XTANDI (enzalutamide): A New Treatment for Metastatic Castration-Resistant Prostate Cancer

Introduction

Since the 1940s, it has been understood that androgen deprivation therapy (ADT) could slow the progression of prostate cancer [1].

Hormonal therapies act to inhibit the actions of androgens (testosterone and dihydrotestosterone [DHT]), which drive prostate cancer growth. Men whose prostate cancer returns following initial treatments with surgery or radiation are usually treated with therapies to lower their androgen levels (ADT), such as Lupron, Eligard, Zoladex, Trelstar, Vantas, Firmagon or surgical removal of the testicles. Despite these treatments, prostate cancer sometimes returns. This state is referred to as castration-resistant prostate cancer, or CRPC.

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Until recently, few treatment options were available to men with CRPC.

Prior to the 2004 regulatory approval of docetaxel (Taxotere®) chemotherapy, no drugs were FDA-approved and labeled to treat CRPC. Though anti-androgens, such as bicalutamide (Casodex®) and nilutamide (Nilandron®), have been used after androgen deprivation therapy has failed, their actual approvals are for the treatment of metastatic prostate cancer (D2).

Within the last three years, however, several new treatment options for patients with CRPC have become available, including abiraterone acetate taken in combination with prednisone (Zytiga®, 2011), sipuleucel-T (Provenge®, 2010), cabazitaxel (Jevtana®, 2010), and denosumab (XGEVA®). Enzalutamide (XTANDI®), approved in May 2012 for the treatment of metastatic CRPC following docetaxel, is the newest therapy approved. Another treatment in development and showing efficacy in a phase III trial is radium-223 (Alpharadin®) for the treatment of bone-metastatic CRPC (see the February 2012 issue of PCRI Insights for more information on Alpharadin). This article is designed to help patients understand how enzalutamide, an androgen receptor inhibitor, was designed and developed as a treatment for patients with CRPC. Enzalutamide is the generic name for the drug previously referred to by its research compound name, MDV3100, now available under the brand name XTANDI®.

How Androgens and the Androgen Receptor Drive Prostate Cancer

Inside both normal cells and cancer cells, androgens activate the androgen receptor [2]. In normal cells, androgens work through the androgen receptor to enable the development and maintenance of secondary male characteristics and spermatogenesis [1].

In the prostate cancer tumor cell, growth depends on activation of the androgen receptor by the androgens as well. The activated androgen receptor moves into the nucleus of the cell and binds to the DNA, causing the production of different molecules that drive cancer growth.

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DEFINITIONS

Androgen - a hormone responsible for male characteristics.
Secondary male characteristics - Non-sexual characteristics that distinguish a man from a woman, such as facial hair, broad shoulders, and muscle mass.
Spermatogenesis - the process and formation of sperm.
An increase in PSA level is a consequence of androgen receptor-driven genes in prostate cancer cells. The goal of hormonal cancer treatments in prostate cancer is to inhibit the action of the androgen receptor.

The androgen, testosterone, is synthesized primarily in the testicles (~90%), but is also synthesized by the adrenal gland, and by the prostate tumor itself. Patients who are on ADT have very low levels of testosterone in their blood. Despite these low (and sometimes even undetectable) blood levels of testosterone in patients with CRPC, the androgen receptor continues to be active in cancer-promoting tumor growth.

In patients with CPRC, prostate cancer cells adapt to low-circulating androgen levels, and continue to activate the androgen receptor by numerous mechanisms: mutations to make the androgen receptor more responsive to androgens or other steroids, increasing the number of androgen receptor molecules in the cell, and mutations that activate the androgen receptor in the absence of androgens. Additionally, it has been reported that prostate cancer cells can produce androgens themselves by alternate mechanisms [1]. Thus, treatments that directly inhibit the androgen receptor may be of value.

**Anti-Androgens Bind to Androgen Receptors**

Anti-androgens (such as bicalutamide and nilutamide) have been shown to bind to the androgen receptor and inhibit its activity, at least initially. This is called antagonism. However, these drugs have a much lower binding affinity for the androgen receptor compared to androgens such as DHT. In some situations, anti-androgens have been shown to have opposite effect, and may actually activate the androgen receptor (agonist activity) [3]. In cases like this, your doctor may stop your anti-androgen therapy as a form of treatment. This has been called anti-androgen withdrawal response (AAWR), and has not been shown so far to be a problem with Xtandi.

**Enzalutamide is a multi-acting androgen receptor signaling inhibitor.**

Enzalutamide was specifically designed to overcome AR resistance common in CRPC patients and to avoid agonist activity [3]. It is the first and only androgen receptor inhibitor that targets multiple steps in the androgen receptor signaling pathway (Figure 1).

**FIGURE 1**

![Diagram of Enzalutamide's mechanism of action](image)

A = androgen AR = androgen receptor

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In addition to strongly binding to the androgen receptor, enzalutamide inhibits the movement of the activated androgen receptor to the nucleus. For those activated androgen receptors that do get through, it inhibits binding of the activated androgen receptor with DNA, even in the CRPC patient [3]. In animal models, enzalutamide has been shown to decrease the growth of prostate cancer cells, induce cancer cell death, and reduce tumor size. Another plus is that it does not have androgen receptor agonist activity.

The recommended dose of enzalutamide is 160 mg taken orally, once a day, and can be taken with or without food. Enzalutamide is available as 40 mg capsules.

In clinical trials, corticosteroids (e.g., prednisone) were allowed but not required. Evidence for the anti-tumor activity of enzalutamide comes primarily from two clinical trials: a smaller open-label Phase 1-2 trial (NCT00510718), which determined the maximum tolerated dose and evaluated the antitumor activity, along with safety and tolerability [4]; and a large, randomized placebo-controlled trial that evaluated the efficacy and safety of enzalutamide (The Phase 3 AFFIRM trial, NCT00974311) [5].

In the Phase 1-2 trial, enzalutamide was found to have antitumor effects. This study enrolled 140 patients: 65 with no previous chemotherapy (chemo-naive) and 75 who had previously received docetaxel (post-chemo). Groups of patients were treated with doses ranging from 30 to 600 mg per day. Percentage of patients with a 50% or greater decrease in PSA from baseline is a useful measure of anti-tumor response. The percentage of responders among post-chemo patients was 51% and was 62% in the pre-chemo patients. Fatigue was the most frequently reported adverse event among 11% of patients who reported significant fatigue. In this trial, three patients (~2%) were reported to have had a seizure, all of whom took enzalutamide above the maximum tolerated dose of 240 mg/day. The FDA-approved dose is 160 mg/day.

The larger blinded, randomized, placebo-controlled trial (the AFFIRM trial) included men with CRPC who had previously been treated with docetaxel. Eight hundred men took 160 mg of enzalutamide once a day and 399 took placebo. Patients in the trial were required to continue taking an LHRH (luteinizing hormone-releasing hormone) agent or to have had orchietomy. The median duration of treatment with enzalutamide was 8.3 months, while with placebo it was 3.0 months. Patients were allowed, but not required, to take prednisone.

In the AFFIRM trial, the median overall survival was longer on enzalutamide compared to placebo treatment: 18.4 months for patients taking enzalutamide compared to 13.6 months for placebo (Hazard ratio=0.63, P<0.001) [5].

The most common side effects reported in patients receiving enzalutamide in the AFFIRM trial were fatigue (34% enzalutamide vs 29% placebo), diarrhea (21% vs 18%), and hot flashes (20% vs 10%). Severe side effects (grade three or higher) were reported by 45% of the patients taking enzalutamide and 53% of the patients on placebo. Serious side effects were reported by 34% of patients on enzalutamide and 39% of patients on placebo. There was no evidence of hepatotoxicity (liver toxicity) in either trial; in AFFIRM, liver function abnormalities were reported in 1% of the enzalutamide patients and 2% of the placebo patients, and all were mild to moderate in severity.

XTANDI has been associated with an increased risk of seizure. In the AFFIRM trial, five patients (0.6%) were reported to have had a seizure, whereas no seizures occurred in patients treated with placebo. Confounding factors may have contributed to the occurrence of seizures in several of these cases, including brain metastases, alcoholism, or the use of medications known to predispose a patient to seizure. When a patient experienced a seizure, enzalutamide was discontinued, and all seizures resolved. Based on data from the Phase 1-2 trial, the enzalutamide dose appears to be an important predictor of seizure, with a greater risk of seizure at daily doses higher than 160 mg. In the Phase 1-2 trial, no seizures were reported at daily doses ≤ 240 mg; whereas seizures were reported in one patient each at 360, 480, and 600 mg per day. Patients should discuss with their healthcare provider any conditions that may predispose them to seizures, and any medications they may be taking that lower the seizure threshold.

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Healthcare providers should advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

In the last few years, therapeutic options for patients with advanced prostate cancer, specifically CRPC, have witnessed an exceptional and dramatic improvement in effective treatments. Both clinicians and patients are awaiting further trials to evaluate the ideal sequencing and combination strategies to ensure safety while maximizing the potential efficacy of these new therapies.

Given enzalutamide’s unique and multi-targeted mechanism of action, its once a day oral administration, avoidance of accompanying requirement of a steroid, and its established safety and efficacy data, it appears to be a very promising therapy. Future studies should investigate both combination strategies with other approved prostate cancer drugs, as well as the potential role of enzalutamide in earlier stages of both CRPC and androgen-sensitive prostate cancer.

**REFERENCES**


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