**DRUG REVIEW** 

# Enzalutamide as Promising Therapy in Castrate Resistant Prostate Cancer

JK SCIENCE

## Harmanjit Singh, Ekta Arora\*, Pugazhenthan T, Bikash Medhi

## Introduction

Advanced prostate cancer has been known by a number of names over the years, including hormoneresistant prostate cancer (HRPC) and androgeninsensitive prostate cancer. Most recently, the terms "castrate-resistant" or "castration-recurrent" prostate cancer (CRPC) were introduced (1).CRPC presents a spectrum of disease ranging from rising PSA levels in the absence of metastases or symptoms and despite androgen-deprivation therapy, to metastases and significant debilitation from cancer symptoms. CRPC is usually suspected in patients with new symptoms on androgen deprivation therapy, with a rising PSA, or with new evidence of disease on bone scans or computed tomography scans (2). Prostate Cancer Working Group (PCWG2) defined CRPC as a continuum on the basis of whether metastases are detectable (clinically or by imaging) and whether serum testosterone is in the castrate range (<1.7 nmol/L) because of a surgical castration or medical therapy (3).Reactivation of the disease despite castrate levels of testosterone represents a transition to the lethal phenotype of CRPC(4,5). This state was previously called androgen-independent or hormonerefractory prostate cancer but is now recognized to be driven by androgen-receptor (AR) signalling, in part due to over-expression of the AR itself (6,7).

### Role of AR in Development of CRPC

The AR is a transcription factor that mediates the biological effects of androgens, testosterone and dihydrotestosterone (DHT). It is vital for the development and progression of prostate cancer. It is seen that after an initial response to androgen ablation therapy and subsequent suppression of AR signalling, the majority of advanced tumors eventually transform to the currently incurable androgen-independent or CRPC (8,9). Importantly, CRPC continues to be highly dependent on the persistent expression and function of AR to survive and progress (10,11). Studies reporting significant

inhibition of in-vitro and in-vivo growth of CRPC following disruption of AR expression and/or functions have generated much interest in the AR as a key therapeutic target, and have intensified efforts to uncover potent AR inhibitors (12,13). In preclinical models of prostate cancer, it has been found that AR over-expression shortens the tumor latency period and confers resistance to our conventional antiandrogen drugs, such as bicalutamide (14).It is well established that the AR signalling remains active even when castration levels of serum testosterone are achieved. Induction of the activity of CYP17 (cytochrome P-450c17), an enzyme that catalyzes key reactions in extragonadal androgen biosynthesis, is one way to maintain the hypersensitivity of the AR (15) another interesting point is the presence of certain AR mutants which are able to bind promiscuous steroids, and may convert AR antagonists to agonists (16).

### **Enzalutamide and its Pharmacological Properties**

Enzalutamide (formerly MDV3100) is an androgen receptor-signaling inhibitor chosen for clinical development on the basis of activity in prostate-cancer models with over- expression of the AR. Enzalutamide is distinct from the currently available anti-androgen agents in that it inhibits nuclear translocation of the androgen receptor, DNA binding, and co-activator recruitment. It also has a greater affinity for the receptor, induces tumor shrinkage in xenograft models (in which conventional agents only retard growth), and has no known agonistic effects (17, 18). Enzalutamide has approximately five fold higher binding affinity for the AR compared to the bicalutamide. As compared to bicalutamide, it does not promote translocation of AR to the nucleus and in addition prevents binding of AR to DNA and AR to co-activator proteins. Importantly, it does not require the co-administration of corticosteroids which might be important in patients with co-morbidities such as diabetes, but also in preserving muscle strength, skin integrity and other important, but

From the Department of Pharmacology, PGIMER, Chandigarh and \*AIIMS New Delhi 160012 Correspondence to : Dr. Bikash Medhi, Additional Professor, Department of Pharmacology, PGIMER, Chandigarh-160012



often overlooked, quality-of-life issues. The advanced prostate cancer patients usually live longer and the need for chronic steroid therapy is becoming a burden and enzalutamide offers an important therapeutic option that avoids steroids altogether (19).

At oral dose of 160 mg daily in patients with metastatic CRPC, the median time to reach maximum plasma Cmax was 1 hour, ranging from 0.5 to 3 hours. At steady state, the plasma mean Cmax values for enzalutamide and its active metabolite N-desmethyl enzalutamide were16.6 microg/mL and 12.7 microg/mL (20). The steady state is achieved by Day 28 when it was given as daily regimen; no major daily fluctuations in plasma concentrations are seen. At steady state. It shows approximately dose proportional pharmacokinetics (daily dose range of 30 to 360 mg). The mean apparent volume of distribution after a single oral dose is 110 L and it is 97% to 98% plasma protein bound mainly albumin. CYP2C8 metabolizes enzalutamide to its active metabolite i.e. N-desmethyl enzalutamide. It is primarily eliminated by hepatic metabolism and the mean terminal half-life for in patients after a single oral dose is 5.8 days, ranging from 2.8 to 10.2 days. A single oral dose of 160 mg in healthy volunteers has mean terminal t1/2 for N-desmethyl enzalutamide approximately 7.8 to 8.6 days (20).

# Preclinical and Clinical Research on Enzalutamide

Enzalutamide has significant preclinical activity even in the presence of AR gene amplification. In VcaP (Vertebral cancer of the prostate) cells which over express AR, enzalutamide induced apoptosis whereas bicalutamide did not. Furthermore enzalutamide exerts only antagonist properties at androgen receptor. No partial or full agonistic property has been seen (14).

It has greater affinity to AR than bicalutamide does in a competition assay with 16 beta-[18F] fluoro-5alpha-DHT (18-FDHT) in castration-resistant LNCaP/AR prostate cancer cells (AR-overexpressing). While MDV3100 shows no agonism in LNCaP/AR prostate cells (in contrast to bicalutamide which behaved as an agonist). It antagonized induction of prostate-specific antigen (PSA) and transmembrane serine protease 2 (TMPRSS2), combination with the synthetic androgen R1881 in parental LNCaP cells. In addition, MDV3100 inhibited the transcriptional activity of a mutant AR protein (W741C, mutation of Trp 741 to Cys) isolated from a patient with acquired resistance to bicalutamide. The W741C substitution in the AR ligand binding domain (LBD) causes bicalutamide to act as a pure agonist. MDV3100 also prevents nuclear translocation and co-

activator recruitment of the ligand-receptor complex. (14, 18, 21). A phase I-II study of escalating doses of enzalutamide showed favourable efficacy and toxicity profiles in heavily pretreated patients with metastatic CRPC who had previously received chemotherapy and/ or ketoconazole. This phase 1-2 study was undertaken in five US centres in 140 patients. Patients with progressive, metastatic, castration-resistant prostate cancer were enrolled in dose-escalation cohorts of three to six patients and given an oral daily starting dose of enzalutamide 30 mg to max dose of 600 mg (n=3). Anti-tumor effects were noted at all doses, including decreases in serum prostate-specific antigen of 50% or more in 78 (56%) patients, responses in soft tissue in 13 (22%) of 59 patients, stabilized bone disease in 61 (56%) of 109 patients, and conversion from unfavourable to favourable circulating tumor cell counts in 25 (49%) of the 51 patients. PET imaging of 22 patients to assess androgenreceptor blockade showed decreased (18) F-fluoro-5alpha-dihydrotestosterone binding at doses from 60 mg to 480 mg per day (range 20-100%). The median time to progression was 47 weeks (95% CI 34-not reached) for radiological progression. The maximum tolerated dose for sustained treatment (>28 days) was 240 mg. The most common grade 3-4 adverse event was dosedependent fatigue (in 11% patients), which generally resolved after dose reduction (19).

The AFFIRM trial (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy) (22) was a phase 3, randomized, double-blind, placebo-controlled, multinational trial evaluating enzalutamide (160 mg/day) versus placebo in 1,199 men with CRPC who were previously treated with docetaxel-based chemotherapy. The median overall survival was 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (HR for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001. These data demonstrated that treatment with enzalutamide resulted in a significantly higher response rate in health-related quality of life as compared to placebo (43.2% vs. 18.3%; p<0.0001). Median time to occurrence of the first skeletal-related event in enzalutamide treated patients was 16.7 months as compared to 13.6 months with placebo (p=0.0001, HR=0.621). The drug was generally well tolerated: common side-effects observed more frequently in enzalutamide included fatigue, diarrhea and hot flushes.



Seizure was reported in <1% of enzalutamide treated patients. Serious adverse events and adverse events causing death were all lower in the enzalutamide group than in the placebo group. Data from clinical studies, including the phase III AFFIRM study, have demonstrated that enzalutamide significantly improves overall survival. **Ongoing Trials** 

A phase III trial, known as PREVAIL is in progress that is investigating the effectiveness of enzalutamide with patients who have not yet received chemotherapy. In addition, a phase II trial began in March 2011 comparing enzalutamide with a commonly used anti-androgen, bicalutamide, in prostate cancer patients who have progressed while on LHRH analogue therapy (e,g., leuprorelin) or surgical castration (23,24).

## Conclusion

Enzalutamide seems to be a promising therapy which is anticipated to join the therapeutic class of anticancer drugs that confer a survival benefit in men with castrationresistant prostate cancer.

#### References

- 1. Mostaghel EA, Page ST, Lin DW, *et al.* Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer Res* 2007; 67:5033-41
- 2. Saad F, Hotte SJ. Guidelines for the management of castrateresistant prostate cancer. *Can Urol Assoc J* 2010;4(6):380-4
- 3. Scher HI, Halabi S, Tannock I, *et al.* Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; 26:1148-59
- 4. Attard G, Richards J, de Bono JS. New strategies in metastatic prostate cancer: targeting the androgen receptor signalling pathway. *Clin Cancer Res* 2011; 17:1649-57
- 5. Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. *Endocr Relat Cancer* 2004; 11:459-76.
- 6. Holzbeierlein J, Lal P, LaTulippe E, *et al.* Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. *Am J Pathol* 2004; 164:217-27
- 7. Visakorpi T, Hyytinen E, Koivisto P, *et al.* In vivo amplification of the androgen receptor gene and progression of human prostate cancer. *Nat Genet* 1995; 9:401-06.
- 8. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. *Nat Clin Pract Urol* 2009; 6:76-85.

- 9. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA* 2005; 294:238-44.
- Scher HI, Sawyers CL. Biology of progressive, castrationresistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005; 23:8253-61
- 11. Grossmann ME, Huang H, Tindall DJ. Androgen receptor signaling in androgen-refractory prostate cancer. *J Natl Cancer Inst* 2001; 93:1687-97
- 12. Liao X, Tang S, Thrasher JB, Griebling TL, Li B. Smallinterfering RNA-induced androgen receptor silencing leads to apoptotic cell death in prostate cancer. *Mol Cancer Ther* 2005; 4:505-15
- 13. Zegarra-Moro OL, Schmidt LJ, Huang H, Tindall DJ. Disruption of androgen receptor function inhibits proliferation of androgen-refractory prostate cancer cells. *Cancer Res* 2002; 62: 1008-13
- Chen CD, Welsbie DS, Tran C, *et al.* Molecular determinants of resistance to antiandrogen therapy. *Nat Med* 2004; 10: 33-9
- 15. Attard G, Reid AH, Olmos D, de Bono JS. Antitumor activity with CYP17 blockade indicates that castration-resistant prostate cancer frequently remains hormone driven. *Cancer Res* 2009; 69: 4937-40
- Bonkhoff H, Berges R. From pathogenesis to prevention of castration resistant prostate cancer. *Prostate* 2010; 70: 100-112.
- 17. Jung ME, Ouk S, Yoo D, *et al.* Structure- activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J Med Chem* 2010; 53: 2779-96.
- Tran C, Ouk S, Clegg NJ, *et al.* Development of a secondgeneration antiandrogen for treatment of advanced prostate cancer. *Science* 2009; 324: 787-90.
- 19. Scher HI, Beer TM, Higano CS, *et al.* Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* 2010; 375:1437-46
- 20. Xtandi (enzalutamide) full prescribing information. Available from http:// www. accessdata.fda. gov/drugsatfda\_docs / label/2012/203415lbl. pdf. Accessed on 26-04-2013.
- Yoshida T, Kinoshita H, Segawa T, *et al.* Antiandrogen bicalutamide promotes tumor growth in a novel androgendependent prostate cancer xenograft model derived from a bicalutamide-treated patient. *Cancer Res* 2005; 65(21): 9611-6
- 22. Scher HI, Fizazi K, Saad FT, *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367:1187-97.
- 23. A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer (PREVAIL). Available from http:// www.clinicaltrials.gov/ct2/show/NCT01212991. Accessed on 26-04-2013.
- 24. A Study of MDV3100 versus Bicalutamide in Castrate Men with Metastatic Prostate Cancer. Available from http://clinicaltrials.gov/show/NCT01288911. Accessed on 26-04-2013.