Efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone: A multicenter, single-arm, open-label study

Johann S. de Bono,[1] Simon Chowdhury,[2] Susan Feyerabend,[3] Tony Elliott,[4] Enrique Grande,[5] Amal Melhem-Bertrandt,[6] Benoit Baron,[7] Mohammad Hirmand,[8] Patrick Werbrouck,[9] Karim Fizazi[10]

[1]The Institute of Cancer Research, London, UK; [2]Guy's, King's and St Thomas' Hospitals, London, UK; [3]Studienpraxis Urologie, Nürtingen, Germany; [4]The Christie Hospital, Manchester, UK; [5]Hospital Universitario Ramon y Cajal, Madrid, Spain; [6]Astellas Pharma, Inc., Northbrook, IL, USA; [7]Astellas Pharma, Inc., Leiden, the Netherlands; [8]Medivation, Inc., San Francisco, CA, USA, Medivation was acquired by Pfizer, Inc. in September 2016; [9]AZ Groeninge, Kortrijk, Belgium; [10]Institut Gustave Roussy, Villejuif, France

BACKGROUND

- Prostate cancer remains the second most common form of cancer among men worldwide,[1] and the care paradigms of these patients continue to change with the approval of targeted agents such as enzalutamide and abiraterone acetate.[2,3]
- Enzalutamide, an androgen receptor inhibitor, significantly prolonged overall survival (OS) versus placebo for chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC) and men who had progressed on docetaxel therapy (PREVAIL, NCT01212991 and AFFIRM, NCT00974311, respectively).[4,5]
- Enzalutamide also significantly prolonged progression-free survival versus bicalutamide in chemotherapy-naïve men with non-metastatic prostate cancer (STRIVE, NCT01664923)[6] and mCRPC (STRIVE, NCT01664923 and TERRAIN, NCT01288911).[6,7]
- Abiraterone acetate, a steroidal 17α-hydroxylase/17,20-lyase (CYP17A1) inhibitor, plus prednisone significantly prolonged OS versus prednisone alone for chemotherapy-naïve men (COU-AA-302, NCT00887198)[8,9] and men who had progressed on docetaxel therapy (COU-AA-301, NCT00638690).[10]
  - However, a more modest response to abiraterone acetate plus prednisone, including a 3–8% PSA response rate (i.e. ⩾50% PSA decline) was observed in patients with mCRPC who had progressed on docetaxel and enzalutamide.[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 acetate plus prednisone treatment.
- In response, this post-registration study (NCT02116582) was performed to evaluate the efficacy and safety of enzalutamide treatment in patients with mCRPC following disease progression after at least 24 weeks of treatment with abiraterone acetate plus prednisone.

METHODS

Study design

- This Phase 4, multicenter, open-label, single-arm study of enzalutamide enrolled patients with mCRPC who had progressive disease following prior treatment with abiraterone acetate plus prednisone.
  - Patients must have received a minimum of 24 weeks of treatment with abiraterone acetate plus prednisone and discontinued its use for ⩾4 weeks prior to enzalutamide treatment in the study.
- Key inclusion criteria included:
  - Histologically confirmed adenocarcinoma of the prostate without neuroendocrine features.
  - Serum testosterone of ⩽1.7 nmol/L (or ⩽50 ng/dL).
  - Progressive metastatic disease defined as PSA rise determined by a minimum of two rising PSA levels with an interval of ⩾1 week between each assessment. The PSA value at the screening visit was ⩾2 ng/mL.
  - Eastern Cooperative Oncology Group performance status of 0 or 1.
- Key exclusion criteria included:
  - Previous treatment with ketoconazole, cabazitaxel, or enzalutamide.
  - Previous treatment with anti-androgens and/or chemotherapy following discontinuation of abiraterone acetate plus prednisone and prior to the start of enzalutamide on day 1.
  - History of seizure or significant cardiovascular disease.
- Patients received enzalutamide 160 mg/day.
  - All patients continued ongoing androgen deprivation with luteinizing hormone-releasing hormone analogs for the duration of the study unless they had a bilateral orchiectomy.
- The primary study end point was radiographic progression-free survival (rPFS), defined as the time from the first dose of enzalutamide to the first objective evidence of radiographic disease progression or death from any cause, whichever occurred first.
  - Radiological assessments were performed every 12 weeks.
  - Bone disease progression was considered when ⩾2 new lesions were observed, but if progression was first observed at (or before) week 13, a confirmatory scan demonstrating ⩾2 new additional lesions had to be performed after ⩾6 weeks.
  - If progression was first observed after week 13, a confirmatory scan was also performed ⩾6 weeks later, prior to study drug discontinuation, and must have shown persistence of the new lesions.
  - If there was unequivocal evidence of bone disease progression after week 13 (i.e. multiple new lesions of uptake were observed), no confirmatory scan was required.
  - Soft tissue disease progression was defined by Response Evaluation Criteria in Solid Tumors, version 1.1.
  - Unconfirmed progression on bone scan was not considered an event.
- Secondary end points included:
  - OS; prostate-specific antigen (PSA) response; and time to PSA progression, with PSA progression defined as a ⩾25% increase and an absolute increase of ⩾2 μg/L above the nadir, confirmed by a second consecutive value obtained ⩾3 weeks later.
- PSA, soft tissue disease on computed tomography scan or magnetic resonance imaging, and bone disease on radionuclide bone scans data were collected every 12 weeks until the analysis data cut-off point or treatment discontinuation, whichever occurred first. Safety data were also collected throughout the study.

Statistical analyses

- Kaplan-Meier methods were used to descriptively analyze time to event end points (i.e. 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.
- PSA decline of 50% was analyzed descriptively, and the PSA response rate was calculated along with a two-sided 95% CI using the Clopper-Pearson method based on exact binomial distribution.

RESULTS

Patient disposition and baseline characteristics

- A total of 215 patients were enrolled in this study, of which 214 patients received at least one dose of enzalutamide.
  - The primary reason for treatment discontinuation in the overall population was disease progression (n=140, 65.1%).
- **Table 1** summarizes patient demographics, baseline disease characteristics, and treatment history.

Treatment duration

- The median duration of treatment was 5.7 months for all patients (**Table 2**).

Table 1. Baseline characteristics

Characteristic	Previous chemotherapy (n=69)	Chemotherapy-naive (n=145)	Total (n=214)
Demographics			
Race, n (%)			
White	57 (82.6)	107 (73.8)	164 (76.6)
Black	0	2 (1.4)	2 (0.9)
Other	0	1 (0.7)	1 (0.5)
Not collected*	12 (17.4)	35 (24.1)	47 (22.0)
Age, years, n (%)			
<65	9 (13)	15 (10.3)	24 (11.2)
65–74	33 (47.8)	66 (45.5)	99 (46.3)
⩾75	27 (39.1)	64 (44.1)	91 (42.5)
Median (minimum, maximum)	72.0 (53, 89)	73.0 (50, 89)	73.0 (50, 89)
ECOG, n (%), grade			
0	28 (40.6)	72 (49.7)	100 (46.7)
1	41 (59.4)	72 (49.7)	113 (52.8)
2	0	1 (0.7)	1 (0.5)
PSA, μg/L, median (minimum, maximum)	71.1 (3.3, 4189.0)	52.7 (2.4, 2799.0)	58.7 (2.4, 4189.0)
Cancer-related disease history			
Prostate cancer duration, years, median (minimum, maximum)	7.1 (2.3, 22.2)	6.7 (1.1, 21.7)	6.9 (1.1, 22.2)
Duration of prior abi, weeks, median (minimum, maximum)	60.0 (21.4, 193.1)	51.6 (22.7, 379.1)	54.2 (21.4, 379.1)
Time from abi end to study treatment start, days, n (%)			
<28	1 (1.4)	3 (2.1)	4 (1.9)
28–90	58 (84.1)	132 (91.0)	190 (88.8)
91–180	7 (10.1)	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 (43.5)	74 (51.0)	104 (48.6)
High (8–10)	32 (46.4)	61 (42.1)	93 (43.5)
Missing	6 (8.7)	7 (4.8)	13 (6.1)
Distant metastasis (M1) at initial diagnosis, n (%)	21 (30.4)	33 (22.8)	54 (25.2)
LHRHa initiation or bilateral orchiectomy relative to diagnosis of metastasis, n (%)			
Before	39 (56.5)	83 (57.2)	122 (57.0)
After	30 (43.5)	62 (42.8)	92 (43.0)
Metastasis assessment at screening and cancer treatment history			
Metastases, n (%)			
No	0	1 (0.7)	1 (0.5)
Yes	69 (100)	144 (99.3)	213 (99.5)
Metastases location, n (%)			
Bone only	38 (55.1)	68 (46.9)	106 (49.5)
Soft tissue only	6 (8.7)	19 (13.1)	25 (11.7)
Both	25 (36.2)	57 (39.3)	82 (38.3)
Previous radiation therapy, n (%)			
No	24 (34.8)	56 (38.6)	80 (37.4)
Yes	45 (65.2)	89 (61.4)	134 (62.6)
Responsive to abi for metastatic disease†, n (%)			
No	31 (44.9)	45 (31.0)	76 (35.5)
Yes	18 (26.1)	35 (24.1)	53 (24.8)
Unknown	20 (29.0)	65 (44.8)	85 (39.7)

*Not collected due to regulatory reasons; †Response to treatment with abiraterone acetate plus prednisone was defined according to Response Evaluation Criteria in Solid Tumors and/or Prostate Cancer Working Group 2 criteria.
Abi=abiraterone acetate plus prednisone; ECOG=Eastern Cooperative Oncology Group; LHRHa=luteinizing hormone-releasing hormone agonist/antagonist; PSA=prostate-specific antigen.

Table 2. Enzalutamide treatment duration

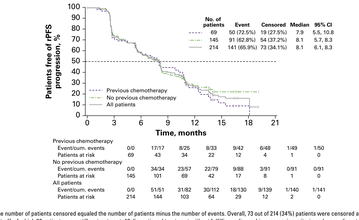
Characteristic	Previous chemotherapy (n=69)	Chemotherapy-naive (n=145)	Total (n=214)
Exposure duration,* months, median (minimum, maximum)	5.5 (0.4, 18.3)	5.9 (0.03, 19.9)	5.7 (0.03, 19.9)
Patients on treatment at: n (%)			
3 months	45 (65.2)	109 (75.2)	154 (72.0)
6 months	27 (39.1)	72 (49.7)	99 (46.3)
9 months	12 (17.4)	52 (35.9)	64 (29.9)
12 months	8 (11.6)	27 (18.6)	35 (16.4)
Patients with ⩾1 dose reduction to AE, n (%)	0	3 (2.1)	3 (1.4)

*Duration of exposure in days is calculated as the number of days between the first and last date of dosing +1 and then converted to months. The cut-off date is used as the last date of dosing for patients still on treatment by the cut-off date.
AE=adverse event.

rPFS

- A total of 141 of 214 (65.9%) patients had disease progression, 101 (47.2%) with radiographic progression and 40 (18.7%) deaths (**Figure 1**).
- Overall, the median duration of rPFS was 8.1 months (95% CI 6.1, 8.3) and was similar in chemotherapy-naïve patients and patients previously treated with chemotherapy before abiraterone acetate plus prednisone.

Figure 1. Kaplan-Meier plot of rPFS

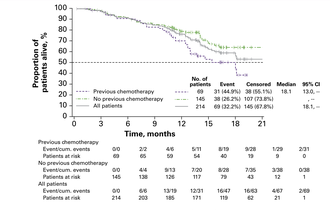


The number of patients censored equaled the number of patients minus the number of events. Overall, 73 out of 214 (34%) patients were censored at data cut-off, of which 30 patients were still on treatment; 43 discontinued treatment without fulfilling radiographic progression criteria and were alive at the time of data cut-off.
CI=confidence interval; rPFS=radiographic progression-free survival.

Overall survival

- A total of 69 of 214 (32.2%) patients had died from any cause at the data cut-off (**Figure 2**).

Figure 2. Kaplan-Meier plot of OS



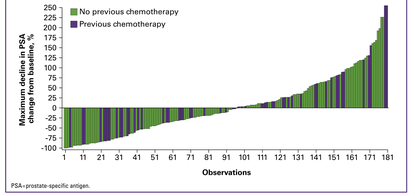
The number of patients censored equaled the number of patients minus the number of events. Approximately two-thirds of patients had no events (i.e. alive at cut-off date) and were therefore censored. Thirty of 145 (20.7%) patients were still on treatment by the cut-off date.
CI=confidence interval; OS=overall survival.

- Median OS time was not reached for the overall population or for chemotherapy-naïve patients.
- Median OS time for patients previously treated with chemotherapy before abiraterone acetate plus prednisone was 18.1 months (95% CI 13.0, –).

Rate of ⩾50% decline in PSA from baseline

- Overall, in 181 patients with at least one post-baseline PSA assessment, the unconfirmed PSA response rate was 26.5% (95% CI 20.3, 33.6), with 48 patients having a ⩾50% decrease in PSA from baseline (**Figure 3**).
  - The (unconfirmed) response rate was 28.1% (16 out of 57; 95% CI 17.0, 41.5) and 25.8% (32 out of 124; 95% CI 18.4, 34.4) for patients with previous chemotherapy and chemotherapy-naïve patients, respectively.
  - This ⩾50% decline in PSA from baseline was confirmed by a subsequent PSA measurement in 35 out of 48 patients.

Figure 3. Waterfall plot of maximum decline (%) in PSA

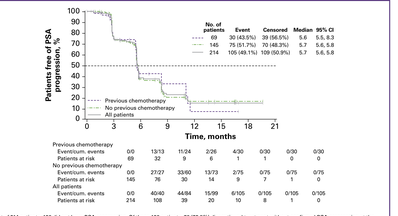


PSA=prostate-specific antigen.

PSA progression

- PSA progression was observed in 105 patients in the overall population (49.1%) at any time during the study (**Figure 4**).
- The median time to PSA progression was 5.7 months (95% CI 5.6, 5.8) in the overall population (**Figure 4**).

Figure 4. Kaplan-Meier plot of time to PSA progression



Out of 214 patients, 109 did not have PSA progression. Of these 109 patients, 79 (72.5%) discontinued treatment without confirmed PSA progression at the time of data cut-off.
CI=confidence interval; PSA=prostate-specific antigen.

Safety

- The safety profile was similar in both the chemotherapy-naïve patients and patients with chemotherapy before abiraterone acetate plus prednisone (**Table 3**).
- The most frequently reported (⩾5% overall) study drug-related treatment-emergent adverse events were fatigue (26.6%), decreased appetite (12.6%), asthenia (8.9%), nausea (7.9%), and constipation (5.6%). There were no seizures reported.

Table 3. Treatment-emergent adverse events

Adverse event, n (%)	Total (n=214)
Any TEAE	199 (93.0)
NCI-CTCAE Grade ⩾3	93 (43.5)
Drug-related	127 (59.3)
Drug-related NCI-CTCAE Grade ⩾3	18 (8.4)
TEAEs with death as an outcome	19 (8.9)
SAEs*	81 (37.9)
Drug-related† SAEs*	8 (3.7)
TEAEs leading to study drug discontinuation	70 (32.7)
Drug-related† TEAEs leading to study drug discontinuation	22 (10.3)

*Included SAEs upgraded by the sponsor based on review of the sponsor's list of always serious terms, if any upgrade was done; †Possible or probable, as assessed by the investigator or records where relationship was missing.
NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs=serious adverse events; TEAEs=treatment-emergent adverse events.

STUDY LIMITATIONS

- This was a single-arm study design, which is not generally used as confirmation of efficacy. The study was not designed to provide definitive answers regarding treatment sequencing, and further studies would be needed to address treatment sequencing.
- Symptomatic improvement and symptomatic deterioration, measured using patient-related outcomes, were not assessed in this trial.

CONCLUSIONS

- In this study, enzalutamide demonstrated anti-tumor activity in some patients with mCRPC who had previously progressed following at least 24 weeks of treatment with abiraterone acetate plus prednisone:
  - rPFS was 8.1 months (95% CI 6.1, 8.3).
  - The median OS time was not reached for the overall population.
  - PSA response rate was 26.5% (95% CI 20.3, 33.6).
  - The median time to PSA progression was 5.7 months (95% CI 5.6, 5.8).
- In these patients who were treated with abiraterone acetate plus prednisone prior to enzalutamide, similar outcomes were observed between chemotherapy-naïve patients and patients who received chemotherapy prior to abiraterone acetate plus prednisone.
- Adverse events reported were consistent with the established safety profile of enzalutamide.

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REFERENCES

1. Ferlay J et al. 2014. Available at: http://globocan.iarc.fr.
2. Astellas Pharma US, Inc., Medivation, Inc. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf.
3. Centocor Ortho Biotech Inc. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf.
4. Beer TM et al. N Engl J Med 2014; 371: 424-433.
5. Scher HI et al. N Engl J Med 2012; 367: 1187-1197.
6. Penson DF et al. J Clin Oncol 2016; 34: 2098-2106.
7. Shore ND et al. Lancet Oncol 2016; 17: 153-163.
8. Rathkopf DE et al. Eur Urol 2014; 66: 815-825.
9. Ryan CJ et al. N Engl J Med 2013; 368: 138-148.
10. Fizazi K et al. Lancet Oncol 2012; 13: 983-992.
11. Loriot Y et al. Ann Oncol 2013; 24: 1807-1812.
12. Noonan KL et al. Ann Oncol 2013; 24: 1802-1807.