EDITORIAL

From the COO’s Desk

Cathy Williams, Chief Operating Officer

“Without continual growth and progress, such words as improvement, achievement, and success have no meaning.” - Benjamin Franklin

I agree with Franklin’s quote on success. It’s easy to pat yourself on the back when you hear praises from countless people:

The conference was a great success!

Words are easy to come by. But what action lies behind the words? Why was the 2012 conference more successful than in previous years?

It’s possible that this success was a result of adding more support group sessions to meet individual needs, or giving attendees the opportunity to ask questions directly of each speaker.

Or could it perhaps be attributed to the Saturday night gala, where attendees heard the inspiring story of our new medical director, and danced to the sounds of Motown by Larry Peters and Friends? Or is it as simple as a staff and board of directors who are committed to going the extra mile for a prostate cancer survivor and his family?

XTANDI® is a success!

The success of a new cancer treatment has the potential to help thousands of men with prostate cancer, where there may previously have been little hope. Dr. Shore’s article on XTANDI® (enzalutamide) on page 3 shows progress and gives new hope for men who have castration-resistant prostate cancer.

The report from my last doctor’s visit was a success!

For a prostate cancer survivor, success comes in many forms. A decline in PSA, an intimate moment with a partner, a good laugh, an even better cry - these are all signs of progress in the journey of a prostate cancer survivor, as illustrated by Rikki and Terry Robinson’s story on page 17.

The PCRI is successful, and continues to experience growth and progress. Thanks to your generous donations, we have been able to add a medical director, Dr. Dean Foster, to lead us down the path of even greater success. Dr. Foster will guide us towards improved education, awareness, and research for prostate cancer; with new programs such as the Mentor Program to help educate support group leaders, and improvements to our website.

The real success of the PCRI, however, is you. Each one of you means something to all of us. It means something to educate and empower those of you who reach out to our Helpline, and to hear your stories. Because of you, our mission is to educate and empower those of you who have prostate cancer; with new programs such as the Mentor Program to help educate support group leaders, or giving attendees the opportunity to ask questions directly of each speaker.

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Whatever you are able to donate means something to us. The PCRI staff takes your giving seriously, and is devoted to being good stewards of your generosity. We know that at year-end, many worthy organizations are asking for your donations. We want to thank all of you for contributing to our continued success of reaching more people more effectively.

The saying “your success is our success” has never been more true. May you have a healthy, prosperous and successful holiday season and new year!
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 CRPC, 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 withdraw response (AAWR), and has not been shown so far to be a problem with Xandi.

**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**

![Tumor Death](Image)

- **A** = androgen receptor
- **AR** = androgen receptor
- **Enzalutamide**
- **Inhibits Binding of Androgens to AR**
- **Inhibits Nuclear Translocation of AR**
- **Inhibits Association of AR with DNA**

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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 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 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 including 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 orchectomy. 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.
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, avoiding 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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