



Published in final edited form as:

Transl Androl Urol. 2013 June ; 2(2): 119–120.

Enzalutamide: The emperor of all anti-androgens

Emmanuel S. Antonarakis, M.D.

Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Bunting-Blaustein Cancer Research Building, 1650 Orleans St – Room 1M45, Baltimore, MD 21231; phone 443-287-0553; fax 410-614-8397

Emmanuel S. Antonarakis: eantona1@jhmi.edu

In the last few years, there has been a rekindled interest in the androgen receptor (AR) and AR signaling as valid therapeutic targets in prostate cancer. While the primary goal of therapy for recurrent or advanced prostate cancer has long been to reduce circulating and intratumoral androgen levels, recent laboratory and clinical data have shown that AR signaling remains active (and continues to drive tumor growth) even in the castration-resistant state (1). In addition, while first-generation AR blockers (*e.g.* flutamide, bicalutamide, nilutamide) have been used clinically with some success, none of these secondary hormonal manipulations have demonstrated an unequivocal survival benefit in men with prostate cancer. These anti-androgens have several shortcomings, including that they are only weak antagonists of the AR and that they may also function as partial AR agonists (especially with prolonged use).

Enzalutamide (Xtandi[®], Medivation Inc. and Astellas Inc), previously known as MDV3100, is a next-generation anti-androgen that has at least 3 separate activities: it functions as a potent and irreversible inhibitor of the AR, it impairs translocation of the AR from the cell cytosol into the nucleus, and it blocks the interaction of the AR with DNA androgen-response elements at the transcription complex. For these reasons, enzalutamide has also been described as an AR signaling inhibitor. In a recent issue of the *New England Journal of Medicine*, Scher and colleagues (2) report the mature results of the AFFIRM study, a multinational phase III randomized trial of enzalutamide versus placebo in men with metastatic castration-resistant prostate cancer who had developed disease progression despite docetaxel chemotherapy. A total of 1199 men were randomized (2:1) to receive either oral enzalutamide 160 mg daily (800 patients) or placebo (399 patients). The primary endpoint was overall survival, and the trial was halted early after a planned interim analysis which revealed a significant prolongation of median survival in the enzalutamide arm compared to the placebo arm (18.4 months versus 13.6 months, hazard ratio 0.63, $P<0.001$). In addition, enzalutamide showed overwhelming evidence of clinical benefit with respect to all pre-planned secondary endpoints, proving superior to placebo in terms of radiographic progression-free survival (8.3 versus 2.9 months, hazard ratio 0.40, $P<0.001$), PSA response rate (54% versus 2%, $P<0.001$), time to PSA progression (8.3 versus 3.0 months, hazard ratio 0.25, $P<0.001$), radiographic response rate (29% versus 4%, $P<0.001$), and time to first skeletal-related event (16.7 versus 13.3 months, hazard ratio 0.69, $P<0.001$). In addition, data presented at the 2012 Annual ASCO meeting revealed that enzalutamide produced improvements in several quality-of-life measures including pain palliation, physical wellbeing, functional wellbeing, social wellbeing, and emotional wellbeing (3). Enzalutamide was generally very well tolerated, with the most common adverse events being fatigue (34%), diarrhea (21%), hot flashes (20%), and headache (12%). Notably, about

Disclosure: The author declares no conflict of interest.

1% of patients receiving enzalutamide experienced a seizure (compared to 0% in the placebo arm), necessitating discontinuation of the study drug. The results of this trial led to the FDA approval of enzalutamide on August 31, 2012 for the treatment of men with metastatic docetaxel-pretreated castration-resistant prostate cancer.

The current study is important because it provides a proof-of-principle that a continued assault on the AR can be a fruitful therapeutic endeavor even in men with castration-resistant prostate cancer who have progressed despite multiple additional lines of hormonal therapy. It also validates the AR as a *bona fide* therapeutic target in castration-resistant prostate cancer. However, many intriguing questions remain: What is the predominant mechanism of resistance to enzalutamide? Should enzalutamide be used in patients who have not received prior chemotherapy? Will enzalutamide be effective in men who have previously received novel androgen-synthesis inhibitors such as abiraterone? The last question is especially relevant, because all patients on the AFFIRM study were abiraterone-naïve due to the trial's eligibility criteria. An additional intriguing observation is that a substantial number of patients who progressed on enzalutamide showed evidence of PSA elevations after an initial decline in PSA. Because PSA itself is an AR-regulated protein, it can be hypothesized that AR signaling still remains active even after enzalutamide resistance develops. To this end, preclinical experiments have shown that one potential mechanism of enzalutamide resistance may be an increased expression of truncated AR splice variants that lack the androgen-binding domain but remain constitutively active (4). Because enzalutamide acts at the ligand-binding domain, such truncated AR variants would not be expected to be inhibited by this drug, although novel small molecules that target the AR splice variants are on the horizon (5).

A potentially concerning adverse effect of enzalutamide is the occurrence of seizures. Convulsions are a known dose-dependent toxicity of enzalutamide when given at supratherapeutic levels in animal models, and the mechanism of seizures is thought to be related to inhibition of gamma-aminobutyric acid (GABA) receptors in the brain. Although the incidence of seizures in the AFFIRM trial was small (approximately 1%), it should be remembered that eligible patients were required to have a low seizure risk at the time of enrolment (*i.e.* no prior seizures, no brain metastases, no recent stroke, no concomitant medications known to lower the seizure threshold), suggesting that the true incidence of seizures in an unselected patient population may be even higher. The presence of a seizure would generally necessitate discontinuation of enzalutamide. In conclusion, enzalutamide is the first AR blocker to demonstrate an unequivocal survival benefit in men with castration-resistant prostate cancer, and has been hailed by some as the “emperor of all anti-androgens”. While the benefits of enzalutamide in chemotherapy-refractory patients are now confirmed, it remains to be seen if this drug will prove equally effective in a broader range of men with castration-resistant prostate cancer. In addition, the use of enzalutamide in earlier disease settings (*i.e.* the non-castrate PSA-recurrent state) is an exciting possibility of the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

NCI Grant P50 CA058236

References

1. Schweizer MT, Antonarakis ES. Abiraterone and other novel androgen-directed strategies for the treatment of prostate cancer: a new era of hormonal therapies is born. *Ther Adv Urol.* 2012; 4:167–78. [PubMed: 22852027]
2. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012; 367:1187–97. [PubMed: 22894553]
3. De Bono JS, Fizazi K, Saad F, et al. Primary, secondary, and quality-of-life endpoint results from the phase III AFFIRM study of MDV3100, an androgen receptor signaling inhibitor. *J Clin Oncol.* 2012; 30:abstract 4519.
4. Hu R, Lu C, Mostaghel EA, et al. Distinct transcriptional programs mediated by the ligand-dependent full-length androgen receptor and its splice variants in castration-resistant prostate cancer. *Cancer Res.* 2012; 72:3457–62. [PubMed: 22710436]
5. Andersen RJ, Mawji NR, Wang J, et al. Regression of castrate-recurrent prostate cancer by a small-molecule inhibitor of the amino-terminus domain of the androgen receptor. *Cancer Cell.* 2010; 17:535–46. [PubMed: 20541699]