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# Treatment of metastatic castration-resistant prostate cancer (mCRPC) with enzalutamide

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ABSTRACT

Prostate cancer is initially responsive to androgen deprivation therapy, but most patients eventually develop castration-resistant disease. Enzalutamide is an androgen receptor (AR) inhibitor that targets several steps in the AR signaling pathway and has shown significant efficacy in the treatment of metastatic castration-resistant prostate cancer in patients with or without prior chemotherapy. To provide optimal treatment, it is important to understand the implications of enzalutamide use in the context of other therapies, as recent findings have suggested cross-resistance occurs between and within drug classes. Mutations and splice variants of AR also impact the course of prostate cancer. Future strategies involving enzalutamide should account for previous exposure to taxanes or antiandrogen therapies and the presence of AR variants that could affect efficacy.



*Abbreviations:* ADT, androgen deprivation therapy; AR, androgen receptor; AR-V, androgen receptor splice variant; AR-V7, androgen receptor splice variant 7; ASCO, American Society of Clinical Oncology; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cells; GR, glucocorticoid receptor; HR, hazard ratio; HRQoL, health-related quality of life; LBD, ligand-binding domain; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PFS, progression-free survival; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival; SRE, skeletal-related event.

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## 1. Introduction

Prostate cancer is the leading cancer in men and the second most common cause of cancer death in the United States, and it is estimated that more than 180,000 new cases of prostate cancer will be diagnosed in the United States in 2016 (Siegel et al., 2016). Prostate cancer tumor growth is driven by the androgen receptor (AR), a receptor that, when bound by androgens, acts as a transcription factor (Zarif and Miranti, 2016) and activates nongenomic cytoplasmic signaling cascades (Foradori et al., 2008). Tumors are initially responsive to androgen-deprivation therapy (ADT), which reduces AR signaling. However, most tumors eventually become resistant to ADT and patients develop castration-resistant prostate cancer (CPRC). Tumors resistant to ADT continue to secrete prostate-specific antigen (PSA), which is indicative of AR reactivation (Agoulnik and Weigel, 2006; Chen et al., 2008). Activation of AR, despite castrate levels of testosterone, can occur through several different mechanisms, including AR overexpression, AR mutations, development of splice variants, changes in AR signaling cross talk, and upregulation of AR cofactors.

In 2004, docetaxel (a member of the taxane family of microtubule stabilizer/inhibitors) plus prednisone became the standard treatment for patients with advanced prostate cancer who showed disease progression on ADT (Tannock et al., 2004). In recent years, a number of agents have shown a benefit in overall survival (OS) in the treatment of metastatic CRPC (mCRPC), including cabazitaxel (De Bono et al., 2010), abiraterone acetate (De Bono et al., 2011; Fizazi et al., 2012), radium-223 (Parker et al., 2013), sipuleucel-T (Kantoff et al., 2010), and enzalutamide (Beer et al., 2014; Scher et al., 2012).

Enzalutamide is a nonsteroidal AR inhibitor that binds the AR with higher affinity than conventional antiandrogens and impairs AR nuclear localization and transcriptional activity even under conditions of AR overexpression (Tran et al., 2009). Enzalutamide has been approved in the United States and Europe for the treatment of patients with mCRPC before or after docetaxel chemotherapy. This review focuses on the trials involving enzalutamide and its potential role in combination therapy and sequencing.

## 2. Preclinical and phase I/II studies

### 2.1. Preclinical discovery of enzalutamide

Enzalutamide was characterized in a preclinical study evaluating potential AR inhibitors in the context of elevated AR expression (Tran et al., 2009). Tran et al. found that enzalutamide had five- to eight-fold greater affinity for the AR than bicalutamide (a first-generation antiandrogen), and two- to three-fold lesser affinity than dihydrotestosterone. Unlike bicalutamide, which has partial agonist activity in cells overexpressing the AR (Culig et al., 1999), enzalutamide did not have an agonistic effect on the receptor and induced apoptosis in prostate cancer cell lines. Furthermore, enzalutamide inhibited the activity and impaired the DNA binding of mutant ARs isolated from bicalutamide-resistant cells. Castrated male mice with tumor xenografts consisting of LNCaP cells engineered to overexpress the AR (LNCaP/AR) were treated with enzalutamide, and all showed volume regression. Bicalutamide had little activity in similar experiments: only one of 12 tumors in bicalutamide-treated mice showed a 50% volume reduction and four tumors remained stable. Based on positive results in this xenograft model and its drug-like properties, enzalutamide was preferred for assessment in a phase I/II trial.

### 2.2. Safety and efficacy of enzalutamide

In the multicenter phase I/II trial of enzalutamide, 140 patients (65 chemotherapy-naïve and 75 postchemotherapy) with CRPC were enrolled (Scher et al., 2010). Median age was 68 years, 13 patients had visceral lesions, and seven patients had no evidence of metastatic disease. Previous treatments with antiandrogen therapies and chemotherapy were allowed. Enzalutamide was administered orally with daily doses ranging from 30 to 600 mg. Chemistry panels, PSA and creatinine levels, and complete blood counts were evaluated monthly, while radiographic imaging was repeated every 3 months for patients with metastatic disease and every 6 months in patients with biochemical progression only. Antitumor effects were assessed in compliance with Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (Scher et al., 2008).

Enzalutamide was generally well tolerated, with the most common adverse events grade 2 or less being anorexia, diarrhea, nausea, and constipation. The most common adverse event overall was fatigue; 16 patients dosed at 240 mg/day or more experienced grade 3 or greater fatigue that necessitated dose reduction in nine of these patients (Scher et al., 2010). Although two patients treated at 360 mg/day and 600 mg/day, respectively, had confirmed seizures, both were on medications that could have reduced their seizure thresholds and had other medical problems (*i.e.*, hypocalcemia, anemia, and brain metastasis) that may have contributed to seizures. However, on the basis of these documented seizures and increased frequency of grade 3 or greater fatigue at dosages of 360 mg/day or more, the maximum tolerated dose for future trials was defined as 240 mg. Recently, 3-year follow-up data from this trial were released that showed little change in the overall safety profile (Higano et al., 2015). Of the chemotherapy-naïve patients, 31% remained on enzalutamide for more than 2 years and 17% for more than 4 years, whereas only 5% of postchemotherapy patients remained on therapy after 2 years.

Maximal and 12-week post-therapy changes in serum PSA levels were reduced at all drug dosages, and both the degree of decline and proportion of patients with observed declines were dose-dependent between 30 and 150 mg/day, with no additional benefit derived from higher dosages (Scher et al., 2010). Treatment was associated with radiological soft-tissue tumor regression in 22% of patients, stable disease in 49%, and stable bone disease in 56%. The median time to PCWG2-defined PSA progression was 32 weeks for all patients, and median time to radiological progression was 47 weeks. Circulating tumor cells (CTCs) were enumerated in 128 patients, and of the 51 with unfavorable counts (defined as $\geq$5 cells/7.5 mL of blood) at baseline, 25 (49%) converted to favorable counts after treatment; of the 77 patients with favorable counts at baseline, 70 (91%) still had favorable counts after treatment.

On the basis of radiological and biochemical measures of tumor progression, CTC conversion rates and demonstrated safety profile, enzalutamide entered phase III trials.

## 3. Pivotal phase III trials of enzalutamide

There were two international, randomized, double-blind placebo-controlled phase III trials that demonstrated the efficacy of enzalutamide in men with mCRPC: AFFIRM and PREVAIL.