The Prostate 75:836–844 (2015)

Safety of Enzalutamide in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel: Expanded Access in North America

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BACKGROUND. The open-label, single-arm enzalutamide expanded access program (EAP) in the United States and Canada evaluated the safety of enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) who had previously received docetaxel.
METHODS. Patients (n = 507) received enzalutamide 160 mg/day until disease progression, intolerable adverse events (AEs), or commercial availability occurred. AEs and other safety variables were assessed on day 1, weeks 4 and 12, and every 12 weeks thereafter. Data following transition to commercial drug were not collected.

[The copyright line for this article was updated in April 2015 after initial online publication.]
Grant sponsor: Astellas Pharma, Inc. and Medivation, Inc.; ClinicalTrials.gov; Grant number: NCT01606982.

FINANCIAL DISCLOSURES: AMJ received research funding from Astellas and Janssen. NDS received research/consulting funding from Astellas, Bayer, Dendreon, Janssen, Medivation, Pfizer, and Millennium. F.S. has served as a consultant and conducted research funded by Astellas. K.N.C. served a consultant role with Astellas. C.A.O. received research funding from National Cancer Institute, Dendreon, Exosome Diagnostics Inc., Astellas, and Medivation; has partial ownership of a patent used by Dianon; and owns stock in Egenix. U.E. received grant funding from Astellas, served a consultant role with Amgen, Astellas, Bayer, Janssen, Novartis, and Sanofi-Aventis, and received funding support from Exelixis. M.S. has no relevant financial disclosures. W.B. participated in Astellas and Medivation speakers bureaus and advisory boards. S.D.M. received funding from Astellas, Janssen, and Amgen. E.W. and N.B.H. have no relevant financial disclosures. M.A.F., C.D., and N.H. are employed by Astellas. F.P. was an employee of Astellas at the time of project initiation. M.H. is an employee of Medivation and owns stock in Medivation. D.R. received research funding from Astellas and Medivation.

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Received 25 September 2014; Accepted 29 December 2014
DOI 10.1002/pros.22965
Published online 14 February 2015 in Wiley Online Library (wileyonlinelibrary.com).

RESULTS. Median age was 71 years (range 43–97); 426 patients (83.9%) had a baseline ECOG score of $\leq$1. In addition to docetaxel, the majority of patients had received prior prostate cancer treatments such as abiraterone (76.1%) or cabazitaxel (28.6%). Median study treatment duration was 2.6 months (range 0.03–9.07). The most frequently reported reasons for discontinuation were commercial availability of enzalutamide (46.7%) and progressive disease (33.7%). A total of 88.2% of patients experienced AEs; 45.4% experienced AEs with a maximum grade of 1 or 2. Fatigue (39.1%), nausea (22.7%), and anorexia (14.8%) were the most commonly reported AEs. Seizure was reported in four patients (0.8%). The most commonly reported event leading to death was progression of metastatic prostate cancer (7.7%).
CONCLUSION. In this heavily pretreated EAP population with progressive mCRPC, enzalutamide was well tolerated and the safety profile was consistent with that of the AFFIRM trial. *Prostate 75:836–844, 2015.*

KEY WORDS: **enzalutamide; metastatic castration-resistant prostate cancer; expanded access program; safety; treatment exposure**

INTRODUCTION

The first approved treatment for metastatic castration-resistant prostate cancer (mCRPC) was docetaxel plus prednisone, based on the survival benefit demonstrated in the TAX327 trial [1,2]. However, as with other approved mCRPC therapies, patients subsequently experience disease progression due to inherent or acquired resistance, or because they are unable to tolerate associated toxicities, with a median overall survival period typically of less than 20 months [1–3]. Until recently, treatment options for patients progressing on or after docetaxel were limited. Enzalutamide is an oral androgen receptor (AR) inhibitor currently available for patients with mCRPC who have previously received docetaxel; recently, approval was expanded in the United States and European Union to include patients with mCRPC who have not yet received chemotherapy. Other treatments approved in patients with mCRPC include abiraterone, cabazitaxel, sipuleucel-T, and radium-223 [4–8]. The AR signaling pathway continues to play an important role in prostate cancer progression after patients become castration resistant, in part due to overexpression of the AR itself and intracrine testosterone synthesis [9–11], and represents a therapeutic target for treating disease progression post-docetaxel. Enzalutamide is unique among non-steroidal antiandrogens in that it has minimal agonist activity against wild-type AR [12]. Its mechanism of action is also distinct in that it blocks multiple steps in the AR signaling pathway, potentially leading to induction of cancer cell death and tumor regression [13].

Approval of enzalutamide post-docetaxel in patients with mCRPC was based on the results of the randomized, double-blind, placebo-controlled, multinational, Phase III AFFIRM study which evaluated the efficacy, safety, and tolerability of enzalutamide in men with mCRPC who had previously received docetaxel [14]. In AFFIRM, the median overall survival of patients treated with enzalutamide was 18.4 months versus 13.6 months for patients who received placebo (hazard ratio for death vs. placebo, 0.63; 95% CI: 0.53–0.75; $P < 0.0001$). While the period of observation for the enzalutamide group was more than double that for the placebo group, the rate of adverse events (AEs) was generally similar between the two treatment arms. AEs reported in a greater proportion of patients treated with enzalutamide compared with placebo included seizures[1] (0.6% vs. 0%), cardiac disorders (8% vs. 6%), and hypertension or significantly increased blood pressure above baseline (6.6% vs. 3.3%) [14].

After successful completion of the AFFIRM study and prior to the commercial availability of enzalutamide in North America, an expanded access program (EAP) study was conducted to enable patients with advanced prostate cancer to have access to enzalutamide before a final regulatory decision was available [15]. The objective of the open-label EAP was to provide access to enzalutamide to patients with progressive mCRPC previously treated with docetaxel for whom there was no comparable or satisfactory alternative therapy (in the investigator's judgment) and to monitor safety outcomes associated with enzalutamide administration.

The EAP study reported here describes a safety profile of enzalutamide that would more closely reflect the experience of patients observed in real-world clinical practice.

[1] In addition to the five patients with an AE of seizure reported on study prior to the interim analysis cut-off date in AFFIRM, one additional study patient was identified with an event term syncope with features suggestive of a seizure, and another patient was diagnosed with a seizure after the interim analysis cut-off date.

MATERIALS AND METHODS

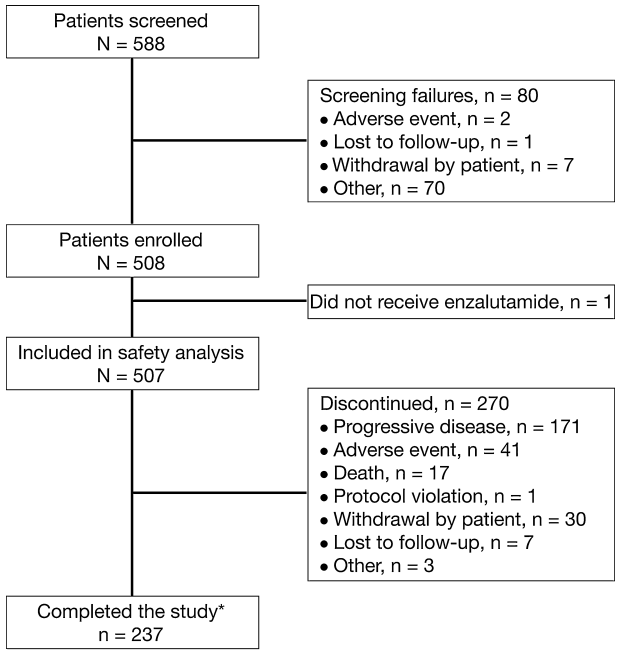
Study Design

This multicenter, single-arm, open-label study was conducted at 54 sites across the United States (38) and Canada (16) in patients with progressive mCRPC previously treated with docetaxel-based chemotherapy for whom, in the judgment of the investigator, there was no comparable or satisfactory alternative therapy (NCT01606982). Written informed consent was obtained from study participants before any study procedures were initiated. The study protocol was reviewed by independent ethics committees or institutional review boards and was conducted according to the ethical principles of the Declaration of Helsinki.

Male patients were eligible for study participation if they had histologically or cytologically confirmed adenocarcinoma of the prostate; ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analogue (agonist or antagonist), or orchiectomy (i.e., surgical or medical castration); at least one prior chemotherapy regimen for mCRPC with at least one regimen containing docetaxel; progressive disease as per determination of the investigator (prostate-specific antigen rise, or radiographic or clinical worsening of disease); and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Patients were excluded if they received hormonal therapy, chemotherapy, or biologic therapy for prostate cancer (other than bone-targeting agents such as bisphosphonates or denosumab, GnRH analogue therapy, or glucocorticoids, which were allowed) within 3 weeks from baseline, radiation therapy within 3 weeks from baseline (2 weeks if single fraction of radiotherapy), or radionuclide therapy within 8 weeks from baseline. Patients with a history of seizures or a condition that could predispose them to seizures, a history of loss of consciousness, or transient ischemic attack within 12 months from study entry were also excluded.

Eligible patients received oral enzalutamide 160 mg/day until disease progression, intolerable AEs including any seizure, or commercial availability of enzalutamide occurred. Patients were discontinued from the study if they were unable to maintain an absolute neutrophil count >500/μl, platelet count >25,000/μl, or if they had elevations in liver function tests such as alanine or aspartate aminotransferase values >8 times the upper limit of normal. Patients completed assessments on day 1 (baseline), week 4, week 12, and every subsequent 12 weeks until discontinued from the study (Fig. 1). Although efficacy data were not collected in this study, the treatment protocol recommended that investigators perform regular disease assessments including clinical, radiographic, and/or prostate-specific antigen assessments at least every 12 weeks. An end-of-study visit was performed 30 days after the last dose of study treatment, prior to the initiation of commercially supplied enzalutamide, or prior to the initiation of another anticancer therapy, whichever occurred first. Upon commercial availability of enzalutamide in a given country, enrollment was stopped and patients who were still on the study drug were deemed "study completers" and discontinued from the expanded access treatment protocol (and offered the option to transition to commercially available enzalutamide). Data were not collected following transition to commercially available enzalutamide.



*On study drug at the time enzalutamide became commercially available in the patient's country

Fig. 1. Patient flow diagram.

Safety Assessments

Reporting of AEs, serious AEs (SAEs; defined as any AE that resulted in death, was life threatening, resulted in persistent or significant incapacity or disruption of normal life functions, required or prolonged hospitalization, or any other medically important event), vital signs, and routine laboratory measurements (hematology and chemistry) were performed at all study visits. SAEs, including death, were collected from the time the patient signed the consent form until the end-of-study visit. Patients who transitioned to commercially supplied enzalutamide after the end-of-study visit had safety monitored by the treating physician, with spontaneous reporting of AEs in the post-marketing period.

Statistical Analysis

As this was an open-label, expanded access treatment protocol, no formal sample size calculation was performed. All patients who received at least one dose of enzalutamide were analyzed for safety. All safety assessments were summarized with descriptive statistics. Study exposure was evaluated in patients with a last dose date. Kaplan–Meier methods were used to estimate the median time to discontinuation due to either disease progression or death in patients with evaluable study drug exposure. Patients that discontinued due to reasons other than progressive disease or death were censored at last dose date.

RESULTS

Baseline Demographics and Medical History

In the United States, enrollment into the EAP began in May 2012 and enzalutamide became commercially available 4 months later (September 2012). In Canada, EAP enrollment began in November 2012 and enzalutamide became commercially available 7 months later (June 2013). Overall, 508 patients were enrolled in the study; 507 patients (United States, 282; Canada, 225) received at least one dose of enzalutamide and were included in the safety analysis. At baseline, the median age was 71.0 years; the majority of patients (56.1%) had a baseline ECOG performance status of 1 (Table I). Two-hundred-and-ninety patients (57.2%) had a history of hypertension and 133 patients (26.2%) had a history of cardiac disorders (Table I). The study population was heavily pretreated for prostate cancer, with a median of five prior unique antineoplastic therapies per patient. In addition, 146 patients (28.7%) had received two prior unique chemotherapies and 79 patients (15.6%) had received three or more. The majority of patients (76.1%) had previously received abiraterone, 28.6% had received prior cabazitaxel, and 24.9% had received both abiraterone and cabazitaxel (Table II).

TABLE I. Baseline Demographics and Disease Characteristics

Characteristic	Enzalutamide 160 mg/day (n = 508)[a]
Median (range) age, years	71 (43-97)
Race: White, n (%)	448 (88.2)
ECOG performance status, n (%)	
0	141 (27.8)
1	285 (56.1)
2	81 (15.9)
Gleason score ≥8 at initial diagnosis, n (%)	269 (53.0)
Mean LDH, IU/L	367.7
Mean alkaline phosphatase, U/L	231.1
Prior medical history, n (%)	
Cardiac disorders	133 (26.2)
Hypertension[b]	290 (57.2)

ECOG, Eastern Cooperative Oncology Group; IU/L, international units per liter; LDH, lactate dehydrogenase; U/L, units per liter.
[a]One patient did not receive treatment and was excluded from the safety analysis.
[b]Includes essential hypertension.

Study Completers

At the time enzalutamide became commercially available and the sponsor halted enrollment, 237 patients (46.7%) were on the study drug (United States, n = 140; Canada, n = 97); these patients were deemed "study completers." All study completers were offered the option to transition to commercially supplied enzalutamide; 227 (95.8%) transitioned (United States, n = 130; Canada, n = 97).

Study Drug Exposure

In the overall study population with evaluable study drug exposure (i.e., patients with a last dose date, n = 502), the median duration of exposure to enzalutamide was 2.6 months (range 0.03–9.07). Patients in the United States, where enzalutamide became commercially available more quickly after initiation of EAP enrollment than in Canada, had a slightly shorter median duration of exposure (2.3 months [range 0.03–6.0]) compared with patients in Canada (2.8 months [range 0.3–9.1]). In a post hoc analysis to further investigate treatment exposure, the median exposure for patients who completed the study was slightly longer (2.8 months [range 0.9–9.1]) than that of the overall population. In contrast, patients who discontinued from the study for any reason other than commercial availability of enzalutamide had a shorter median exposure (2.2 months [range 0.03–8.7]).

Patients who discontinued from the study due to disease progression had a median exposure of 2.5 months (range 0.4–8.1). For the total study population (i.e., 502 patients with evaluable study drug exposure), the median time to discontinuation due to progression or death, adjusted for censoring, is 4.6 months (95%CI: 3.8–5.4). Prior prostate cancer treatment in patients who discontinued due to disease progression was more frequent (abiraterone, 78.9%; cabazitaxel, 31.0%; both abiraterone and cabazitaxel, 25.7%) compared with patients who completed the study (abiraterone, 70.5%; cabazitaxel, 22.8%; both abiraterone and cabazitaxel,

TABLE II. Prior Prostate Cancer Treatment Before Entering the Expanded Access Program

Treatment, n (%)	Enzalutamide 160 mg/day (n = 507)
Chemotherapy	
Docetaxel	507 (100)
Cabazitaxel[a]	145 (28.6)
Anthracycline	33 (6.5)
Androgen synthesis or androgen receptor blocker	
Bicalutamide	433 (85.4)
Nilutamide	86 (17.0)
Flutamide	81 (16.0)
Ketoconazole	124 (24.5)
Abiraterone[a]	386 (76.1)

[a]126 patients (24.9%) received both cabazitaxel and abiraterone.

18.6%). It should be noted that >95% of study completers transitioned to commercially available enzalutamide; however, the duration of this subsequent treatment was not assessed. For the 382 patients with evaluable study drug exposure and prior abiraterone use, the median time to discontinuation due to progression or death, adjusted for censoring, is 4.4 months (95%CI: 3.5–5.3).

Study Discontinuations, Adverse Events, and Other Safety Assessments

In the safety population (n = 507), the most frequent reason for study discontinuation other than commercial availability of enzalutamide was disease progression (overall population, n = 171 [33.7%]; United States, n = 82 [29%]; Canada, n = 89 [40%]). AEs led to discontinuation in 8.1% (n = 41) of the overall population (United States, n = 18; Canada, n = 23). Drug-related AEs leading to treatment discontinuation occurred in 19 patients (3.7%); those that occurred in at least two patients were fatigue (n = 4 [0.8%]), seizures (n = 3 [0.6%]), and dyspnea (n = 2 [0.4%]).

In this population of patients with progressive mCRPC, most patients reported at least one AE (88.2%) (Table III). Grade 1 or 2 AEs (45.4%) were more frequent than grade 3 (29.0%), grade 4 (3.9%), or grade 5 (9.9%) AEs. Drug-related AEs that were grade ≥3 were reported in 72 patients (14.2%). The most commonly reported AEs (any grade) were fatigue (39.1%), nausea (22.7%), and anorexia (14.8%). SAEs were reported by 143 patients (28.2%) and the most frequently reported (>1%) were disease progression (n = 40 [7.9%]), pneumonia (n = 10 [2.0%]), asthenia (n = 9 [1.8%]), anemia (n = 8 [1.6%]), and back pain (n = 7 [1.4%]). Drug-related SAEs reported in more than one patient were seizure (n = 4 [0.8%]), asthenia (n = 3 [0.6%]), and vomiting (n = 2 [0.4%]). AEs leading to dose reduction occurred in 17 patients (3.4%); the most common (>1%) event was fatigue (n = 9 [1.6%]). AEs leading to dose interruption occurred in 60 patients (11.8%); the most common (>1%) events were fatigue (n = 9 [1.8%]), nausea (n = 7 [1.4%]), and asthenia (n = 6 [1.2%]). Among AEs of interest (targeted medical events) (Table III), seizure was reported in four patients (0.8%), of whom two were found to have brain metastases, one had encephalomalacia with associated hemorrhagic contusions, and no confounding factor was identified for the fourth patient.

Hypertension was reported in 12 patients (2.4%), most of whom had grade 2 (n = 8 [1.6%]) events, with the maximum being grade 3 (n = 3 [0.6%]) (Table III). Five events of hypertension were reported as related to the study drug; four were deemed grade 2 and one as grade 3. No SAEs of hypertension were reported. Clinically significant systolic blood pressure elevation (i.e., ≥180 mm Hg and ≥20 mm Hg increase from baseline) occurred in four patients (0.8%), and clinically significant diastolic blood pressure elevation (i.e., ≥105 mm Hg and ≥15 mm Hg increase from baseline) occurred in one additional patient (0.2%). All five patients had a medical history of hypertension.

No additional safety signals were observed in the clinical laboratory measurements throughout the study and there was no clinical laboratory evidence of drug-related hepatotoxicity.

Deaths

AEs leading to death occurred in 50 patients (9.9%). The most commonly reported event leading to death was malignant neoplasm progression in 39 patients (7.7%), among whom two patients also had another AE leading to death (gastrointestinal perforation, n = 1; wound sepsis, n = 1); none were considered related to treatment. Seven additional patients had other non-drug-related AEs leading to death: embolic stroke; metastases to the central nervous system; anemia; death (not otherwise specified); congestive heart failure; hepatic failure associated with metastases to the liver; and (in the same patient) cardiac arrest and lower gastrointestinal hemorrhage.

Drug-related treatment-emergent AEs leading to death occurred in four patients (0.8%); of these, three were considered to be possibly drug-related (cerebrovascular accident, acute myocardial infarction, and myocardial infarction) and relationship to treatment was not reported for the remaining event (death not otherwise specified) and was thus considered possibly drug related as per the protocol.

TABLE III. Summary of Adverse Events According to Grade[a]

Adverse event, n (%)	Any grade (n = 507)	≥Grade 3 (n = 507)
≥1 AE	447 (88.2)	217 (42.8)
≥1 serious AE	143 (28.2)	128 (25.2)
AE leading to death	50 (9.9)	50 (9.9)
≥1 drug-related AE[b]	280 (55.2)	72 (14.2)
Frequent (≥10%) AEs		
Fatigue	198 (39.1)	50 (9.9)
Nausea	115 (22.7)	12 (2.4)
Anorexia	75 (14.8)	8 (1.6)
Anemia	60 (11.8)	33 (6.5)
Peripheral edema	58 (11.4)	1 (0.2)
Back pain	52 (10.3)	14 (2.8)
Vomiting	52 (10.3)	8 (1.6)
Arthralgia	51 (10.1)	9 (1.8)
AEs of interest[c]		
Falls	12 (2.4)	3 (0.6)
Decreased neutrophil count	7 (1.4)	4 (0.8)
Non-pathological fractures	7 (1.4)	4 (0.8)
Loss of consciousness	1 (0.2)	1 (0.2)
Seizure	4 (0.8)	3 (0.6)
Cognitive disorder/memory impairment[d]	23 (4.5)	6 (1.2)
Hallucination[e]	8 (1.6)	0
Hypertension	12 (2.4)	3 (0.6)

AE, adverse event.
[a]AE severity was graded according to the Cancer Therapy and Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, ranging from 1 (mild) to 5 (death related to AE).
[b]AEs considered by the investigator to be possibly or probably related to enzalutamide.
[c]AEs of interest were targeted medical events derived using preferred terms, high-level terms, and standard Medical Dictionary for Regulatory Activities queries.
[d]Includes amnesia, memory impairment, cognitive disorder, disturbance in attention.
[e]Includes hallucination, hallucination auditory, and hallucination visual.

DISCUSSION

In this expanded access population in the United States and Canada, enzalutamide was well tolerated in patients with mCRPC previously treated with docetaxel. The majority of AEs were grade 1 or 2 and the most frequently reported AEs (of any grade) were fatigue, nausea, and anorexia. At the time that enzalutamide became commercially available in the United States or Canada, approximately 47% of patients included in the EAP were still on the study drug and were considered to have completed the study; of these completers, approximately 96% of patients transitioned to commercially available enzalutamide.

There were a number of important differences between the EAP population and the patients treated in the Phase III AFFIRM study. The EAP population may have had more advanced disease and thus may also have received more extensive pretreatment regimens of antineoplastic therapies, as AFFIRM only allowed up to two prior chemotherapy regimens and excluded prior abiraterone use [14]. In contrast, in the EAP, a median of five prior unique antineoplastic therapies was received per patient, 15.6% of patients (79 out of 507) had received at least three prior unique chemotherapy agents, and 76.1% of patients (386 out of 507) had previously received abiraterone. Abiraterone and cabazitaxel were approved in North America for the treatment of patients with mCRPC post-docetaxel after the initiation of AFFIRM and substantial numbers of patients in the EAP received these drugs. In addition, almost twice as many EAP patients had an ECOG performance status of 2 (15.9%) compared with patients who received enzalutamide in the AFFIRM study (8.8%).

Despite these differences between the patient populations, the overall safety profile of enzalutamide in this heavily pretreated EAP population was generally consistent with that seen in the AFFIRM study. Fatigue (all grades) was the most frequently reported AE in both studies; it was reported by 39.1% of patients in the EAP, which is a slightly higher incidence than that reported by enzalutamide-treated

patients in the AFFIRM trial (34.0%; 29% with placebo). In the EAP study, the reported fatigue was clinically manageable, with the majority of events classified as grade 1 or 2 (148 of 198 events; 75% of the fatigue events) and with 5 of 507 patients (1%) discontinuing the study due to fatigue (four events were considered treatment-related). The observed small differences in the incidence of fatigue reported in the EAP and AFFIRM could be related to differences in the study design (i.e., observational vs. randomized, double-blind study), as well as to the different disease stage the enrolled patients were in, with EAP enrolling more severely ill and more progressed patient population than AFFIRM. Seizures were reported by a similarly low proportion (<1%) of patients treated with enzalutamide in the two studies; none were reported in the placebo arm of AFFIRM. Brain metastases were detected after the seizure event in two of the four patients reporting seizure in the EAP and in two of the five patients reporting seizure in the AFFIRM study. Hypertension was reported in 6.6% of patients treated with enzalutamide in AFFIRM versus 2.4% of patients in the EAP. The rates of other commonly reported AEs were generally lower with enzalutamide in the EAP than in AFFIRM (nausea, 23% vs. 33%; anorexia, 15% vs. 25%). The observed differences in these AE rates may reflect the shorter median treatment duration in the EAP versus AFFIRM [14].

The median treatment duration with enzalutamide in the EAP was influenced by the early commercial availability of the drug in the United States and Canada after EAP initiation; consequently, the median treatment duration was 2.6 months, considerably shorter than in the AFFIRM study (8.3 months) [14]. It is notable that almost all of the patients who were on the study drug when enzalutamide became commercially available and "completed" the study opted to transition to commercial enzalutamide; subsequent exposure to commercial enzalutamide was not recorded. The shorter median treatment duration in the EAP versus AFFIRM may thus underestimate the total enzalutamide exposure time of patients who transitioned to commercial enzalutamide.

The North American EAP reported here is the largest population to date (>500 patients) in which the safety of enzalutamide was investigated in patients who more closely reflect a real-world clinical population compared with patients included in clinical trials (due to typically more stringent inclusion and exclusion criteria in the latter). The results reported here are generally consistent with smaller retrospective and prospective reports on the tolerability of enzalutamide treatment. In retrospective evaluations of EAPs for enzalutamide in patients with mCRPC who had previously received both docetaxel and abiraterone in the Netherlands (n = 69) [16], the UK (n = 39) [17], or one of four European compassionate use programs (n = 137) [18], the median duration of enzalutamide treatment was 14.9 weeks (interquartile range 11.1–20.0 weeks), 2.9 months (95% CI: 1.7–4.0), and 3.2 months, respectively, similar to that reported in the current North American EAP. In these other EAPs [16,17], fatigue was also the most frequently reported AE with enzalutamide treatment. In contrast, in a German compassionate use program for patients with mCRPC (n = 35) who received enzalutamide after both taxane-based chemotherapy and abiraterone treatment, anemia and weight loss were the most common events of any grade reported by patients and median treatment duration on enzalutamide was 2.8 months [19]. In addition to tolerability, these EAPs and other studies also investigated the efficacy of enzalutamide to assess the potential cross-resistance with enzalutamide after docetaxel and abiraterone therapy [16,17,19,20] or prior to abiraterone treatment [21,22]. Their results suggested more modest antitumor activity for enzalutamide after prior treatment with docetaxel/abiraterone, or for abiraterone after previous treatment with docetaxel and enzalutamide [16,17,19–22]. The potential influence of prior abiraterone use on the impact of enzalutamide treatment can also be observed in this study, wherein time to study drug discontinuation due to progressive disease or death for all patients who received enzalutamide with evaluable study drug exposure was 4.6 months (95%CI: 3.8–5.4), which is slightly longer than the 4.4 months (95%CI: 3.5–5.3) for the subgroup of patients with evaluable study drug exposure and prior abiraterone use.

There were several limitations to this study. The EAP study was an open-label, non-comparative study; therefore, its results should be interpreted with caution. In addition, this EAP study did not include efficacy assessments and was thus unable to provide information regarding the efficacy of enzalutamide in this patient population. Other limitations included the lack of data collection regarding exposure information following transition to commercially available enzalutamide and other subsequent prostate cancer treatments, which could have provided more insights regarding enzalutamide tolerability with longer treatment duration.

CONCLUSION

The safety profile of enzalutamide in this EAP in the United States and Canada was consistent with the profile seen in the AFFIRM trial. No additional safety signals were identified in patients with mCRPC

heavily pretreated with prostate cancer therapies prior to enzalutamide treatment.

ACKNOWLEDGMENTS

The authors had full access to the data and participated in reviewing and interpreting the data and paper. They would like to thank Dr. Joy Ramos at Complete HealthVizion for assistance with writing and revising the draft manuscript, based on detailed discussion and feedback from all authors. Writing and copy-editing assistance was funded by Astellas Pharma, Inc. and Medivation, Inc. Primary responsibility for opinions, conclusions, and interpretation of data lies with the authors. All authors read and approved the final version of this manuscript.

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