Enzalutamide: A Novel Antiandrogen for Patients with Castrate-Resistant Prostate Cancer

Jean Hoffman-Censits and Wm. Kevin Kelly

Abstract

Enzalutamide (MDV3100, Xtandi, Medivation\Astellas) is an oral inhibitor of androgen receptor signaling that blocks androgen receptor interaction, inhibits translocation of the androgen receptor to the nucleus, impairs androgen receptor binding to DNA, and inhibits coactivator recruitment and receptor-mediated DNA transcription. In a phase III randomized study comparing enzalutamide with placebo in men with progressive castration-resistant prostate cancer (CRPC) who were previously treated with docetaxel, enzalutamide showed an improvement in overall survival (18.4 vs. 13.6 months, HR, 0.63; P < 0.001). In addition, all secondary endpoints including proportion of patients with prostate-specific antigen (PSA) decline, soft-tissue response, quality-of-life response, time to PSA progression, radiographic progression-free survival, and the time to the first radiographic skeletal event all significantly favored patients treated with enzalutamide. Fatigue, diarrhea, and hot flashes were common in patients treated with enzalutamide, with seizures reported in 5 (0.6%) of the patients. Enzalutamide is a novel therapy that very potently blocks the androgen signaling pathway, which is unregulated during the development of CRPC. The preclinical studies along with the pivotal trials that led to its approval by the U.S. Food and Drug Administration (FDA) in September 2012 will be reviewed. Clin Cancer Res; 19(6); 1335–9. ©2012 AACR.

Introduction

Suppression of testosterone production by medical or surgical castration is standard first-line treatment for men with advanced prostate cancer. Over time, nearly all men will develop progressive prostate cancer despite castrate levels of testosterone and are considered to have castration-resistant prostate cancer (CRPC). Previous clinical dogma for this disease state was reflected in its nomenclature, with terms such as androgen-independent and hormone-refractory, which was replaced by CRPC as greater understanding of androgen signaling in the castrate state has been established. In 2004, docetaxel chemotherapy administered intravenously every 3 weeks became the first therapy that showed a survival advantage in patients with CRPC; however, response was modest and median survival for patients was approximately 19 months, (1, 2). To improve outcomes, an understanding of the development of CRPC was needed, and work from many showed that restoration of the androgen signaling pathway was a driving force for the development of CRPC. This could occur through amplification or overexpression of androgen receptor (AR), gain-of-function somatic mutation of AR, aberrant AR posttranslational modification (frequently driven by growth factor or cytokine signaling), alternative splicing events that result in hyperactive receptors, and cofactor dysregulation and/or intracrine androgen synthesis (3).

This provided the rationale for the development of several novel agents including the CYP 17 α-hydroxylase/17,20-lyase inhibitor abiraterone acetate (Zytiga, Johnson & Johnson), which, in part, inhibits intratumoral production of androgens (4).

In men with CRPC previously treated with docetaxel, abiraterone acetate and prednisone compared with prednisone alone conferred a statistically significant improvement in overall survival (14.8 vs. 10.9 months, HR, 0.65; P < 0.001), which led to U.S. Food and Drug Administration (FDA) approval of abiraterone acetate in 2011. This clinical benefit observed with abiraterone acetate by inhibiting androgen synthesis further shows the critical role of androgen signaling in CRPC (5). Recently, the FDA has approved enzalutamide, which belongs to another novel class of agents that represents a very potent inhibitor of the androgen receptor signaling pathway.

Preclinical Data

Upon the basis of the better understanding of the crystal structure of AR/bicalutamide interaction, Sawyers and colleagues modified and optimized the chemical scaffolding of the more potent antiandrogen RU59063 to develop 2 oral diaryl-thiohydantoin, RD 162 and MDV3100 (enzalutamide; refs. 6,7). Both of these agents bound the AR 5- to 80-fold greater than bicalutamide and showed no agonist
activity in LNCaP/AR cell lines. Importantly, MDV3100 (enzalutamide) and RD162, and not bicalutamide, decreased cell growth and induced apoptosis in the VCaP cell line, which has an endogenous AR gene amplification. In a mutated cell line derived from a patient with bicalutamide resistance and in which bicalutamide potentiated androgen-dependent signaling, enzalutamide inhibited cell growth. Unlike bicalutamide, neither of these novel antiandrogens recruited AR to the enhancer regions and coactivators to nuclear transcription complexes. Further studies in live LNCaP cells have shown that RD162 and enzalutamide reduced the nuclear-to-cytoplasmic AR ratio when compared with bicalutamide and that these drugs appear to inhibit the binding of AR to DNA. The nuclear localization of ligand-bound AR with subsequent conformational changes allowing for cofactor recruitment and formation of the AR transcription complex and AR-dependent DNA transcription was impaired by enzalutamide in AR-upregulated cell lines. This action was enhanced by bicalutamide (6). Enzalutamide was selected for further clinical testing based on these and other preclinical studies coupled with a more favorable pharmacokinetic profile of this agent versus others in early development.

Early Clinical Development

In animal models of castrate-resistant cell line–derived LNCaP/AR tumors in castrate male mice, enzalutamide led to superior tumor responses over bicalutamide in a dose-dependent fashion. These and other data led to the initial phase I/II study that was initiated in 2007 and conducted at 5 centers through the Prostate Cancer Clinical Trials Consortium (7). Men with progressive CRPC and an increasing PSA with or without radiographic metastasis were eligible to participate. In the phase I portion, dose exposure ranged from 30 to 600 mg orally daily, with only patients refractory to chemotherapy in the 480 and 600 mg cohorts. Pharmacokinetic analyses revealed rapid drug absorption and peak serum concentration from 30 minutes to 4 hours, with an approximate 7 day half-life. At all dose levels and in a dose-dependent fashion up to 150 mg, significant decreases in PSA were shown regardless of prior chemotherapy exposure. It was observed in this phase I study that chemotherapy-naive men had a higher proportion of PSA decline, of more than 50% at 12 weeks, and patients with prior exposure to ketoconazole had a diminished PSA response when administered enzalutamide.

In these early studies, time to PSA progression [Prostate Cancer Working Group 2 (PCWG2) definition of PSA progression, ≥25% increase from nadir PSA] was 41, 32, and 21 weeks, respectively, for chemonaive men, all men, and men previously exposed to chemotherapy. The median time to radiographic progression was 47 weeks for all participants, and the time to progression was significantly different in men previously treated with chemotherapy compared with chemonaive men (29 weeks vs. not yet reached; \( P = 0.01 \)). Exploratory studies using 16b-[18F] fluoro-5α-dihydrotestosterone (FDHT) imaging and circulating tumor cells showed improvement posttreatment in subsets of patients, which correlated with clinical outcomes. Long-term follow-up data presented in 2011 showed median time to radiographic progression of 56 weeks in chemotherapy-naive men and 24 weeks in men previously treated with chemotherapy (8).

Fatigue was the most common reported toxicity and led to dose reductions at levels of 240 mg and above. No dose reductions for fatigue were required in men receiving 150 mg or less, and the most common reported toxicities were grade 2 fatigue, nausea, dyspnea, anorexia, and back pain. Witnessed seizures were reported in 1 patient each at the 360 and 600 mg dose levels, and a possible seizure event at the 480 mg dose level was also reported. Other adverse events which lead to treatment discontinuation were rash, nausea and vomiting, fatigue and myocardial infarction, none of which occurred at the 150 mg and below dose levels. Other grade 3 and 4 events were anemia, arthralgia, and asthenia, which generally occurred at higher rates in the elevated dose levels. The maximum tolerated dose selected for phase II study was 240 mg daily. In all dose levels, partial responses in soft-tissue disease were observed in 22% of the men, and stable bone scan at 12 weeks in 56% of the men, with chemonaive men having higher rates of radiographic responses than those with previous chemotherapy exposure.

Late Clinical Development

AFFIRM, a phase III study evaluating the efficacy and safety of investigational drug enzalutamide (NCT00974311), compared enzalutamide with placebo and randomized (in a 2:1 ratio) 1,199 men with CRPC who progressed on at least one prior chemotherapy from September 2009 through November 2010 at 156 centers in 15 countries (9). Patients with castrate levels of testosterone, disease progression by PCWG2 criteria, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, or 2, and adequate hematologic, hepatic, and renal function were eligible to participate. Men were administered enzalutamide 160 mg orally daily or matched placebo and the use of prednisone was allowed but not required. The dose of 160 mg/d of enzalutamide was chosen for this registration study as there was comparable clinical benefit seen in the phase I/II study among men treated in the 150 and 240 mg cohorts but increased incidence of adverse events with the higher dose.

Baseline patient and disease characteristics were well-balanced between placebo and enzalutamide-treated men. The median age of men on study was 69 years (range, 41–92), median Gleason score was 8 in both groups, and the majority of patients had reported ECOG PS of 0 or 1. More than 70% of men in each group had received only one prior chemotherapy regimen with median of 8.5 and 8 prior cycles of docetaxel in the enzalutamide and placebo arms, respectively. At the planned interim analysis, following 520 deaths on study, the median overall survival of patients in
Drug concentration and off-target mechanism is partly explained by central nervous system (CNS) seizure events. Animal studies suggest that seizure mechanisms are speculated to have contributed to the Predisposing dural or brain metastases and concomitant in prostate cancer therapeutic studies, was reported in this phase I/II study, and which is an uncommon adverse event group.

Clinically significant electrocardiographic changes in either men compared with 3.3% of placebo-treated men, with no significant differences reported in the infrequent metabolizer diarrhea, hot flashes, musculoskeletal pain, and headache reporting any grade of fatigue, with similar rates of enzalutamide-treated and 29% of placebo-treated men reported adverse event in both groups, with 34% of who received enzalutamide, suggesting that a significant events was higher in the placebo-treated men than in men who received enzalutamide, suggesting that a significant cause of on-study adverse events was related to underlying disease progression. Fatigue was the most commonly reported adverse event in both groups, with 34% of enzalutamide-treated and 29% of placebo-treated men reporting any grade of fatigue, with similar rates of ≥grade 3 fatigue, 6% and 7% respectively. More frequent rates of diarrhea, hot flashes, musculoskeletal pain, and headache were reported in the enzalutamide-treated men, with no significant differences reported in the infrequent metabolizer and hepatic function related events between the groups. Hypertension was noted in 6.6% of enzalutamide-treated men compared with 3.3% of placebo-treated men, with no clinically significant electrocardiographic changes in either group.

Seizure, which was noted at the higher dosages in the phase I/II study, and which is an uncommon adverse event in prostate cancer therapeutic studies, was reported in this trial as well. Five of the 800 enzalutamide-treated men (0.6%), compared with none of the placebo-treated men, experienced a witnessed or unwatched seizure on study. Predisposing dural or brain metastases and concomitant medications are speculated to have contributed to the seizure events. Animal studies suggest that seizure mechanism is partly explained by central nervous system (CNS) drug concentration and off-target γ-amino butyric acid-A (GABA-A) inhibition by enzalutamide. Similar animal data supporting this mechanism of seizure were reported for another novel AR antagonist, BMS-641988, the development of which was halted following phase 1 data showing only modest clinical effect and seizure activity in 1 patient (10, 11).

**Advantage over Antiandrogens and Other Agents**

Enzalutamide lacks the partial agonist activity notable with other nonsteroidal antiandrogens, and, given its activity not just as an inhibitor of the androgen receptor, but preclinically to inhibit nuclear translocation of the AR and inhibit the association of AR with DNA, further differentiates it from other antiandrogens (Fig. 1). Enzalutamide represents the third pharmaceutical agent to significantly increase survival in men with CRPC following docetaxel (Table 1). While there have been no comparative studies between the other 2 agents, cabazitaxel (Jevtana, Sanofi-Aventis) and abiraterone acetate (Zytiga, Johnson & Johnson), the HRs are similar between all 3 of the agents. It is important to note that the abiraterone acetate and cabazitaxel studies had control arms that included agents with antitumor activity (prednisone and mitoxantrone/prednisone, respectively) compared with placebo-controlled arm in the AFFIRM study. Approximately 30% of patients in both the AFFIRM enzalutamide and placebo arms were receiving corticosteroids at baseline, which was associated with reduced survival regardless of study treatment (12). Overall, enzalutamide has a favorable toxicity profile. Unlike cabazitaxel, enzalutamide was not reported to cause neuropathy or myelosuppression, 2 significant toxicities that can lead to morbidity and limit additional therapy in patients with CRPC (13).

Enzalutamide also lacks the detrimental effects of mineralocorticoid excess induced by abiraterone acetate and thus does not require coadministration with steroids, which often complicates CRPC treatment. Similar to abiraterone acetate, which showed a statistically significant improvement in radiographic progression-free survival in an interim analysis, enzalutamide has also been studied in the CRPC chemotherapy-naive population, with data currently maturing (14). Based upon improvement in radiographic progression-free survival and a trend toward improved overall survival, the use of abiraterone acetate and prednisone in chemotherapy-naive men has recently been endorsed (15).

**Future Development**

Currently, enzalutamide is being evaluated in multiple earlier disease states in prostate cancer, as well as in ongoing studies in patients with hormone-refractory breast cancer. In patients with newly diagnosed localized prostate cancer, men will be randomized to enzalutamide alone or enzalutamide, leuprolide acetate, and dutasteride for 6 months before radical prostatectomy, with
primary outcome of pathologic complete response rate (NCT01547299). A single-arm phase II study of enzalutamide in men with normal serum testosterone levels who are candidates for castration for advanced prostate cancer has completed accrual, with primary endpoint of PSA progression (NCT01302041). In the castrate-resistant setting, men with either PSA, bone, or visceral progression will be randomized in a phase II study to receive bicalutamide or enzalutamide, with primary endpoint of progression-free survival (STRIVE, NCT01664923). A similar ongoing phase II TERRAIN trial enrolling only patients with radiographic progression is being conducted, predominantly in Europe. The phase III PREVAIL trial is a randomized, double-blind, placebo-controlled study in men with CRPC who have failed antiandrogen treatment, before receiving chemotherapy. The study completed target accrual of 1,680 patients in May 2012, and the primary endpoints are overall survival and radiographic progression-free survival. The ongoing phase II study of the combination of enzalutamide and abiraterone acetate in patients with CRPC with bone disease is supported by data that showed increased bone marrow testosterone in enzalutamide-treated patients and increased nuclear AR expression in

<table>
<thead>
<tr>
<th>Table 1. Overall survival benefit in recent CRPC trials</th>
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<tr>
<td><strong>Agent (trial, year)</strong></td>
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<tr>
<td>Docetaxel/Taxotere (1) (TAX327, 2004)</td>
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<tr>
<td>Radium-223/Alpharadin (17) (ALSYMPCA, 2011)</td>
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<tr>
<td>Cabazitaxel/Jevtana (13) (TROPIC, 2010)</td>
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<tr>
<td>Sipuleucel-T/Provenge (18) (IMPACT, 2010)</td>
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<tr>
<td>Abiraterone/Zytiga (5) (COU-AA-301, 2010)</td>
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<tr>
<td>MDV-3100 (9) (AFFIRM, 2011)</td>
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Figure 1. Mechanisms of action of enzalutamide and bicalutamide. 1. Enzalutamide inhibits AR–testosterone binding with higher affinity than bicalutamide. 2. Enzalutamide receptor inhibition blocks the activational change induced by AR–testosterone binding. 3. Enzalutamide inhibits AR–testosterone nuclear translocation and DNA transcription. 4. Enzalutamide lacks partial AR agonist activity that occurs with bicalutamide resistance.
abiraterone-treated patients, suggesting that these agents will work synergistically (NCT01650194; ref. 16). Finally, a phase Ib study of enzalutamide in combination with docetaxel has completed enrollment, with final reporting of data pending (NCT01565928). Enzalutamide is an exciting novel agent for prostate cancer and these ongoing trials will further define the appropriate use of enzalutamide in prostate cancer.

References


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