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REVIEW

Metastatic Castration-Resistant Prostate Cancer: Critical Review of Enzalutamide

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Abstract: Enzalutamide, previously known as MDV300, is an oral, second-generation androgen receptor (AR) signaling inhibitor or antagonist that was approved by the Food and Drug Administration in 2012 for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) postdocetaxel. Preclinical studies have demonstrated impressive affinity to the AR compared to the first-generation AR inhibitors. The landmark Phase III AFFIRM trial demonstrated improved overall survival benefit compared to placebo in addition to improvement in all tested parameters. Enzalutamide is currently being studied in several trials prechemotherapy and in earlier settings of prostate cancer. This review will discuss the mechanism of action of enzalutamide, its pharmacokinetics, the preclinical and clinical trials that led to its approval, the ongoing clinical trials, its safety and efficacy, as well as patterns of resistance, and discusses its place in therapy within the context of several recently approved agents for mCRPC.

Keywords: enzalutamide, androgen receptor, metastatic castrate resistant prostate cancer, MDV30

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Introduction

Prostate cancer in the United States is expected to result in 239,000 cases in 2013 with a projected death of 29,700.[1] Growth, as well as differentiation of the prostate gland, is largely dependent on androgens such as testosterone and dihydrotestosterone. Upon malignant transformation, prostate tumor growth is also driven by androgen signaling. In the 1940s, Huggins and Hodges[2] first showed that the effects of surgical orchiectomy could lead to prostate cancer regression.[2] Since that time, androgen suppression therapy (AST), through the use of gonadotropin-releasing hormone (GnRH) agents (predominantly agonists and until recently, antagonists), has become the cornerstone of systemic treatment for metastatic prostate cancer. While AST results in prostate-specific antigen (PSA) responses in a majority of cases, relapse almost invariably ensues. Higher post-AST PSA levels predict recurrence, which signals expression of androgen-regulated genes.[3] Relapse usually occurs within 12 to 24 months, as demonstrated by either rising PSA, radiologic worsening, or deterioration of disease-related symptoms.[4] Disease at this juncture has previously been considered to be "androgen-independent," or "hormone-refractory," or "hormone-resistant." However, these terms are both a misnomer and misleading, since androgen receptor expression is almost never lost. Further evidence and observation has shown that in many cases, the response to residual levels of androgens or other circulating hormones in a particular patient could be amplified due to one of several factors including mutation of the androgen receptor (AR) and alteration in levels of cofactor proteins, and thus would still be sensitive to further hormonal manipulation.[5] Therefore, the term "castration-resistant" is now widely accepted and preferred.

In 2004, docetaxel was the first approved agent showing a survival advantage in men with metastatic castration-resistant prostate cancer (mCRPC) based on the two pivotal trials, SWOG 9916 and TAX-327, both of which demonstrated superior overall survival (OS) outcomes in men treated with docetaxel and prednisone compared with mitoxantrone and prednisone in the frontline setting,[6,7] with updated results showing a sustained survival advantage.[8] During this subsequent era, efforts have been made to search for varying targets as well as combinations with docetaxel, with the belief that once castration-resistance ensues, the AR ceases to be a target.[9] In June 2010, a novel taxane that was primarily studied in taxane-resistant models, cabazitaxel, was approved in the second-line setting based on the pivotal TROPIC trial.[10] Several recent studies in mCRPC have made it apparent that prostate cancer growth remains dependent on androgen supply after the disease becomes unresponsive to standard hormonal therapy.[11] Based on these findings, renewed interest in using new therapeutic agents to target androgen-signaling for mCRPC patients was seen. Abiraterone acetate, an inhibitor of cytochrome P450 17 (CYP17), in conjunction with prednisone, received approval in April 2011 for mCRPC after docetaxel failure based on the COU-AA-301 trial.[12] Almost in parallel, enzalutamide (formerly MDV3100), an oral, second-generation AR inhibitor that competitively inhibits androgen binding to the AR and inhibits its nuclear translocation and interaction with deoxyribonucleic acid (DNA) was being developed. This review describes the pharmacologic parameters of this agent, its mechanism of action, and the clinical trials that led to its approval by the United States Food and Drug Administration (FDA), its safety and efficacy, and discusses its place in the proper sequencing treatment of prostate cancer.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Mechanism of action

The AR is a 919-amino acid member of the steroid receptor transcription factor superfamily with different domains including an N-terminal regulation domain, a central DNA binding domain, and a C-terminal domain, which includes the ligand-binding domain incorporated within its protein structure.[13] Shortly after the initial discovery of the AR in the late 1960s, AR blockers have historically been included in the backbone of prostate cancer therapy. AR inhibitors serve as oral competitive inhibitors to endogenous ligands to the AR that when bound, induces a conformational change that ultimately result in the transcription of AR-regulated genes. The initial steroidal antiandrogens had significant progestational effects, with compounds such as cyproterone acetate and megestrol acetate. Nonsteroidal antiandrogens were then developed and are more specific to the AR.[14] Flutamide was discovered in the 1970s and was later

approved for use in treating prostate cancer in 1989. In 1995, bicalutamide was also approved and nilutamide followed a year later. In the 1980s, an approach of complete androgen blockade (CAB) or maximal androgen blockade, with a combination of antiandrogen antagonists and AST in an effort to eliminate or block all testicular and adrenal sources of androgen, was introduced.[15] CAB garnered widespread support at one time, but because of potential added costs and toxicity in the setting of minimal added benefit,[16] it was not uniformly adopted in practice. In addition, observations on the progression of use of peripheral androgen blockade, as well as a phenomenon of clinical benefit upon discontinuation of antiandrogens has led to the antiandrogen withdrawal syndrome, which formed the basis to further understand androgen resistance since antiandrogens function as partial agonists instead of antagonists.[17] In addition, Sawyers et al[18] found that this resistance may partly be due to upregulation in AR expression.[18]

The new AR antagonist, enzalutamide, soon represented the latest addition in the arsenal of secondary hormonal manipulating agents. Enzalutamide was selected from a library of compounds for clinical development, not only because of its favorable drug-like properties[19] and its effect on castration-resistant prostate cancer (CRPC) xenograft models, but also due to its ability to inhibit AR signaling in the overexpression of AR cells with high binding affinity to the AR and lack of agonist activity.[20,21] Unlike previous antiandrogens, enzalutamide targets multiple steps in the androgen-signaling pathway (see Fig. 1). Enzalutamide bound to the AR in a castration-resistant LNCaP/AR human prostate cancer cell model demonstrated an eightfold greater affinity than bicalutamide when evaluated using an 18-fluoro-deoxyglucose-dihydrotestosterone scan to measure relative AR binding affinity in a competition assay.[20] In addition to an increased binding affinity when bound to enzalutamide, the AR translocates into the nucleus far less efficiently, and a significant AR fraction remains in the cytosol. Enzalutamide induces regression of established LNCaP/AR xenograft tumor cells, which overexpress ARs, growing in castrated male mice. Bicalutamide treatment, on the other hand, was shown to only retard growth. Enzalutamide antagonized induction of PSA and transmembrane serine protease 2, indicating a lack of agonist activity. Regression seen with enzalutamide is associated with continued evidence of apoptosis up to 25 days after initiation of treatment.

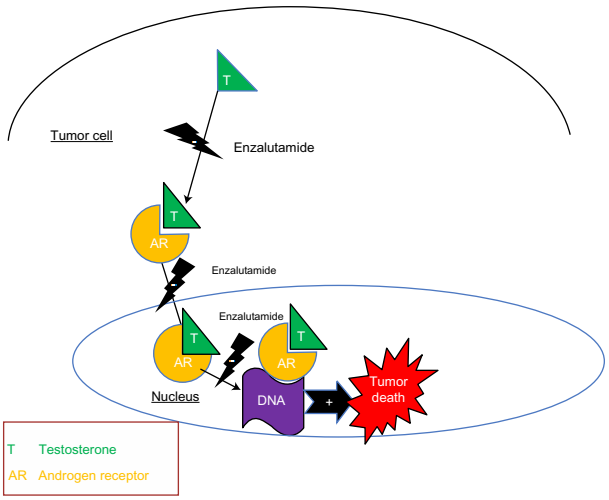

Figure 1. Mechanism of action of enzalutamide. Enzalutamide has high affinity for the androgen receptor (AR) and does not promote translocation of the AR to the nucleus and its binding to DNA, thus leading to tumor death.

Metabolism and pharmacokinetic profile

Based on the work done at Sawyers et al's[19] lab, a nonsteroidal thiohydantoin agonist was selected as the initial chemical framework due to its high affinity and selectivity for the AR. After 200 derivatives were screened, the diarylthiohydantoin MDV3100 or enzalutamide, was selected for further preclinical and subsequently clinical studies.[19] The pharmacokinetics of enzalutamide (formula $C_{21}H_{16}F_4N_4O_2S$) and its major metabolite, N-desmethyl enzalutamide, were evaluated in patients with mCRPC and healthy male volunteers. The plasma enzalutamide pharmacokinetics, in the studied dose range between 30 mg to 480 mg given orally, exhibited a linear, two-compartmental model with first-order absorption.[22] Following administration of one dose at 160 mg, enzalutamide was absorbed rapidly in patients with mCRPC, with median time to maximum plasma concentration of 1 hour, ranging between 30 minutes and 3 hours. The terminal elimination half-life, in the same subset of patients following a single dose, was noted to be 5.8 days with a range from 2.8 days to 10.2 days. Plasma concentrations reached a steady state by day 28 of daily treatment and accumulated approximately 8.3-fold relative to a single dose, with low daily fluctuations in plasma concentrations.

In patients with mCRPC, the mean (%CV) predose Cmin or trough values for enzalutamide and N-desmethyl enzalutamide were 11.4 (25.9%) µg/mL and 13.0 (29.9%) µg/mL, respectively. The mean apparent total plasma clearance of enzalutamide was 0.56 L/hour (%CV: 29.9%).[23] Enzalutamide was found to be mainly metabolized by cytochrome P450 and more specifically, in vitro human CYP2C8 and CYP3A4. CYP2C8 is responsible for the formation of the active metabolite, N-desmethyl enzalutamide. Following a single dose of ^{14}C-enzalutamide 160 mg, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days postdose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C-AUC0-inf. Enzalutamide is excreted in the urine (71%) and feces (14%) mainly as inactive metabolites. The plasma pharmacokinetics of enzalutamide and N-desmethyl enzalutamide were examined in volunteers with normal renal and hepatic function, as well as those with mild (CrCl 60 to <90 mL/minute) and moderate (CrCl 30 to <60 mL/minute) renal impairment, as well as those with mild (Child Pugh Class A) and moderate hepatic impairment (Child Pugh Class B). The apparent clearance and composite area under the curve of enzalutamide was similar in patients with preexisting mild and moderate renal impairment, as well as in those with mild to moderate baseline hepatic impairment, respectively, compared to patients and volunteers with normal renal and hepatic function; hence, there are no recommendations for initial dose adjustments or modifications for patients who have mild to moderate renal or hepatic impairment.

The metabolism of enzalutamide may be modified by the concomitant administration of drugs that are known inducers of CYP2C8 or CYP3A4. However, no formal drug interaction studies have evaluated the effect of specific inducers on enzalutamide pharmacokinetics. In vivo, the sum of enzalutamide and N-desmethyl enzalutamide exposure was increased by 2.2-fold and 1.3-fold when it was coadministered with gemfibrozil (strong CYP2C8 inhibitor) or itraconazole (strong CYP3A4) inhibitor), respectively, suggesting the need for avoidance of such coadministration.[23]

Clinical Studies: Preliminary Studies/Clinical Studies

Given the important role of the AR in the pathogenesis of prostate cancer, inhibition of the AR in addition to AST has been the subject of study in metastatic prostate cancer. However, the earlier AR inhibitors, bicalutamide and flutamide, demonstrated no significant improvement in OS in patients with hormone-sensitive metastatic prostate cancer.[24–26] Certainly, limitations of the first-generation AR inhibitors included their partial agonist activity in the presence of overexpression of the AR.[18] In addition, compared to dihydrotestosterone, bicalutamide has a lower affinity for the AR.[27] In early preclinical trials, enzalutamide showed a potency that was higher than earlier generations of antiandrogens including flutamide, nilutamide, and bicalutamide.[20] Enzalutamide was found to have a ten-times greater affinity relative to bicalutamide, and contrary to the latter, was shown to be a pure antagonist to the AR. The encouraging preclinical results led to the initiation of a Phase I/II trial in humans.

Phase I/II study

In a Phase I/II trial assessing the efficacy and safety of enzalutamide, 140 patients with CRPC were enrolled at multiple centers to receive enzalutamide orally at doses ranging from 30 mg to 600 mg daily.[22] The vast majority of the patients (78%) included in this trial had metastatic disease. Around 44% of the patients have not previously received treatment to the primary tumor, whereas 30% have previously undergone surgery and 26% have previously received definitive radiation therapy. Around half of the patients have previously received chemotherapy and over 75% of the patients have previously received at least two lines of hormonal therapy. The maximum tolerated dose was determined to be 240 mg daily, and there was no additional benefit obtained from instituting higher dosages. Antitumor activity was observed at all tested dosages. The median time to radiological progression was 47 weeks for all patients and it was more prolonged in the chemotherapy-naïve group (>60 weeks) than in the chemotherapy pretreated group (29 weeks). Of the patients who had measurable disease, 22% had soft tissue response and of the patients who had bone disease, 56% had stabilized bone disease lasting 12 or more weeks. In addition,

49% of the patients had conversion from unfavorable (>5/7.5 mL) to favorable (<5/7.5 mL) circulating tumor cell counts, indicating a favorable effect on this adverse prognostic group of patients. The main side effects included headache, hot flashes, and fatigue. Fatigue was dose-dependent and occurred in 11% of the patients. Three patients developed seizures and those three patients were receiving the 360 mg dosage or higher, and two of the patients were on medications that lowered the seizure threshold. At longer follow-up and at the time of updated analysis, 18 of the enrolled patients remained in the study, with a median time on therapy of 131 weeks.[28] The median time to PSA progression [as assessed by the Prostate Cancer Working Group 2 (PCWG2)][29] was 41 weeks and 20 weeks in the chemotherapy-naïve and the chemotherapy-pretreated groups, respectively. The median radiographic PFS was 56 weeks and 24 weeks in the chemotherapy-naïve and the chemotherapy-pretreated group, respectively.

Phase III study: The AFFIRM study

Following the encouraging results of the Phase I/II trial, the Phase III AFFIRM trial (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was designed. The AFFIRM trial was an international double-blind placebo controlled trial in men with mCRPC who have failed prior docetaxel-containing chemotherapy regimens.[30] A total of 1,199 men with mCRPC from 166 sites were randomized in a 2:1 manner to receive either enzalutamide 160 mg daily (n = 800) or placebo (n = 399). Glucocorticoids were not required, but were allowed and were seen in about 30% of patients in both arms. The primary endpoint of the trial was OS. Secondary endpoints included radiographic PFS, time to PSA progression, quality of life, and time to the first skeletal-related event (SRE). Patients were eligible to be enrolled in the trial if they had progressed on prior chemotherapy which contained docetaxel, they had adequated organ function, an Eastern Cooperative Oncology group (ECOG) performance status of 0–2. Around 50% of the patients in both arms had received at least three prior lines of hormonal therapy, and 24% of the patients had received two prior lines of therapy. An interim analysis was planned after a total of 520 deaths had occurred.

In view of the improved OS favoring enzalutamide, the study was unblinded at the recommendation of the Data and Safety Monitoring Committee, and the patients on placebo were allowed to cross-over to receive enzalutamide. Despite this cross-over, after a median follow-up of 14 months, the median OS was significantly improved in the enzalutamide arm versus the placebo arm [18.4 months versus 13.6 months, respectively; hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.53–0.75; $P < 0.0001$]. This 4.8-month difference in OS translated in a 37% reduction in the risk of death of any cause in the enzalutamide arm. A subgroup analysis showed that enzalutamide was superior to placebo, even in poor-risk categories including those with lower hemoglobin, higher alkaline phosphatase, worse Eastern Cooperative Oncology Group (ECOG) status, the presence of visceral disease, and the presence of pain. The group of patients who did not appear to benefit from enzalutamide was the one that included patients who received two or more prior chemotherapy regimens. Enzalutamide was superior to placebo in all the examined secondary endpoints. Enzalutamide was associated with improved time to PSA progression by 5.3 months (8.3 months versus 3 months; HR, 0.25; $P < 0.001$) and improved median radiographic PFS by 5.4 months (8.3 months versus 2.9 months; HR, 0.40; $P < 0.001$). Enzalutamide also demonstrated a superior PSA response with at least a 50% PSA reduction in 54% of the treated patients compared with 1.5% in the placebo arm ($P < 0.001$) and at least a 90% PSA reduction in 25% of the treated patients compared to 1% in the placebo arm ($P < 0.001$). Among patients who had measurable disease, Response Evaluation Criteria In Solid Tumors overall response rates (ORRs) were 29% in the enzalutamide arm compared to 4% in the placebo arm ($P < 0.0001$). Enzalutamide also resulted in an improvement in the time to first SRE (16.7 months versus 13.3 months; HR, 0.62; $P < 0.0001$) and quality of life response rate as determined by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) (43% versus 18%; $P < 0.0001$). There were also beneficial effects on health-related quality of life, as reported in an updated analysis.[31] Pain palliation was defined as >30% decline in the median pain score after 12 weeks of treatment compared to pretreatment pain score without a >30% increase in the use of analgesics. Pain palliation was achieved in 45% and 7% of the patients in the enzalutamide and placebo arms respectively ($P = 0.008$), and pain progression

occurred in 28% of the patient on enzalutamide compared to 39% in the patients on placebo ($P = 0.002$). Median time to pain progression on the FACT-P scale was not reached for the enzalutamide arm compared to 13.8 months for the placebo arm, thus representing a 44% risk reduction (HR, 0.56; $P = 0.0004$). Interestingly a post hoc analysis showed that patients who were taking corticosteroids at baseline in both arms had inferior survival compared to those who were not on steroids.[32] In addition, on-study corticosteroid use was also associated with inferior OS and a significantly worse side-effect profile compared to the placebo group (grade 3–4 adverse events of 63.3% in the corticosteroid cohort versus 34.4% in the noncorticosteroid cohort).[33] One explanation could be that the patients who had introduced steroids to their therapy might have had more severe disease at baseline. This is evident also in the recent American Society of Clinical Oncology (ASCO) presentation on the effect of baseline corticosteroid use in men undergoing the COU-AA-301 trial, which showed that while there is a decline in the OS and a worse time to progression on baseline corticosteroid use, this may be a mere reflection of a preexisting, overall poorer prognostic risk of patients.[34] Subsequent anticancer therapy was common in both arms (41% of the enzalutamide patients and 58% of the patients on placebo). The most common posttrial therapies included abiraterone (21% and 24% in the enzalutamide and placebo arms, respectively), cabazitaxel (10% and 14% in the enzalutamide and placebo arms, respectively), docetaxel (9% and 14% in the enzalutamide and placebo arms, respectively), and mitoxantrone (3% and 11% in the enzalutamide and placebo arms, respectively). On August 31, 2012, based on the overwhelming positive findings seen from the AFFIRM trial, the FDA approved enzalutamide given at 160 mg daily for men with mCRPC who had already received a docetaxel-containing chemotherapy regimen.

Recent and ongoing trials

A Phase II trial evaluated the role of enzalutamide as monotherapy in hormone-naïve prostate cancer, and the results of the trial were reported at the ASCO 2013 annual meeting.[35,36] The trial included 67 patients, 39% of whom had metastatic disease, 36% had prior prostatectomy, and 24% had radiation therapy. Enzalutamide achieved a high median PSA response of 93% with a marked PSA decline of –99.6%. In contrast to castration, there was no change in the measured bone density or in the measured metabolic variables such as body fat mass, or glycemic and lipid profiles. The preliminary results of the Phase I study that evaluated the combination of enzalutamide with docetaxel in the chemotherapy-naïve mCRPC setting were also presented at the ASCO 2013 meeting.[37] In that Phase I trial, enzalutamide did not appear to alter tolerability to docetaxel or affect its pharmacokinetics.[37]

A number of trials are currently underway to evaluate the role of enzalutamide in a wide range of patient populations and clinical settings. The safety of the combination of the new novel agents, abiraterone and enzalutamide, in mCRPC to the bones is being studied in a Phase II trial (NCT01650194). In addition, a Phase III trial comparing abiraterone acetate to abiraterone acetate with prednisone and enzalutamide (Alliance A03121, funded through the Biomarker, Imaging, and Quality of Life Studies Funding Program of the National Cancer Institute) seeks to enroll 1428 mCRPC chemotherapy-naïve patients with an endpoint of OS. Two Phase II randomized trials are comparing the combination of the PSA-TRICOM vaccine with enzalutamide to enzalutamide alone both in the hormone-sensitive chemotherapy-naïve metastatic setting and the nonmetastatic setting (NCT01867333 and NCT01875250). To ascertain whether enzalutamide would have a place in the prechemotherapy setting, a Phase III randomized study of enzalutamide versus placebo in men with chemotherapy-naïve mCRPC (PREVAIL study; NCT01212991) was designed and has completed accrual with the results eagerly awaited. Enzalutamide is being compared to bicalutamide in the prechemotherapy setting in two Phase II trials, both in the nonmetastatic and the metastatic setting (NCT01288911, NCT01664923). A selected list of these trials is shown in Table 1.

Safety

Enzalutamide seems to be very well tolerated with a favorable side effect profile. In the Phase I/II study,[22] the most common grade 3–4 adverse event was dose-dependent fatigue (11% of patients), which was only observed at doses of 240 mg or greater, and generally resolved after dose reduction. In this trial, the three patients who developed seizures were receiving the

Table 1. Selected ongoing and recently completed trials of enzalutamide in patients with prostate cancer.

Identifier (status)	Title of the study	Primary endpoint	Phase	Population	Treatment
NCT01650194 (recruiting)	A study to determine safety and tolerability of enzalutamide (MDV3100) in combination with abiraterone acetate in bone metastatic castration-resistant prostate cancer patients	Nature, frequency and severity of adverse events	Phase II	Bone—mCRPC who have received no >2 prior chemotherapy regimen	Abiraterone + enzalutamide
NCT01664923 (recruiting)	Safety and efficacy study of enzalutamide versus bicalutamide in men with prostate cancer (STRIVE)	PFS	Phase II randomized	Recurrent prostate cancer with disease progression despite androgen suppression therapy (non-metastatic patients included)	Enzalutamide versus bicalutamide
NCT01288911 (recruiting)	A study of MDV3100 versus bicalutamide in castrate men with metastatic prostate cancer (TERRAIN)	PFS	Phase II randomized	mCRPC chemotherapy-naïve	Enzalutamide versus bicalutamide
NCT01547299 (completed accrual)	Study of MDV3100 as a neoadjuvant therapy for patients undergoing prostatectomy for localized prostate cancer	Pathological complete response rate	Phase II randomized	Patients with localized prostate cancer undergoing prostatectomy	Neoadjuvant enzalutamide versus enzalutamide + leuprolide + dutasteride
NCT01867333 (recruiting)	Enzalutamide with or without vaccine therapy for advanced prostate cancer	Time to progression	Phase II randomized	Minimally symptomatic chemotherapy-naïve mCRPC with progressive disease	Enzalutamide versus enzalutamide + PSA-TRICOM
NCT01302041 (completed accrual-results presented at ASCO 2013)	A study to test if MDV3100 is effective and safe in prostate cancer patients who have never had hormone therapy	Proportion of patients with PSA response	Phase II	Recurrent prostate cancer, hormone and chemotherapy naive	Enzalutamide
NCT01875250 (recruiting)	Enzalutamide in combination with PSA-TRICOM in patients with non-metastatic castration sensitive prostate cancer	Decrease in tumor regrowth rate	Phase II randomized	Non-metastatic prostate cancer, hormone sensitive	Enzalutamide + PSA TRICOM versus enzalutamide alone
NCT01565928 (completed accrual-results presented at ASCO 2013)	A phase 1b, open-label, safety and tolerability study of oral MDV3100 in combination with docetaxel in men with advanced prostate cancer	Safety and tolerability	Phase Ib	Chemotherapy naïve mCRPC	Enzalutamide + docetaxel

Abbreviations: PFS, Progression-Free Survival; mCRPC, metastatic Castration-Resistant Prostate Cancer.

360 mg dose or higher, and two of the patients were on medications that lowered the seizure threshold. In the AFFIRM study,[30] there were few toxicities that were more common in the enzalutamide arm, and these included fatigue (all grades, 34% versus 29.1%), diarrhea, musculoskeletal pain, headache, hypertension, and hot flashes. Overall, the enzalutamide group had a lower incidence of grade 3–4 adverse events (45.3% versus 53.1%). Enzalutamide was also fairly well tolerated, with the most common adverse reactions (occurring in >5% of patients) including asthenia (34%), back pain, diarrhea (21%), arthralgia, hot flashes (20%), peripheral edema, respiratory infection, muscular weakness, musculoskeletal pain, headache (12%), dizziness, insomnia, upper or lower respiratory infection, anxiety, hypertension, spinal cord compression, cauda equina syndrome, paresthesias, and hematuria, although a number of these latter adverse events were perhaps secondary to prostate cancer itself rather than medication-induced side effects. Their incidence was equally present in both the treatment and the placebo arms. Seizure was reported in five patients in the enzalutamide arm (versus none in the placebo arm) during the Phase III trial with two further seizure events reported in the follow-up data.[23] However, certain risk factors for lowering the threshold for seizure may have been identified in these studies. Of the five patients who experienced seizures, two had brain metastases, one received lidocaine, and one patient had brain atrophy due to alcohol. There have been no reported seizures following discontinuation of enzalutamide. The occurrence of seizure is postulated to be related to the inhibition of γ-aminobutyric acid (GABA)-gated chloride channels by enzalutamide. In the AFFIRM study, patients with history of seizures or those who were on medications that lowered the seizure threshold were excluded from the Phase III trial. Including the two patients that experienced seizures in the longer follow-up of the AFFIRM study, the overall combined seizure risk was 1% (ten out of 940 patients). As outlined in the pharmacokinetics section, several drugs that are strong CYP2C8 inhibitors should be avoided since increased plasma exposure to enzalutamide can be seen, as well as avoidance of strong or moderate CYP3A4 or CYP2C8 inducers and substrates to CYP3A4, CYP2C9, and CYP2C19 with narrow therapeutic indices.[23]

Efficacy

The efficacy of enzalutamide has been widely demonstrated by the AFFIRM trial.[30] Although the Phase I/II study showed that toxicity was significantly increased at doses higher than 240 mg, there was no additional benefit observed beyond the dose of 160 mg daily. Therefore, the 160 mg daily dose was selected as the optimal dosing regimen in the Phase III AFFIRM study that formed the basis of FDA approval. The Phase I/II study demonstrated that enzalutamide was effective both in the chemotherapy-naïve and the chemotherapy pretreated group. The AFFIRM study included only patients postdocetaxel, and demonstrated that all endpoints including OS, radiographic PFS, time to PSA progression, quality of life, pain palliation, and time to the first SRE were improved with enzalutamide. The anticipated results of the PREVAIL study will ascertain whether enzalutamide will play a role in the prechemotherapy setting and will likely further change the therapeutic landscape in prostate cancer.

Patient Preference

Since the approval of docetaxel in 2004, there are now five agents that have shown to improve survival in mCRPC and these include sipuleucel-T,[38] cabazitaxel,[10] abiraterone,[39] and radium 223,[40] in addition to enzalutamide. Enzalutamide is the second oral hormonal agent (after abiraterone) that can extend survival in patients with mCRPC who were previously treated with docetaxel. No direct comparison with abiraterone acetate is available. One advantage of enzalutamide over abiraterone is that it does not require the coadministration of corticosteroids, and thus be a better treatment option in the patient population with comorbidities where corticosteroids have the potential for significant side effects. On the other hand, enzalutamide might not be suitable for patients with a history of seizures or who are concurrently receiving medications that lower the seizure threshold—a side effect not seen with abiraterone use. However, there is currently no specific guidelines or biomarkers that would predict the best sequence,[41] timing, and specific population of patients that would benefit from each of those agents. Several groups have advocated for specific guidance on the use of varying approved therapies that look mainly at symptoms, such as the American Urologic Association[42]

and the National Cancer Comprehensive Network (NCCN),[43] though with the understanding that given the rapidly evolving changes in the field, tailoring treatment as the therapeutic landscape changes will become appropriate as the literature changes.

Place in Therapy

The positive effects seen in the AFFIRM trial led to the approval by the US FDA of enzalutamide in the postchemotherapy setting. Currently, this is the setting that has garnered widespread acceptance in therap. However, results of the PREVAIL study (which entailed enzalutamide given prior to chemotherapy) are eagerly awaited and may soon join the ranks of abiraterone given prechemotherapy. The exact role of the sequencing of these agents, or perhaps their use in combination, remains uncertain. The aforementioned Alliance A03121 trial may further inform the utility of the combination of abiraterone acetate with enzalutamide versus abiraterone monotherapy in the prechemotherapypre-chemotherapy mCRPC setting. Given the currently available literature, per the NCCN for instance, enzalutamide has a category 1 recommendation postdocetaxel chemotherapy, but has a category 2A recommendation, which equates to a consensus based on lower-level evidence for docetaxel-naïve men.[44] Furthermore, varying studies are now looking at the utility of combining enzalutamide with a vaccine, or combination with abiraterone, or using it in an earlier setting, as has been shown in the enzalutamide monotherapy for hormone-naïve prostate cancer.[35,36]

Concerns remain regarding the emergence of resistance, especially since resistance invariably occurs with these agents. There are emerging retrospective data on the modest clinical activity observed, as well as on the brief duration of responses with the use of abiraterone after failure of prior docetaxel and enzalutamide therapy.[45,46] Given initial approval and widespread use of abiraterone in 2011, and before approval of enzalutamide in 2012, most patients who would have received abiraterone and subsequently switched to enzalutamide may not experience the same benefit as was seen in the AFFIRM trial.[41] Further analysis of the AFFIRM trial also shows that in the subgroup analyses, men who had two or more prior chemotherapy treatments did not do as well (with HRs based on the nonstratified proportional hazards model approaching 1), leading perhaps to consideration for earlier hierarchy in the sequencing.[47] There have been varying hypotheses on the mechanisms of resistance,[48] but cross-resistance conceivably be seen with these agents as well. One such mechanism suggests that treatment with enzalutamide or abiraterone leads to an adaptive shift towards an AR-splice-variant signaling, which gives rise to an increase in the constitutively active AR-splice variants that lack the AR-binding domain in prostate cancer.[49] This is further elucidated by restoration of responsiveness to antiandrogens by knock-down experiments of AR-V expression.[50] Another potential mechanism postulates an association with cellular Fas-associated death domain-like interleukin 1β-converting enzyme inhibitory protein expression, which plays a key role in mediating therapeutic resistance and maintaining viability of prostate cancer cells.[51] A recent study that highlights the development of cell lines that were resistant to both enzalutamide and ARN-509, another novel antiandrogen, showed that the presence of a missense mutation (F876L) in the ligand-binding domain of the AR conferred resistance to both compounds[52] by converting to an AR agonist. Interestingly, a molecular dynamics simulation performed led to a chemical screen, which further identified additional novel compounds that effectively antagonized AR F876L to suppress the growth of prostate cancer cells resistant to enzalutamide.[53]

Ultimately, the sequencing of these agents is of paramount importance, as it enables patients to see through all possible treatments that afford clinical benefit and bring about survival. Currently, however, no biomarker exists that would reliably predict responses to one agent over another, although enzalutamide would conceivably be effective even in the setting of low levels of circulating androgens, while higher levels of baseline-circulating androgens such as testosterone and dehydroepiandrostenedione, as well as ETS(erythroblast transformation specific)-related gene rearrangements, may predict the likelihood of response with abiraterone.[54,55]

Conclusion

The design, development, and approval of enzalutamide lend insights into one of the most anticipated successes in prostate cancer therapy. While the approval of enzalutamide currently resides in the postdocetaxel

space, there are promising reports of this drug being used in an earlier setting and may soon change the landscape of treatment for prostate cancer; however, resistance to enzalutamide also inevitably occurs. Thus, by improving the level of understanding of the mechanisms of resistance, the potential for combination with other agents, and the use of this agent across various settings of disease states in prostate cancer have garnered wide research efforts in this field, and will pave the way for better optimization of enzalutamide use in the treatment of prostate cancer.

Author Contributions

Wrote portions of the first draft of the manuscript: JE, NP, AF, JBA. Contributed to the writing of the manuscript: JE, NP, AF, JBA. Agree with manuscript results and conclusions: JE, NP, AF, JBA. Jointly developed the structure and arguments for the paper: JE, NP, AF, JBA. Made critical revisions and approved final version: JE, NP, AF, JBA. All authors reviewed and approved of the final manuscript.

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Competing Interests

All other authors (other than J Aragon-Ching as stated below) have no conflict of interest. Dr. Aragon-Ching has served on the Advisory Board for Amgen and Janssen/Ortho-Biotech, and has served on the Speakers Bureau for Janssen/Ortho-Biotech, Sanofi-Aventis, and Astellas/Medivation.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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