients, some still benefited from enzalutamide treatment.

1. Introduction

Prostate cancer remains the second most common form of cancer among men worldwide [1], and the management of these patients continues to change with the approval of targeted agents such as enzalutamide and abiraterone acetate [2].

Enzalutamide is an androgen receptor inhibitor approved for treating patients with metastatic castration-resistant prostate cancer (mCRPC) [3–5]. It acts by inhibiting the binding of androgens to the androgen receptor, androgen-receptor nuclear translocation, and androgen-receptor-mediated DNA binding [6]. Enzalutamide significantly prolonged overall survival (OS) versus placebo for chemotherapy-naïve men with mCRPC and men who had progressed on docetaxel therapy (PREVAIL and AFFIRM trials, respectively) [3,4]. Enzalutamide also significantly prolonged progression-free survival (PFS) versus bicalutamide in chemotherapy-naïve men with non-metastatic prostate cancer (STRIVE) [7] and mCRPC (STRIVE and TERRAIN) [5,7].

Abiraterone acetate is a steroidal 17α-hydroxylase/17,20-lyase inhibitor approved in combination with prednisone for treating patients with mCRPC [8,9]. Abiraterone acetate plus prednisone (referred to from here on as "abiraterone") significantly prolonged OS versus prednisone alone for chemotherapy-naïve men (COU-AA-302) [9] and men who had progressed on docetaxel (COU-AA-301) [8,10]. However, a more modest response to abiraterone following progression on docetaxel and enzalutamide was observed in a limited number of patients with mCRPC after discontinuation from the AFFIRM trial, including <10% of patients achieving ≥50% decline in prostate-specific antigen (PSA) on subsequent abiraterone [11,12]. Following the publication of these results, the European Medicines Agency requested the developers of enzalutamide to conduct a study to assess the efficacy of enzalutamide in patients who had progressed following abiraterone.

In response, this postregistration study (ClinicalTrials.gov, NCT02116582) was performed to evaluate the efficacy and safety of enzalutamide treatment in patients with mCRPC following disease progression after at least 24 wk of abiraterone.

2. Patients and methods

2.1. Study design

This phase 4, open-label, single-arm study of enzalutamide enrolled patients with mCRPC who had progressive disease following prior abiraterone treatment from multiple clinical sites in Europe. The study protocol was approved by the review boards of participating institutions, and the trial was in accordance with the Declaration of Helsinki. Written informed consent from the patients were obtained prior to any study-related screening procedures.

Patients must have had metastatic disease (Supplementary data) and must have received a minimum of 24 wk of abiraterone treatment and discontinued its use for ≥4 wk prior to enzalutamide treatment in the study (this inclusion criterion was an amendment to the initial study design). Previous chemotherapy for prostate cancer was limited to ≤1 prior line of docetaxel, which must have been prior to abiraterone treatment. Patients received enzalutamide 160 mg/d orally and continued ongoing androgen deprivation with luteinising hormone-releasing hormone analogues for the duration of the study, or had a bilateral orchiectomy (Supplementary Fig. 1). More details regarding the study methodology, including key inclusion and exclusion criteria, are described in the Supplementary data.

2.2. Outcomes

The primary study endpoint was radiographic PFS (rPFS), defined as the time from the first dose of enzalutamide to objective evidence of radiographic disease progression or death from any cause, whichever occurred first. Bone disease progression was considered when ≥2 new lesions were observed, but if progression was first observed at (or before) wk 13, a confirmatory scan demonstrating ≥2 new additional lesions had to be performed after ≥6 wk. More details regarding confirmation of rPFS are described in the Supplementary data.

Secondary endpoints included: (1) OS, defined as the time from first dose to death from any cause, (2) PSA response, defined as ≥50% decrease from baseline in PSA, which was a binary variable for achieving (or not achieving) this criterion based on the lowest PSA value observed postbaseline (response confirmation, defined as a second consecutive PSA value obtained ≥3 wk later, was not required), and (3) time-to-PSA progression. More details of secondary and exploratory endpoints are described in the Supplementary data.

2.3. Procedures

PSA, soft tissue disease on computed tomography scan or magnetic resonance imaging, and bone disease on radionuclide bone scans data were collected at baseline, wk 13, and every 12 wk until the analysis data cut-off point or

treatment discontinuation, whichever occurred first. Safety data were also collected throughout the study.

2.4. Statistical analyses

Kaplan-Meier methods were used to descriptively analyse time-to-event endpoints (ie, rPFS, OS, and time-to-PSA progression). A two-sided 95% confidence interval (CI) for the median time was estimated by using the Brookmeyer and Crowley method. The 25th percentile and the 75th percentile estimates were also provided, along with a two-sided 95% CI for the 25th percentile, if the median was not reached.

Rate of ≥50% decline of PSA from baseline was calculated, along with a two-sided 95% CI using the Clopper-Pearson method based on exact binomial distribution.

The sample size (200 patients) was chosen based on discussions with the European Medicines Agency and practical considerations (Supplementary data). The criteria used for data censoring are described in the Supplementary data.

3. Results

3.1. Patient disposition, baseline characteristics, and disease history

The study enrolled patients between May 23, 2014 and May 8, 2015. As of the cut-off date of May 8, 2016, the median follow-up period was 14 mo. Two-hundred-and-seventy-two patients were screened for enrolment and signed an informed consent form (Supplementary Fig. 1). Fifty-seven patients failed screening, 215 were enrolled, and 214 received at least one dose of enzalutamide. Of these, 69 patients had prior treatment with chemotherapy before abiraterone and 145 patients were chemotherapy-naïve. The primary reason for treatment discontinuation in the overall population was disease progression (n = 140; 65%). Other reasons for treatment discontinuation included adverse events (n = 17; 7.9%), withdrawal by patient (n = 8; 3.7%), death (n = 7; 3.3%), protocol violation (n = 3; 1.4%), and other reasons (n = 9; 4.2%).

Demographics and baseline characteristics were generally similar between patients with prior treatment with chemotherapy before abiraterone and chemotherapy-naïve patients (Table 1). Overall, the median duration of previous abiraterone therapy was 54 wk (60 wk for patients previously treated with chemotherapy before abiraterone and 52 wk for chemotherapy-naïve patients; Table 1).

3.2. Enzalutamide treatment duration

The median duration of enzalutamide treatment was 5.7 mo (quartiles: 2.8, 11) for the overall patient population, with 154 (72%), 99 (46%), 64 (30%), and 35 (16%) patients on treatment at 3 mo, 6 mo, 9 mo, and 12 mo, respectively (Supplementary Table 1). The median duration of enzalutamide treatment was similar between patients previously treated with chemotherapy before abiraterone and chemotherapy-naïve patients (5.5 mo and 5.9 mo, respectively; Supplementary Table 1).

3.3. rPFS

In the overall population, the median duration of rPFS was 8.1 mo (95% CI: 6.1–8.3; Fig. 1). The median duration of rPFS was 7.9 mo (95% CI: 5.5–11) for patients previously treated with chemotherapy before abiraterone and 8.1 mo (95% CI: 5.7–8.3) for chemotherapy-naïve patients.

Of the 141 disease progression events observed by the cut-off date in the overall population, 101 (72%) were radiographic progression events and 40 (28%) were deaths that occurred before experiencing radiographic progression (Fig. 1). The remaining 73 patients were censored, of which 45 (62%) discontinued treatment without fulfilling radiographic progression criteria and were alive at the time of data cut-off (Fig. 1, Supplementary Table 2). Fifty patients previously treated with chemotherapy prior to abiraterone experienced a progression event by the cut-off date, of which 31 (62%) were radiographic events and 19 (38%) were deaths. Ninety-one chemotherapy-naïve patients experienced a progression event, of which 70 (77%) were radiographic events and 21 (23%) were deaths.

3.4. OS

Median OS for the overall study population and for chemotherapy-naïve patients were not yet reached at the time of the data cut-off point due to the low number of events (69 out of 214 patients in the overall population and 38 out of 145 chemotherapy-naïve patients had died from any cause prior to the data cut-off; Fig. 2). Median OS for patients previously treated with chemotherapy before abiraterone was 18 mo (95% CI: 13–not yet reached), with 31 deaths prior to the data cut-off (Fig. 2).

3.5. Rate of ≥50% decline in PSA from baseline

Overall, in 181 patients with ≥1 postbaseline PSA assessment, the unconfirmed rate of ≥50% PSA decline from baseline was 27% (95% CI: 20–34), with 48 patients having a ≥50% decrease in PSA from baseline prior to the data cut-off. Thirty-three patients discontinued enzalutamide treatment before having a postbaseline PSA assessment. The unconfirmed rate of ≥50% PSA decline from baseline was 28% (16 of 57; 95% CI: 17–42) and 26% (32 of 124; 95% CI: 18–34) for patients with previous chemotherapy and chemotherapy-naïve patients, respectively (Fig. 3). This ≥50% decline in PSA from baseline was confirmed by a subsequent PSA measurement in 35 of 48 patients.

3.6. PSA progression

The median time-to-PSA progression in the overall population was 5.7 mo (95% CI: 5.6–5.8), with 105 patients experiencing PSA progression (Fig. 4). Similar results were observed in patients previously treated with chemotherapy before abiraterone and chemotherapy-naïve patients

Table 1 – Baseline characteristics

Characteristic	Previous chemotherapy (*n* = 69)	Chemotherapy-naïve (*n* = 145)	Total (*n* = 214)
Demographics			
Race, *n* (%)			
White	57 (83)	107 (74)	164 (77)
Black	0	2 (1.4)	2 (0.9)
Other	0	1 (0.69)	1 (0.47)
Missing[a]	12 (17)	35 (24)	47 (22)
Age, yr, *n* (%)			
<65	9 (13)	15 (10)	24 (11)
65–74	33 (48)	66 (46)	99 (46)
≥75	27 (39)	64 (44)	91 (43)
Median (quartiles)	72 (67, 77)	73 (70, 78)	73 (69, 78)
ECOG, *n* (%), grade			
0	28 (41)	72 (50)	100 (47)
1	41 (59)	72 (50)	113 (53)
2	0	1 (0.7)	1 (0.5)
PSA, µg/l, median (quartiles)	71 (28, 192)	53 (22, 143)	59 (23, 157)
Cancer-related disease history			
Prostate cancer duration, yr, median (quartiles)	7.1 (4.4, 12)	6.8 (3.4, 12)	6.9 (3.7, 12)
Duration of prior abi,[b] wk, median (quartiles)	60 (38, 84)	52 (35, 68)	54 (35, 73)
Time from abi end to study treatment start,[b] d, *n* (%)			
<28	1 (1.4)	3 (2.1)	4 (1.9)
28–90	58 (84)	132 (91)	190 (89)
91–180	7 (10)	10 (6.9)	17 (7.9)
>180	3 (4.3)	0	3 (1.4)
Total Gleason score at initial diagnosis, *n* (%)			
Low (2–4)	1 (1.4)	3 (2.1)	4 (1.9)
Medium (5–7)	30 (44)	74 (51)	104 (49)
High (8–10)	32 (46)	61 (42)	93 (43)
Missing	6 (8.7)	7 (4.8)	13 (6.1)
Distant metastasis at initial diagnosis, *n* (%)	21 (30)	33 (23)	54 (25)
LHRHa initiation or bilateral orchiectomy relative to diagnosis of metastasis, *n* (%)			
Before	39 (57)	83 (57)	122 (57)
After	30 (44)	62 (43)	92 (43)
Metastasis assessment at screening and cancer treatment history			
Metastases,[c] *n* (%)			
Yes	69 (100)	144 (99)	213 (100)
No	0	1 (0.7)	1 (0.5)
Metastases localisation, *n* (%)			
Bone only	38 (55)	68 (47)	106 (50)
Soft tissue only	6 (8.7)	19 (13)	25 (12)
Both	25 (36)	57 (39)	82 (38)
Previous radiation therapy, *n* (%)			
Yes	45 (65)	89 (61)	134 (63)
No	24 (35)	56 (39)	80 (37)
Largest PSA decline ≥50% while on abi			
Yes	40 (58)	82 (57)	122 (57)
No	22 (32)	44 (30)	66 (31)
Unknown	7 (10)	19 (13)	26 (12)
Responsive to abi for metastatic disease,[d] *n* (%)			
Yes	18 (26)	35 (24)	53 (25)
No	31 (45)	45 (31)	76 (36)
Unknown	20 (29)	65 (45)	85 (40)

abi = abiraterone acetate plus prednisone; ECOG = Eastern Cooperative Oncology Group; LHLRa = luteinising hormone-releasing hormone agonist/antagonist; PSA = prostate-specific antigen.

[a] Not collected due to regulatory reasons.

[b] Some patients who were treated with <24 wk of abiraterone acetate plus prednisone and/or with <4 wk of abiraterone acetate plus prednisone prior to the start of enzalutamide treatment were included in the study prior to a protocol amendment to this inclusion criterion.

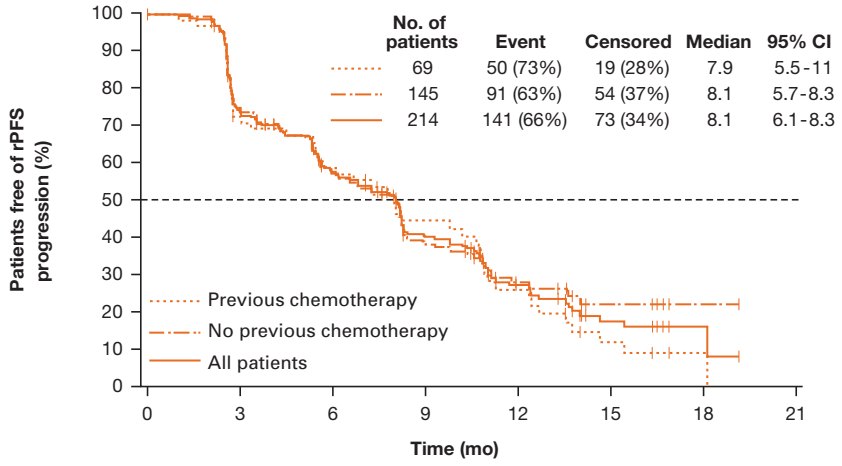
[c] One patient did not have metastatic disease as assessed by a scan performed during screening. However, the patient did present with nodal disease at diagnosis. Nodal disease was confirmed by biopsy but it became immeasurable on the last scan before the patient entered the study and while he was still on abiraterone acetate plus prednisone treatment.

[d] Response to treatment with abiraterone acetate plus prednisone was indicated by study site responses to whether the patient's largest ≥50% PSA decline was observed while on treatment with abiraterone acetate plus prednisone and whether patients were responsive to treatment with abiraterone acetate plus prednisone for metastatic prostate cancer.

(5.6 mo [95% CI: 5.5–8.3] and 5.7 mo [95% CI: 5.6–5.8], respectively). Thirty patients previously treated with chemotherapy before abiraterone and 75 chemotherapy-naïve patients had PSA progression.

3.7. *Time to start of another antineoplastic therapy*

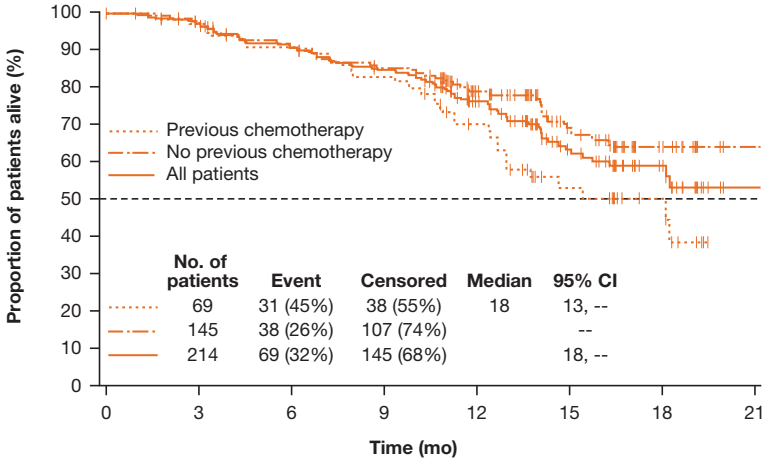
Overall, the median time to the start of other antineoplastic therapy after the first dose of enzalutamide was 12 mo (95%



Previous chemotherapy								
Event/cum. events	0/0	17/17	8/25	8/33	9/42	6/48	1/49	1/50
Patients at risk	69	43	34	22	12	4	1	0
No previous chemotherapy								
Event/cum. events	0/0	34/34	23/57	22/79	9/88	3/91	0/91	0/91
Patients at risk	145	101	69	42	17	8	1	0
All patients								
Event/cum. events	0/0	51/51	31/82	30/112	18/130	9/139	1/140	1/141
Patients at risk	214	144	103	64	29	12	2	0

Fig. 1 – Kaplan-Meier plot of rPFS. The number of patients censored equalled the number of patients minus the number of events. Overall, 73 out of 214 patients were censored at data cut-off, at which 28 patients were still on treatment; 45 discontinued treatment without fulfilling radiographic progression criteria and were alive at the time of data cut-off.
CI = confidence interval; cum = cumulative; rPFS = radiographic progression-free survival.

CI: 9.9–14 mo), and was 10 mo (95% CI: 7–15 mo) for patients previously treated with chemotherapy before abiraterone and 13 mo (95% CI: 11–15 mo) for chemotherapy-naïve patients. Overall, 108 patients initiated another antineoplastic therapy after the first dose of enzalutamide (37 patients who were previously treated with chemotherapy before abiraterone and 71 chemotherapy-naïve patients; Supplementary Table 3).



Previous chemotherapy								
Event/cum. events	0/0	2/2	4/6	5/11	8/19	9/28	1/29	2/31
Patients at risk	69	65	59	54	40	19	9	0
No previous chemotherapy								
Event/cum. events	0/0	4/4	9/13	7/20	8/28	7/35	3/38	0/38
Patients at risk	145	138	126	117	79	43	12	1
All patients								
Event/cum. events	0/0	6/6	13/19	12/31	16/47	16/63	4/67	2/69
Patients at risk	214	203	185	171	119	62	21	1

Fig. 2 – Kaplan-Meier plot of overall survival. The number of patients censored equalled the number of patients minus the number of events. Approximately two-thirds of patients were censored (ie, were alive at the time of data cut-off). Thirty out of 145 (21%) patients were still on treatment at the time of data cut-off.
CI = confidence interval; cum = cumulative.

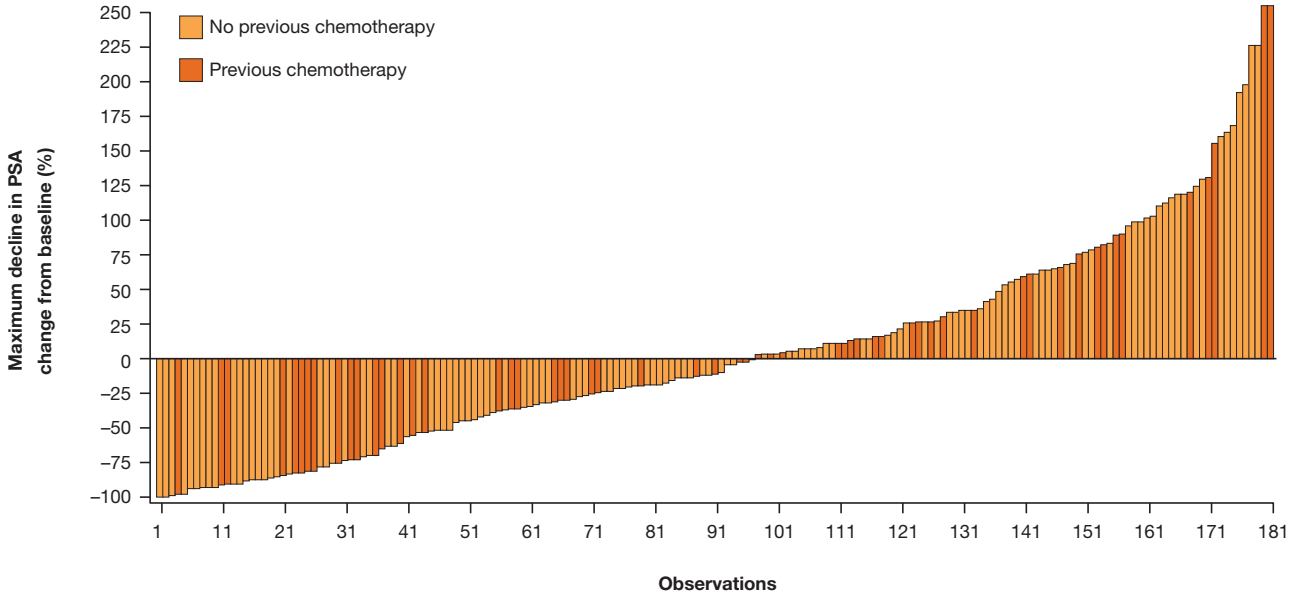


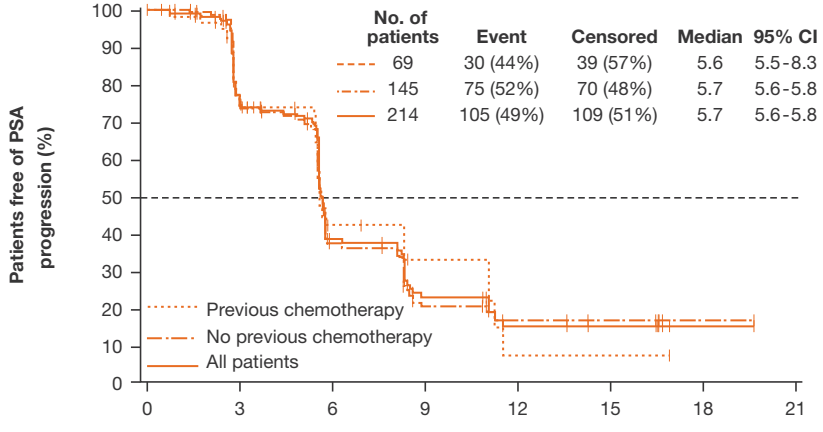
Fig. 3 – Waterfall plot of maximum percentage decline in PSA.
PSA = prostate-specific antigen.

3.8. Quality of life assessed by the European Quality of Life 5-Domain Scale

Overall, the median score at baseline was 79 (quartiles: 60–90), with a higher score indicating better health status. The median baseline score was 75 (quartiles: 60–84) for patients who were previously treated with chemotherapy before abiraterone and 80 (quartiles: 65–90) for chemotherapy-naïve patients. Generally, the European Quality of Life 5-Domain Visual Analogue Scale score did not change greatly during the study and the median score remained above 70% up to wk 49 (Supplementary Table 4).

3.9. Safety

In the overall safety population, 199 out of 214 (93%) patients experienced a treatment-emergent adverse event (TEAE): 93 (43%) experienced at least one grade ≥3 TEAE



Previous chemotherapy								
Event/cum. events	0/0	13/13	11/24	2/26	4/30	0/30	0/30	0/30
Patients at risk	69	32	9	6	1	1	0	0
No previous chemotherapy								
Event/cum. events	0/0	27/27	33/60	13/73	2/75	0/75	0/75	0/75
Patients at risk	145	76	30	14	9	7	1	0
All patients								
Event/cum. events	0/0	40/40	44/84	15/99	6/105	0/105	0/105	0/105
Patients at risk	214	108	39	20	10	8	1	0

Fig. 4 – Kaplan-Meier plot of time-to-PSA progression. The number of patients censored equalled the number of patients minus the number of events. Out of 214 patients, 109 (51%) were censored (ie, did not have a PSA progression event at the time of data cut-off). Of these 109 patients, 94 (86%) discontinued treatment at the time of data cut-off.
CI = confidence interval; cum. = cumulative; PSA = prostate-specific antigen.

Table 2 – Treatment-emergent adverse events (TEAEs)

Adverse event, *n* (%)	Total (*n* = 214)
Any TEAE	199 (93)
NCI-CTCAE grade ≥3	93 (43)
Drug-related	127 (59)
Drug-related NCI-CTCAE grade ≥3	18 (8.4)
TEAEs with death as an outcome	19 (8.9)
SAE[a]	81 (38)
Drug-related[b] SAE[a]	8 (3.7)
Drug-related AE leading to study drug discontinuation[b]	22 (10)
Study drug discontinuation primarily due to an AE	17 (7.9)

AE = adverse event; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event.
[a] Included SAEs upgraded by the sponsor based on review of the sponsor's list of always serious terms, if any upgrade was done.
[b] Possible or probable, as assessed by the investigator or records where relationship was missing.

(Table 2). For 18 (8.4%) patients, the TEAE was considered by the investigator to be possibly or probably related to enzalutamide (Table 2). Seventy (33%) patients reported an adverse event (AE) leading to enzalutamide discontinuation, and 22 (10%) had AEs that were considered to be possibly or probably related to enzalutamide. A TEAE was the primary reason for discontinuation of enzalutamide for 17 (7.9%) out of 214 patients. Study drug-related TEAEs included fatigue (*n* = 57; 27%), decreased appetite (*n* = 27; 13%), asthenia (*n* = 19; 8.9%), nausea (*n* = 17; 7.9%), and constipation (*n* = 12; 5.6%). Of 19 (8.9%) TEAEs that led to death, one cause (cerebral infarction) was considered to be possibly related to enzalutamide treatment. In the overall population, 81 (38%) patients experienced at least one serious AE, of which those reported by eight (3.7%) patients were considered to be possibly related to enzalutamide treatment. Falls were reported in nine (4.2%) patients. There were no seizures reported.

4. Discussion

This study was conducted to evaluate the efficacy and safety of enzalutamide treatment in patients with mCRPC following disease progression after at least 24 wk of abiraterone treatment in order to fulfil a regulatory commitment. In the overall population, the median duration of rPFS was 8.1 mo, median survival time was not reached, and the unconfirmed PSA response rate was 27%. The antitumour activity with enzalutamide in some patients appeared independent of the use of chemotherapy before abiraterone treatment. Reported AEs were consistent with the established safety profile of enzalutamide and were as expected for the study population. No further deterioration of quality of life, as assessed by the European Quality of Life 5-Domain scale, was reported during enzalutamide treatment.

Currently, there is no expert consensus on the use of second-line treatment with enzalutamide or abiraterone in symptomatic men who develop resistance after first-line abiraterone or enzalutamide, respectively, due in part to the absence of prospective clinical data in these settings [13]. The prospective data herein show the antitumour activity of enzalutamide in patients who progressed following ≥24 wk of abiraterone and support the use of enzalutamide in some patients in the postabiraterone setting.

This large study evaluating the antitumour activity of enzalutamide in patients with prostate cancer after progression with abiraterone provides additional prospective data to previously published retrospective studies. In retrospective analyses, patients treated with enzalutamide following progression with abiraterone treatment of any duration reported lower proportions of patients with ≥50% decline in PSA from baseline ranging from 5.0–45.7%, shorter PFS (range, 2.8–18.4 mo), and shorter OS (range, 7.1 mo–not yet reached) compared with the analysis herein [14–21]. In another small, prospective study of 24 patients with mCRPC who were treated with enzalutamide after progression with docetaxel and abiraterone postchemotherapy, PSA response of ≥50% was 17% and median OS was 4.8 mo [22]. Additionally, two retrospective analyses of chemotherapy-naïve patients with mCRPC treated with enzalutamide after progressing with abiraterone reported PSA responses ≥50% of 11.0% and 34.0% and PFS durations of 3.6 mo and 4.7 mo [21,23–25]. A systematic analysis that pooled data from 10 available clinical studies reported a ≥50% PSA response of 22.9% (range, 19.3–27.1%), median PFS of 3.1 mo (range, 1.4–4.9 mo), and median OS of 8.3 mo (range, 2.9–10.6) [26].

The data herein indicate that approximately one-third of patients who had progressed after abiraterone treatment for ≥24 wk remained on the study after 9 mo of enzalutamide treatment, with a median rPFS of 8.1 mo and median time-to-PSA progression of 5.7 mo. The rPFS may have been impacted by the censoring rate due to patients not having radiological progression at time of trial discontinuation. Moreover, per the study design, treatment discontinuation was independent from PSA assessments and enzalutamide treatment was often continued despite the absence of a PSA response. It is also important to note that rate of PSA decline, median rPFS, and median time-to-PSA progression observed in the present study are inferior to those observed in abiraterone-naïve men with mCRPC treated with enzalutamide [3,4,7], suggesting a degree of cross-resistance between these two agents.

Evidence of more modest antitumour activity of abiraterone with the reverse sequence (ie, after progression on enzalutamide) has also been previously reported by small, retrospective analyses of patients with mCRPC who had been enrolled in the AFFIRM study. In these analyses, patients with mCRPC treated with abiraterone after progressing with docetaxel and enzalutamide reported PSA responses ≥50% of 3% and 8%, median PFS of 2.7 mo and 3.6 mo, and OS of 7.2 mo and 11.6 mo [11,12]. A similarly modest clinical response was recently reported in a small retrospective analysis of chemotherapy-naïve patients with mCRPC who were treated with abiraterone after progression with enzalutamide, in which PSA response ≥50% was 7%, median PFS was 3.4 mo, and median OS was 9.1 mo [27].

Overall, a better understanding of the biology of abiraterone and enzalutamide resistance is key to optimise

the use of these agents. A recent study reported the conversion of abiraterone to the more active Δ^4-abiraterone metabolite in mice and patients with prostate cancer [28]. However, conversion of abiraterone to Δ^4-abiraterone is unlikely to have any impact on most enzalutamide-resistant prostate cancer cells expressing constitutively active androgen receptor splice variants (AR-SVs) that lack the ligand-binding carboxy-terminal domain. AR-SVs are believed to drive treatment resistance and may be generated through increased AR splicing under selective therapeutic pressure [29]. A recent study reported that AR-SV expression results in resistance to both abiraterone and enzalutamide [30].

This study's limitations include the single-arm, open-label design, due to the absence of treatment options available at the time of enrolment, and the censoring rate. Furthermore, the study was not designed to provide definitive answers regarding the most appropriate treatment sequence, and additional studies are needed to address this question. A phase 2, randomised study (n = 202) evaluating sequencing for abiraterone and enzalutamide is currently ongoing (ClinicalTrials.gov, NCT02125357). Symptomatic improvement and symptomatic deterioration, measured using patient-related outcomes, were not comprehensively assessed in this trial.

5. Conclusions

In conclusion, enzalutamide showed antitumour activity in some patients with mCRPC who had previously progressed following at least 24 wk of abiraterone treatment, also suggesting an important degree of cross-resistance between the two agents. Median rPFS in patients with prior chemotherapy was consistent with previously reported data for enzalutamide treatment of patients with mCRPC who had received prior chemotherapy and abiraterone. Reported TEAEs were consistent with the known safety profile of enzalutamide.

Author contributions: Johann S. de Bono 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: de Bono, Fizazi, Hirmand, Melhem-Bertrandt.
Acquisition of data: Chowdhury, de Bono, Feyerabend, Fizazi, Grande, Werbrouck.
Analysis and interpretation of data: Chowdhury, Baron, de Bono, Elliott, Feyerabend, Fizazi, Grande, Hirmand, Melhem-Bertrandt.
Drafting of the manuscript: Baron, Chowdhury, de Bono, Elliott, Fizazi.
Critical revision of the manuscript for important intellectual content: Baron, Chowdhury, de Bono, Elliott, Feyerabend, Fizazi, Grande, Hirmand, Melhem-Bertrandt, Werbrouck.
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Trial registration: NCT02116582

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2017.07.035.

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