The evolving role of enzalutamide on the treatment of prostate cancer

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The field of prostate cancer has witnessed incredible progress in the last decade, owing to the approval of multiple survival-prolonging treatments for metastatic castration-resistant prostate cancer (mCRPC). Enzalutamide is a nonsteroidal androgen receptor inhibitor that targets multiple steps in the androgen receptor signaling axis. It has been approved for the treatment of mCRPC both in the postdocetaxel and in the chemotherapy-naïve settings. We summarize the milestones in the development of enzalutamide in patients with prostate cancer. Special focus is placed on the results of the STRIVE Phase II clinical trial comparing head to head enzalutamide and bicalutamide in patients with nonmetastatic and mCRPC who have failed androgen deprivation and in other ongoing trials in the same setting and in earlier disease phases.

First draft submitted: 21 October 2015; Accepted for publication: 7 December 2015; Published online: 3 February 2016

The realization that castration-resistant prostate cancer (CRPC) remains dependent on persistent androgen receptor (AR) signaling is the foundation for a new generation of agents targeting the AR axis. Two of these agents, abiraterone acetate and enzalutamide, have been shown to prolong overall survival (OS) in patients with mCRPC. Both agents received FDA approval based on data from four randomized trials – COU-AA-301 and AFFIRM in the postchemotherapy setting and COU-AA-302 and PREVAIL in the prechemotherapy setting – comparing either enzalutamide or abiraterone to placebo or prednisone [1–4].

Enzalutamide is a second-generation AR inhibitor that blocks multiple steps in the AR signaling pathway [5]. It is a potent AR blocker that competes with dihydrotestosterone, the active metabolite of testosterone. In contrast to first-generation antiandrogens, enzalutamide also prevents the translocation of the AR from the cytoplasm to the nucleus and inhibits AR binding to chromosomal DNA, which prevents further transcription of androgen-responsive genes.

Preclinical & early clinical studies of enzalutamide in mCRPC

The development of enzalutamide reflects our evolving understanding of the biology of CRPC. In preclinical studies, this drug demonstrated the ability to inhibit AR signaling in overexpressing AR cells with higher receptor binding affinity than bicalutamide and lack of agonistic activity [5,6]. It also showed greater regression of tumor cells in a castration-resistant LNCaP/AR human prostate cancer cell model [5,6]. These findings supported the evaluation of enzalutamide

KEYWORDS

- castration-resistant prostate cancer
- enzalutamide
- hormone-sensitive prostate cancer
- prostate cancer
- STRIVE

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in subsequent clinical trials in patients with mCRPC.

A Phase I–II study determined that the maximum tolerated dose was 240 mg, with fatigue as the most frequent adverse event (AE; grade 3–4 in 11% of patients) [7]. The subsequent lower level (150 mg) was established as the dose to be used in further studies, although the final commercialized dose was 160 mg. In this study, 140 patients with mCRPC were enrolled in dose-escalation cohorts of three to six patients. Prostate-specific antigen (PSA) responses were seen at all dose levels, in both chemotherapy-naïve and chemotherapy-treated patients. Partial responses were also observed in 13 (22%) out of 59 patients with soft tissue metastases [7]. In an updated analysis, the investigators have reported on the long-term results and safety of enzalutamide Phase I–II in 65 chemotherapy-naïve and 75 post-chemotherapy patients with mCRPC. Outcomes were analyzed at 17 months follow-up duration for antitumor activity and >4-year follow-up period for safety. The median time to PSA progression was not reached (NR) for chemotherapy-naïve patients and was 45 weeks for chemotherapy-exposed patients. Furthermore, median time to radiographic progression were 56 and 25 weeks for chemotherapy-naïve and chemotherapy pretreated patients, respectively. The updated results of this trial provided valuable insights on long-term use and tolerance of enzalutamide in patients with advanced disease. Fatigue of any grade was again the most common side effect experienced by 70% of patients, with 14% of patients reporting grade 3–4 fatigue in the 4-year follow-up safety report [8].

Enzalutamide for the treatment of CRPC

• AFFIRM & PREVAIL clinical trials

Promising initial results on enzalutamide led to a randomized, controlled, open-label, Phase III trial in patients with mCRPC: AFFIRM in the postchemotherapy setting and PREVAIL in chemo-naïve patients [2,4].

In patients who had progressed after docetaxel therapy, the landmark Phase III AFFIRM trial demonstrated a survival benefit in men treated with enzalutamide, reducing the risk for death by 37% compared with placebo (hazard ratio [HR] for death: 0.63, 95% CI: 0.53–0.75; $p < 0.001$). Enzalutamide was also superior over placebo with respect to all secondary end points, including decline in PSA level by 50% or more; the soft-tissue response rate; the time to

PSA progression, radiographic progression-free survival (PFS) and the time to the first skeletal-related event. Enzalutamide was also associated with significantly greater improvements in overall health-related quality of life (HRQoL; FACT-P total score) [4].

It is important to note that the use of prednisone or other glucocorticoids was permitted but not required. A total of 48% of enzalutamide patients and 46% of patients in the placebo arm were treated with glucocorticoids. A *post hoc* exploratory analysis found that on-study use of corticosteroids led to worse outcomes regardless of whether patients were randomly assigned to enzalutamide or placebo and was associated with higher rates of treatment-emergent grade 3 and 4 AEs.

Additional analyses of the AFFIRM trial have demonstrated that the benefits of enzalutamide are observed across different subgroups. For example, in a *post hoc* analysis, enzalutamide treatment resulted in a similar survival benefit in patients ≥ 75 years and < 75 years – patients < 75 years: HR: 0.63; 95% CI: 0.52, 0.78; median not yet reached versus 13.6 months; and patients ≥ 75 years: HR: 0.61; 95% CI: 0.43–0.86; median: 18.2 versus 13.3 months [9]. Furthermore, enzalutamide consistently improved OS, radiographic PFS and time to PSA progression compared with placebo, regardless of baseline PSA level (subgroups divided by baseline PSA quartile) [10].

In the Phase III PREVAIL study, enzalutamide was compared with placebo in the predocetaxel setting. In a planned interim analysis, more than 1700 patients with chemo-naïve mCRPC were analyzed. The study met its coprimary end points, with significant improvement for enzalutamide versus placebo in both radiographic PFS and OS. Patients treated with enzalutamide had an OS advantage compared with patients who received placebo ($p < 0.0001$). Enzalutamide provided a 30% reduction in the risk of death (HR: 0.70; 95% CI: 0.59–0.83). The survival benefit of enzalutamide was apparent in all prespecified subgroups, including patients with visceral metastases in the lung or liver. Moreover, there was a statistically significant radiographic PFS improvement compared with placebo-treated patients. After 12 months, the rate of radiographic PFS was 65% for enzalutamide-treated patients versus 14% for patients receiving placebo (81% risk reduction; HR: 0.19; 95% CI: 0.15–0.23; $p < 0.001$). A total of 58.5% of enzalutamide-treated

patients, most of them with soft tissue metastatic disease, showed complete or partial response as compared with 5% in placebo-treated patients. HRQoL was also significantly better for patients assigned to enzalutamide. Median time to deterioration (according to the FACT-P scale) was 11.3 months for the enzalutamide arm and 5.3 months for patients who received placebo (HR: 0.63; 95% CI: 0.54–0.72; $p < 0.001$) [2].

Across the placebo-controlled AFFIRM and PREVAIL trials, enzalutamide was well tolerated and has demonstrated a consistent safety and tolerability profile. The AE profile was generally comparable between the two treatment groups, with the exception of hot flash and fatigue, which was more common in those treated with enzalutamide. In the AFFIRM trial, the rates of AEs were similar in the two groups, with fewer AEs of grade 3–5 in the enzalutamide group. Of note, that in this study the period of observation for patients treated with enzalutamide was more than twice that for those receiving placebo. The median time to an AE of grade 3–5 was 8.4 months longer in the enzalutamide group than in the placebo group. Rates of fatigue, diarrhea and hot flashes were higher in the enzalutamide group. In the PREVAIL trial, patients receiving enzalutamide experienced more frequently AEs than those in placebo arm including fatigue and hot flash, and additionally, back pain, asthenia and fall. Hypertension was also reported at a higher rate in the enzalutamide group than in the placebo group in PREVAIL. Grade 3/4 AEs were reported in 43% of the patients in the enzalutamide arm compared with 37% with placebo.

Few seizures were reported in both trials. During the AFFIRM study, five of 800 patients receiving enzalutamide (0.6%) had seizures and two additional patients experienced seizures after data cut-off date. In the PREVAIL trial, only one seizure was reported in the enzalutamide group after the data cut-off date. Most of these patients had recognizable risk factors that may predispose patients for seizures such as brain metastases, use of lidocaine or brain atrophy associated with alcohol use [2,4].

The results of these trials led to the regulatory approval of enzalutamide for the treatment of chemotherapy-naïve or experienced patients with mCRPC. The initial success of these trials resulted in the design and launch of several clinical trials evaluating enzalutamide in distinct prostate cancer clinical settings (Table 1).

• STRIVE & TERRAIN clinical trials

Following the success of the enzalutamide in prior studies, additional clinical investigation in the frontline castrate-resistant setting includes two trials comparing enzalutamide with bicalutamide. The Phase II STRIVE study is a randomized, double-blind trial of enzalutamide head to head against bicalutamide in patients with and without metastatic disease. In parallel, TERRAIN trial, with a very similar design, enrolled only patients with mCRPC. STRIVE was mainly conducted in the USA, while TERRAIN was conducted primarily in Canada and Europe (NCT01288911; NCT01664923). Figure 1 displays STRIVE and TERRAIN trial designs. The initial findings of these trials have been presented at the 2015 European Association of Urology Meeting [11] and 2015 American Urological Association Annual Meeting [12]. Subsequently, results from these two trials were announced by ‘press release’ by Medivation, Inc. and Astellas Pharma Inc.

The purpose of STRIVE trial was to determine the safety and antitumor activity of enzalutamide compared with bicalutamide in nonmetastatic or metastatic patients with CRPC after progression with primary androgen-deprivation therapy (ADT). Three hundred ninety-six patients under castrate levels of testosterone were randomized to receive either 160 mg once daily enzalutamide or bicalutamide at 50 mg once daily. A total of 35% of patients had nonmetastatic disease and 65% had metastasis. At the time of enrollment, 52% had biochemically recurrent disease only, 32% had PSA increase with radiographic progression and 9% had radiographic progression only.

In this study, PFS was the primary end point defined as time from randomization to radiographic (bone or soft tissue) progression, PSA progression (defined by Prostate Cancer Working Group 2 criteria), or death due to any cause, whichever occurred first.

Data cut-off occurred after 236 PFS events. Patients treated with enzalutamide had a median PFS of 19.4 months compared with 5.7 months in the bicalutamide arm (HR: 0.24; 95% CI: 0.18–0.32; $p < 0.0001$). The time to PSA progression significantly favored enzalutamide (HR: 0.19; 95% CI: 0.14–0.26; $p < 0.0001$).

At the time of data cut-off for the primary analysis, secondary end points also favored enzalutamide. Radiographic PFS was not reached with enzalutamide versus 8.3 months in the

Table 1. Selected clinical trials testing enzalutamide in prostate cancer.

Setting	Called	Type of study	Clinical question/end points	Identification
Neoadjuvant	–	Phase II	Pathologic complete response rate following triplet therapy (enzalutamide in combination with leuprolide and dutasteride) and enzalutamide alone when administered as neoadjuvant therapy for 6 months prior to prostatectomy in patients with localized prostate cancer	NCT01547299
	The ANZUP ENZARAD Trial (ANZUP 1303)	Phase III	To determine the effectiveness of enzalutamide as part of adjuvant ADT with a LHRHA in men planned for radiotherapy for localized PC at high risk of recurrence	NCT02446444
	–	Phase II	To evaluate enzalutamide in combination with external beam radiation therapy as a possible treatment for intermediate-risk prostate cancer	NCT02028988
Biochemically Recurrent PC	EMBARK	Phase III	Efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in men with high-risk nonmetastatic prostate cancer progressing after definitive therapy	NCT02319837
	STREAM		To evaluate the efficacy of salvage therapeutic radiation with enzalutamide and ADT in men with recurrent prostate cancer (only rising PSA) after prostatectomy	NCT02057939
M1 HSPC	STAMPEDE	Phase III	To evaluate of drug efficacy – androgen suppression-based therapy alone or combined with zoledronic acid, docetaxel plus prednisolone, celecoxib, zoledronic acid plus docetaxel plus prednisolone, zoledronic acid plus celecoxib, abiraterone, abiraterone plus enzalutamide and/or radiotherapy in treating patients with locally advanced or metastatic prostate cancer	NCT00268476
	ENZAMET, ANZUP (ANZUP 1304)	Phase III	To determine the effectiveness of enzalutamide, vs a conventional NSAA, when combined with a LHRHA or surgical castration, as first line ADT for newly diagnosed metastatic prostate cancer	NCT02446405
Non-metastatic CRPC	PROSPER	Phase III	The purpose of this study is to assess the safety and efficacy of enzalutamide in patients with non-metastatic prostate cancer	NCT02003924
	–	Phase II	To determine the efficacy of enzalutamide in combination with PSA-TRICOM in patients with nonmetastatic castration-sensitive prostate cancer	NCT01875250
M1 CRPC	TERRAIN	Randomized	Phase II To determine the efficacy and safety of oral enzalutamide compared with bicalutamide in castrate men with metastatic prostate cancer who have progressed while on luteinizing hormone receptor hormone agonist/antagonist or after receiving a bilateral orchiectomy	NTC01288911
	STRIVE	Randomized Phase II	To determine the safety and efficacy of enzalutamide vs bicalutamide in asymptomatic or mildly symptomatic patients with prostate cancer who have disease progression despite primary androgen deprivation therapy	NCT01664923
	ARMOR 3	Phase III	To compare galeterone to enzalutamide in men expressing androgen receptor splice variant-7 mRNA (AR-V7) in metastatic castrate-resistant prostate cancer	NCT02438007
Combinations/ sequences	PLATO	Phase IV	To evaluate continued enzalutamide treatment beyond progression (enzalutamide plus abiraterone/prednisone vs placebo plus abiraterone/prednisone) in patients with chemo-naïve mCRPC. Primary end point of PFS	NCT01995513
	PRESIDE	Phase III	To determine the efficacy and safety of continuing enzalutamide in patients with chemo-naïve mCRPC treated with docetaxel plus prednisolone who have progressed on enzalutamide alone	NCT02288247
	ALLIANCE	Phase III	Phase III trial of enzalutamide with or without abiraterone and prednisone for mCRPC	NCT01949337

ADT: Androgen-deprivation therapy; CRPC: Castration-resistant prostate cancer; HSPC: Hormone-sensitive prostate cancer; LHRHA: Luteinizing hormone-releasing hormone analog; mCRPC: Metastatic castration-resistant prostate cancer; NSAA: Nonsteroidal anti-androgen; PC: Prostate cancer; PFS: Progression-free survival; PSA: Prostate-specific antigen.

Table 1. Selected clinical trials testing enzalutamide in prostate cancer (cont.).

Setting	Called	Type of study	Clinical question/end points	Identification
Combinations/ sequences (cont.)	EORTC Peace II		To compare the efficacy of enzalutamide vs a combination of Radium223 and enzalutamide in asymptomatic or mildly symptomatic patients with CRPC patients metastatic to bone	NCT02194842
–		Phase I	To evaluate safety and tolerability of enzalutamide in combination with docetaxel in men with prostate cancer	NCT01565928

ADT: Androgen-deprivation therapy; CRPC: Castration-resistant prostate cancer; HSPC: Hormone-sensitive prostate cancer; LHRHA: Luteinizing hormone-releasing hormone analog; mCRPC: Metastatic castration-resistant prostate cancer; NSAA: Nonsteroidal anti-androgen; PC: Prostate cancer; PFS: Progression-free survival; PSA: Prostate-specific antigen.

bicalutamide group (HR: 0.32; CI: 0.21–0.50; $p < 0.0001$). The median time on treatment was 14.7 months in the enzalutamide arm compared with 8.4 months with bicalutamide. For the patients with non-metastatic disease enrolled in the trial, the median PFS was not yet reached for patients in the enzalutamide arm and it was of 8.6 months in the bicalutamide arm with a HR of 0.24 (95% CI: 0.14–0.42; $p < 0.0001$). In the case of patients with metastatic disease, the median PFS was 16.5 months in the enzalutamide group and 5.5 months in the bicalutamide arm with a HR of 0.24 (95% CI: 0.17–0.34; $p < 0.0001$) [11].

In the safety analysis, treatment discontinuation due to an AE was seen in 6.1% and 7.6% in the bicalutamide group and in the enzalutamide group, respectively. The AE profile of enzalutamide was distinct from bicalutamide with more side effects noted in the enzalutamide arm including fatigue (37.6%), back pain (17.8%),

hot flashes (15.7%), falls (13.7%) and constipation (10.2%). In this study, 29.4% of patients treated with enzalutamide and 28.3% of bicalutamide-treated patients experienced serious AEs. Specifically, 5.1% of patients treated with enzalutamide experienced grade 3 or higher cardiac events, in contrast with 4.0% of bicalutamide-treated patients. One patient in the enzalutamide arm experienced a seizure, but no patients reported seizures in the comparator group [11].

An open-label period has been added to the main protocol. Following study unblinding, study patients receiving enzalutamide or bicalutamide and qualifying patients randomized to bicalutamide who discontinued prior to unblinding will be offered the opportunity to receive open label enzalutamide treatment under this protocol.

Likewise, the TERRAIN trial compared enzalutamide to bicalutamide as upfront therapy in only patients with mCRPC who progressed

Figure 1. Trial design.

p.o.: Orally.

Table 2. Summary of the results of STRIVE and TERRAIN clinical trials.

	STRIVE trial		TERRAIN trial	
	Enzalutamide	Bicalutamide	Enzalutamide	Bicalutamide
Population	Metastatic CRPC No-metastatic CRPC		Only metastatic	
Study arm vs comparator arm	Enzalutamide 160 mg daily	Bicalutamide 50 mg daily	Enzalutamide 160 mg daily	Bicalutamide 50 mg daily
Median PFS	19.4 months	5.4 months	15.4 months	5.8 months
HR (95% CI)	0.24 (0.18–0.32); p < 0.0001		0.44 (0.34–0.57); p < 0.0001	

CRPC: Castration-resistant prostate cancer; HR: Hazard ratio; PFS: Progression-free survival.

despite ADT. This study met its primary end point demonstrating a statistically significant increase in PFS for enzalutamide compared with bicalutamide (HR: 0.44; 95% CI: 0.34–0.57; p < 0.0001). Median PFS was 15.7 months for the patients receiving enzalutamide compared with 5.8 months in the bicalutamide arm. The median time on treatment was also longer for the patients treated with enzalutamide group (11.7 months) compared with 5.8 months in the bicalutamide group [12].

The most common side effects occurring during treatment and more common in the enzalutamide-treated versus bicalutamide-treated patients included fatigue, hot flushes, hypertension, diarrhea, weight loss and extremity pain. In the safety analysis, serious AEs were reported in 31.1% of patients treated with enzalutamide and 23.3% of bicalutamide-treated patients. Grade 3 or higher cardiac AEs were reported in 5.5% of enzalutamide-treated patients versus 2.1% of bicalutamide-treated patients. Regarding specific AEs of interest, the rate of seizures was low in this trial with two seizures reported in the enzalutamide group and one in the bicalutamide group [12].

Results of these two trials suggest a substantial benefit from adding enzalutamide to ADT compared with adding bicalutamide as a frontline therapy in the castration-resistant setting both for non-metastatic and metastatic patients. The effect appears to be more profound in the non-metastatic setting. Table 2 summarize the clinical outcomes of the STRIVE and TERRAIN trials. The PROSPER Phase III, which only includes non-metastatic CRPC patients, will further define the effect of enzalutamide in this specific population with a primary end point of metastasis-free survival. (NCT02003924)

Enzalutamide for the treatment of hormone-sensitive prostate cancer

The next rational step based on the demonstrated activity of enzalutamide in mCRPC

is to turn to earlier stages of the disease. The evaluation of whether enzalutamide can delay metastasis in nonmetastatic patients or be an alternative to ADT in recurrent and metastatic hormone-sensitive prostate cancer (HSPC) is now being tested.

To date, ADT alone continues to be the standard of care treatment for patients with advanced HSPC that are not candidates to receive ADT plus docetaxel as per CHAARTED, GETUP-AFU 15 and STAMPEDE trials [13–15]. Unfortunately, ADT is associated with well-known deleterious effect including bone-mass density and muscle loss, decreased libido, osteoporosis, fatigue, glucose intolerance and changes in lipid profile. With the longer life expectancy of prostate cancer patients, improvement in quality of life has become increasingly important and has led to the search for alternative strategies to standard ADT. Because of the different AE profile – including preserving sexual potency – nonsteroidal antiandrogens, such as bicalutamide have been proposed as an alternative to ADT. However, these agents have only a minimal effect on survival and potential for agonistic effect and are not recommended as single agents in the metastatic setting.

Building on the findings on the antitumor activity and good tolerance with enzalutamide in the castration-resistant setting, a Phase II exploratory, open-label, single-arm trial of enzalutamide in noncastrate patients with HSPC was conducted. In total, 67 patients at any disease stage eligible for ADT were enrolled into the study (M0 52%, M1 15% and Mx, unknown or could not be assessed in 33%). Enzalutamide monotherapy for 25 weeks resulted in a PSA responses (≥ 80% decline from baseline) in 92.5% of patients. Furthermore, patient-reported HRQoL was generally maintained over 24 weeks of enzalutamide treatment [16].

The most commonly reported treatment-emergent AEs up to week 25 were gynecomastia (n = 24), fatigue (n = 23), nipple pain (n = 13)

and hot flushes ($n = 12$). Most treatment-emergent AEs were grade 1 or 2. A total of 12 serious AEs were reported in five patients: grade 1 device dislocation; grade 2 hydronephrosis; grade 3 angina pectoris, atrial fibrillation, pneumonia, bladder transitional cell carcinoma, syncope, seizure and prostatic calcification; grade 4 acute respiratory distress syndrome and urosepsis; and grade 5 cardiac arrest [16].

Very recently, this group reported on the long-term efficacy and safety of this single-arm Phase II trial. This analysis confirmed the profound pharmacodynamic effect of enzalutamide, as illustrated by 81% and 67% of patients with profound PSA response at 49 and 97 week, respectively, in patients at different disease stages of HSPC [17].

One of the mechanisms that may contribute to AR reactivation in patients treated with enzalutamide and limits its effect is an increased accumulation of circulating androgens [18]. The updated analysis on efficacy does not suggest this hypothesis in HSPC, as the majority of patients still had a PSA response at 97 week.

Furthermore, a favorable safety profile associated with this long exposure to enzalutamide was noted. In contrast to castration, bone

mineral density remained stable and metabolic variables such as lean and fat body mass or lipid profile were not substantially impacted with enzalutamide at 1- and 2-year follow-up. This single-arm study raise a number of questions that must be addressed including whether or not enzalutamide as a single agent could be an alternative approach to ADT in patients with HSPC [16,17].

Mechanism of resistant to enzalutamide

The majority of patients progressing on enzalutamide have a rise in PSA, suggesting reactivation of AR or other steroid signaling pathways that could increase PSA transcription [19,20]. Preclinical investigations also indicate that most mechanisms of resistance to enzalutamide involve the AR and might lead to cross-resistance with other AR-targeted therapies, for example, abiraterone (Figure 2).

One of the most clinically relevant mechanisms seems to be the induction of AR splice variants (AR-Vs). Detection of AR-V7 mRNA in circulating tumor cells from patients with mCRPC was associated with resistance to enzalutamide, as well as, abiraterone [21]. Other frequently observed mechanisms of resistance to AR antagonists

Figure 2. Diagram of therapy-related mechanism of resistance in metastatic prostate cancer.

AR: Androgen receptor.

include *AR* gene amplification, receptor mutation and truncation, intracrine synthesis of androgens by the tumor cells, changes in *AR* cofactor balance, as well as multiple other receptor-unrelated mechanisms [20]. Some of these mechanisms have also been observed during enzalutamide treatment and various other new mechanisms have been proposed. For example, a novel, third point mutation in the ligand-binding domain of the AR has been reported to switch enzalutamide activity into an AR agonist. The F876L mutation was identified in an *in vitro* screen for *AR* mutations leading to enzalutamide resistance [22]. This substitution has also been detected in prostate cancer cell lines and xenograft models treated with enzalutamide [23]. However, it is currently unclear how frequently the antagonist-to-agonist switch caused by F876L occurs in enzalutamide-resistant prostate cancer and whether it is clinically significant. More data are required to determine how frequently this mutation causes enzalutamide resistance in mCRPC. In the same line, *AR* gene aberrations – *AR* gene amplifications, copy number increase and/or an exon 8 mutation – including the first reported case of an F876L mutation have been identified in circulating free DNA of patients with enzalutamide-resistant mCRPC [24].

Preclinical studies have also implicated the glucocorticoid receptor (GR) as a mediator of resistance to enzalutamide. Comparative AR and GR transcriptome studies supported a model whereby GR bypasses enzalutamide-mediated AR blockade without the need for any restored AR function [25]. In human samples, a

study also found the GR in bone metastases of enzalutamide-treated patients [25].

The modest response to abiraterone in patients previously treated with enzalutamide and viceversa may be mediated by mechanisms of cross-resistance [26–28]. Reactivation of the androgen–AR axis via *AR* gene aberrations such as *AR* amplification, *AR* exon 8 mutations or presence of AR-Vs has been postulated as potential mechanism of therapeutic resistance to both drugs. Studies using biomarker-enrichment design are needed to evaluate mechanism of cross-resistance to sequential treatment strategies in further detail [21,24].

Conclusion

Enzalutamide was first shown to increase survival and to improve quality of life compared with placebo in chemotherapy-experienced and chemotherapy-naïve patients with mCRPC. However, its role in the treatment of prostate cancer is rapidly evolving. The STRIVE demonstrated that enzalutamide has clinical activity superior to bicalutamide in patients with or without metastases who progressed despite ADT. Similar results were observed in the TERRAIN trial in patients with uniformly metastatic disease. Moreover, initial results in HSPC also showed promising clinical activity as measured by PSA declines, challenging the role of traditional ADT in the HSPC setting. Hopefully, the promising results in the STRIVE and TERRAIN trial will be confirmed in ongoing Phase III trials. For hormone-sensitive patients, we are optimistic that the role of enzalutamide

EXECUTIVE SUMMARY

- Enzalutamide, an orally available nonsteroidal androgen receptor antagonist, acts at multiple points in the androgen receptor signaling pathway.
- Based on the results of the AFFIRM and PREVAIL trials, enzalutamide has been US FDA-approved for the treatment of patient with metastatic castration-resistant prostate cancer (CRPC).
- The STRIVE and the TERRAIN trials are the first Phase II head-to-head studies of enzalutamide versus bicalutamide in patients with CRPC.
- Results of the STRIVE clinical trial shows enzalutamide is superior to bicalutamide in nonmetastatic and metastatic CRPC.
- The TERRAIN trial achieved its primary objective by demonstrating statistically significant superiority in progression-free survival for enzalutamide versus bicalutamide.
- Enzalutamide monotherapy induced striking declines in prostate-specific antigen in a majority of patients with hormone-naïve prostate cancer in a single arm Phase II trial. Enzalutamide appears to have also limited effect on bone mineral density. In the hormone-sensitive setting, clinical trials comparing enzalutamide to androgen-deprivation therapy alone or androgen-deprivation therapy plus docetaxel are warranted.

for these patients will be defined very soon, potentially resulting in a paradigm shift in the management of prostate cancer.

Financial & competing interests disclosure

J Bellmunt has received consultancy and lecture fees from Pierre Fabre, Astellas Pharma and Pfizer and research

funding from Takeda/Millennium. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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