Mini Review
Volume 13:2, 2021

Journal of Cancer Science & Therapy

Open Access

# Use of Enzalutamide in Carcinoma Prostate

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## Abstract

Patients with metastatic prostate cancer are initially treated with androgen deprivation therapy as androgen receptor (AR) signalling is a key pathway in prostate cancer. Castration-resistant prostate cancer (CRPC) is a stage when patients stop responding to androgen deprivation therapy but are still dependent on AR signalling. Enzalutamide, an orally available AR inhibitor, was initially used in the treatment of patients with metastatic CRPC who had previously received docetaxel. The indications have subsequently been extended to include all patients with metastatic CRPC, and most recently to include patients with non-metastatic CRPC. On December 16, 2019, the Food and Drug Administration approved enzalutamide for patients with metastatic castration-sensitive prostate cancer (mCSPC). The most common adverse reactions that have been reported in enzalutamide-treated patients include hot flushes, asthenia/fatigue, hypertension, fractures, and musculoskeletal pain. The recommended dose is 160 mg (four 40 mg capsules) administered orally once daily, with or without food.

**Keywords:** Androgen receptor • Castration-resistant prostatic cancer • Enzalutamide • Prostate-specific antigen • Safety • Treatment outcome

## Introduction

Enzalutamide is an orally administered, small-molecule inhibitor of the androgen receptor that is designed to overcome acquired resistance to first-generation nonsteroidal antiandrogens, including bicalutamide, nilutamide, and flutamide. Its chemical name is (4-(3-(4-cyano-3-(trifluoromethyl) phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoromethyl benzamide) and was synthesized in 2006 using the non-steroidal agonist RU-59063 as a starting chemical scaffold. This starting compound has a high affinity and selectivity for androgen receptor (AR) over other nuclear hormone receptors [1]. Chemical modifications done to improve serum half-life and oral bioavailability, resulted in the identification of a lead compound RD162 [2]. The RD162 has a half maximal inhibitory concentration nearly eight-times lower than that of bicalutamide, excellent activity in castrate resistant prostate cancer (CRPC) cells engineered to express higher levels of wild-type AR (LNCaP/AR), and a pharmacokinetic profile that facilitates oral administration [2,3]. Further modification of RD162 yielded enzalutamide (RD162'; MDV3100), which was chosen as the clinical candidate from this series because it had slightly greater activity in hormone-refractory LNCaP/AR cells and greater ease of manufacture [3].

## Pharmacology of Enzalutamide

Enzalutamide competitively inhibits binding of androgens (Figure 1) to the AR, nuclear translocation of the AR, DNA binding and co-activator recruitment. This impairment of AR DNA binding and AR transcription complex assembly appears to be the basis for the absence of agonistic effects with enzalutamide [2-4]. Partial ageism with first-generation anti androgens, such as bicalutamide, has been attributed to aberrant recruitment of co-activators to transcription complexes and consequent gene activation. Further, it is hypothesized that the lack of AR ageism with enzalutamide is related to specific conformational changes induced upon receptor binding that differ from those with bicalutamide [2].

The half-life of enzalutamide is 5.8 days, which allows for once-daily oral administration in patients with mCRPC. The molecule attains a steady state by day 28, accumulates 8.3-fold with once-daily dosing, exhibits dose proportionality from 30 to 360 mg/day and has low inter-subject variability (≤ 30%) [5]. Food does not influence the effect on total systemic exposure to enzalutamide or its active metabolite, N-desmethyl enzalutamide [5,6]. Enzalutamide is eliminated primarily by hepatic metabolism, with renal excretion being an insignificant elimination pathway for both enzalutamide and N-desmethyl enzalutamide. No enzalutamide dosage adjustment is required for patients with mild, moderate or severe hepatic impairment [5,7].

One needs to be careful of drug–drug interactions so as to evaluate concomitant medications and make dose adjustments. Strong cytochrome P450 (CYP) 2C8 inhibitors can increase composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold, and enzalutamide is a moderate CYP2C9 and CYP2C19 inducer and a strong CYP3A4 inducer. If co-administration with CYP2C8 inhibitors cannot be avoided, the product label recommends dose reduction from 160 to 80 mg once daily. Similarly, a dose increase from 160 to 240 mg once daily is recommended when enzalutamide is taken with strong CYP3A4 inducers. Congruent competencies [8].

## Current Therapeutic Options

Prostate cancer accounts for more than 350,000 deaths worldwide, and represents the fifth leading cause of cancer-related death (~6.6% of total) in males. At the time of clinical presentation metastases are present in approximately 5% of patients [9]. Initial treatment in these patients includes hormonal manipulation in the form of depletion of testosterone and inhibition of AR signalling, which is effective in most patients with metastatic PC. However almost all patients eventually progress to CRPC status [10]. Approximately 25% of the men diagnosed with PC are ≥75 years of age, yet they form 48% of patients with metastases at diagnosis and 53% of cancer related deaths [11].

Prior to 2010, the median survival of patients with CRPC on docetaxel was 19 months from the time of diagnosis. These patients had only symptomatic relief from skeletal-related events (SREs), such as bone pain, fractures, spinal cord compression and vertebral collapse [12]. Introduction of four new noncytotoxic therapies that included an immunotherapeutic agent (sipuleucel T), androgen-signalling inhibitors (abiraterone acetate and enzalutamide) and a bone-targeting radiopharmaceutical (radium-223 dichloride) helped in extending overall survival (OS) in the metastatic setting by approximately 4-5 months and provided varying levels of improvement in health-related quality of life (HRQoL) and pain mitigation (Table 1) [13,14]. In patients with metastatic CRPC (mCRPC) progressing after docetaxel, chemotherapy with Cabazitaxel is also known to prolong OS [15].

Recent efforts to bring about change in high-risk patients with non-metastatic castration-resistant prostate cancer (nmCRPC) have become fruitful, with the introduction of enzalutamide and apalutamide and have shown significant prolongation of metastasis-free survival (MFS). Delaying the time to

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**Received** 02 February 2021; **Accepted** 16 February 2021; **Published** 23 February 2021

metastasis helps to prolong survival and forestall tumor-related complications [16-18].

## Clinical Efficacy of Enzalutamide in Patients with Crpc

Enzalutamide is currently being actively evaluated across the spectrum of disease biology. The Phase III AFFIRM trial (NCT00974311) is a double-blind, placebo-controlled initiative to assess the effectiveness of enzalutamide in patients with mCRPC, who had previously received docetaxel [19]. Earlier in the dose-ranging Phase I/II trial, enzalutamide had shown encouraging clinical activity and acceptable tolerability among chemotherapy-experienced and chemotherapy-naive patients with progressive mCRPC [20].

The Phase III PREVAIL trial (NCT01212991) was conducted based on the need for effective, less toxic treatments in the prechemotherapy setting given that not all mCRPC patients are eligible for or require docetaxel-based chemotherapy because of pre-existing medical conditions or concerns about toxicity [21].

The Phase III PROSPER trial (NCT02003924), double-blind and placebo-controlled, was conducted to determine if enzalutamide could delay progression among nmCRPC patients with rapidly rising PSA levels [16]. Similarly two other Phase III trials are ongoing which should provide valuable information on early AR inhibition in combination with standard treatments in the metastatic hormone-sensitive PC setting. ARCHES (NCT02677896) is investigating enzalutamide with ADT versus ADT alone in men with hormone-sensitive disease and prior chemotherapy. ENZAMET (NCT02446405) will compare enzalutamide with ADT versus conventional antiandrogens (such as bicalutamide) plus ADT. A summary of enzalutamide's efficacy in CRPC is provided in Table 2.

**Affirm:** post-chemotherapy mCRPC: In this trial a total of 1199 docetaxel-experienced patients across 156 sites in 15 countries were randomly assigned 2:1 to receive either enzalutamide (n=800) or placebo (n=399) [19]. At the time of the interim analysis, median OS (primary end point) was longer in the enzalutamide group than in the placebo group (18.4 vs. 13.6 months, hazard ratio [HR]: 0.63; 95% CI: 0.53–0.75; p<0.001). On this basis, AFFIRM was unblended and eligible patients from the placebo group were switched to enzalutamide [19]. Enzalutamide demonstrated superior efficacy to placebo for secondary end point measures, including PSA level, soft-tissue response rates, times to PSA progression, radiographic progression-free survival (rPFS) and first SRE.

**Prevail:** chemotherapy-naive mCRPC: prevail was designed to evaluate enzalutamide in patients who had not yet received chemotherapy and were asymptomatic or mildly symptomatic. PREVAIL introduced the primary end points of OS and rPFS. The trial enrolled 1717 chemotherapy-naive mCRPC patients at 207 sites globally [22]. Patients were randomly assigned 1:1 to receive enzalutamide (n=872) or placebo (n=845). Treatment continued until the occurrence of unacceptable adverse events (AEs) or confirmed radiographic progression and the initiation of chemotherapy or an investigational agent [22]. At a pre-planned interim analysis after 22 months, enzalutamide treatment had significantly decreased the risk of centrally assessed radiographic progression or death by 81% (HR: 0.19; 95% CI: 0.15–0.23; p<0.001) and death by 29% (HR: 0.71; 95% CI: 0.60–0.84; p<0.001) versus placebo. The prevail study was unblinded at this point, and eligible patients in the placebo group were offered enzalutamide. Enzalutamide provided statistically significant benefits across all secondary end points [22].

**Terrain and strive:** Phase II trials of enzalutamide versus bicalutamide

Terrain was carried out in the same population as prevail, using bicalutamide as an active comparator instead of placebo and a broader definition of the progression end point. The trial randomized 375 asymptomatic or mildly symptomatic, chemotherapy-naive, mCRPC patients at 84 sites across North America and Europe to either enzalutamide (n=184) or bicalutamide (n=191) [23]. Treatment continued until a progression event, an AE necessitating discontinuation, or patient withdrawal. The primary end point was PFS, defined as time from randomization to radiographic disease progression, an SRE, initiation of antineoplastic therapy, or death. Median duration of therapy was longer in the enzalutamide group than in the bicalutamide group (11.7 vs. 5.8 months), as was median follow-up time (20.0 vs. 16.7 months). Median

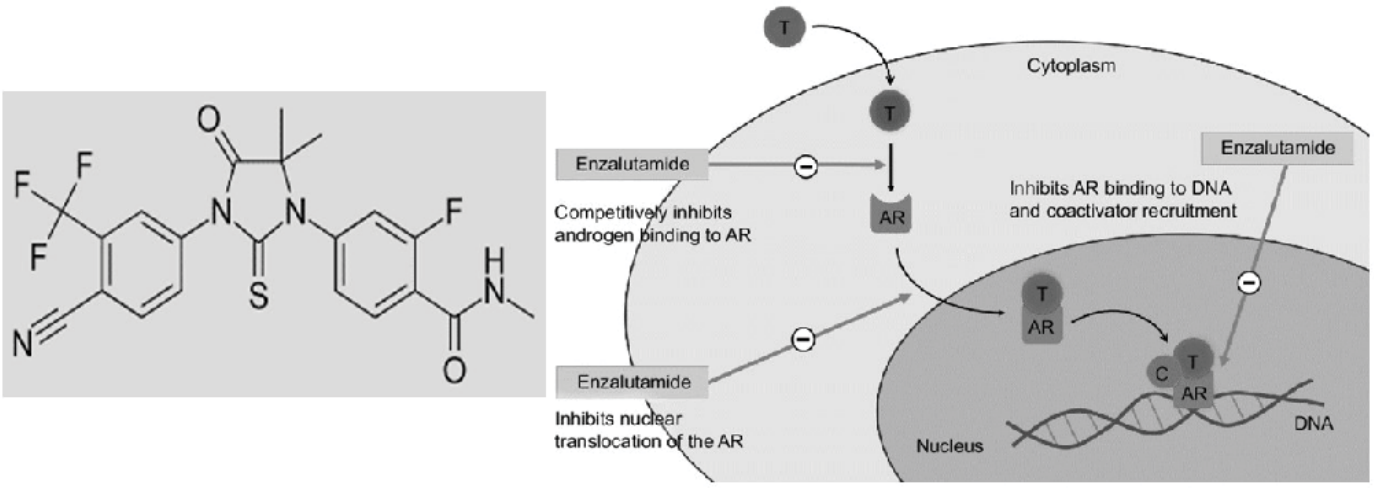


**Figure 1.** Enzalutamide competitively inhibits binding of androgens to the AR.

**Table 1.** Non-cytotoxic therapies for CRPC.

| Drug | Route | Dosage | Frequency | Indications |
|---|---|---|---|---|
| Abiraterone | Oral* | 1000 mg | Daily | mCRPC and mHSPC |
| Enzalutamide | Oral | 160 mg | Daily | M0 and M1 CRPC |
| Apalutamide | Oral | 240 mg | Daily | M0 CRPC |
| Sipuleucel-T | Intravenous | 3 complete doses | Bi-weekly | Asymptomatic mCRPC |
| Radium 223 | Intravenous | 6 injections | 4 weekly | CRPC with bone metastases |

**Table 2.** Overview of enzalutamide clinical trials in castration-resistant prostate cancer.

| Trial | Design | Comparison/intervention | Type of patients | Number of patients | Median age (range), year | Primary end point | Ref. |
|---|---|---|---|---|---|---|---|
| PLATO | Phase IV<br>R, DB | Enzalutamide 160 mg/day until PSA progression (period 1), then AA 1000 mg/day+PRED with either enzalutamide or placebo (period 2) | Metastatic<br>Chemotherapy-naive | 509 (period 1)<br>251 (period 2) | 72 (67-77) | PFS‡‡ | [40] |
| NCT02116582 | Phase IV<br>Single-arm, open-label<br>Ongoing ADT | Enzalutamide 160 mg/day | Metastatic<br>Prior AA + PRED<br>Prior chemotherapy allowed | 214 | 73 (69-78)†† | rPFS | [39] |
| Morris et al. | • Phase Ib | Docetaxel 75 mg/m$^2$+enzalutamide 160 mg/day from day 2 cycle 1 | • Metastatic<br>• Docetaxel-naive | 22 | 70 (46-85) | Safety | [38] |
| NCT01284920 | Phase I/II | Enzalutamide 80–240 mg/day | • Metastatic, progressive<br>• Prior docetaxel<br>• Japanese | 47 | 73 (62-86)¶<br>72 (50-85) | Safety | [37] |
| PROSPER | • Phase III<br>• R, DB<br>• Steroids not required | Enzalutamide 160 mg/day vs. placebo | • M0<br>• Rising PSA§<br>• Ongoing ADT<br>• ECOG PS: 0–1 | 1401 | 74 (50-95) | Metastasis-free survival | [20] |
| STRIVE | • Phase II • R, DB<br>• US sites only<br>• Ongoing ADT<br>• Steroids not required | Enzalutamide 160 mg/day vs. BIC 50 mg/day | • Metastatic and M0<br>• Chemotherapy-naïve<br>• Progressed on ADT<br>• No prior progression on BIC<br>Asymptomatic/mildly symptomatic<br>• ECOG PS: 0–1 | 396 (139 M0 + 257 metastatic) | 73 (46-92) | PFS‡ | [35] |
| TERRAIN | • Phase II • R, DB<br>• Ongoing AD<br>• Steroids permitted | Enzalutamide 160 mg/day vs. BIC 50 mg/day | • Metastatic<br>• Chemotherapy-naive<br>• Progressed on ADT<br>• Not progressed BIC<br>• ECOG PS: 0–1<br>• Asymptomatic/mildly symptomatic<br>• Not requiring opioids | 375 | 71 (50-96) | PFS, safety | [34] |
| PREVAIL | • Phase III<br>• R (2:1), DB<br>• Steroids permitted | Enzalutamide 160 mg/day vs. placebo | • Metastatic<br>• Chemotherapy-naïve<br>• Progressed on ADT<br>• Asymptomatic/mildly symptomatic<br>• ECOG PS: 0–1<br>• Visceral disease allowed | 1717 | 72 (43-93) | rPFS, OS† | [36] |
| AFFIRM | • Phase III<br>• R (2:1), DB<br>• Steroids permitted | Enzalutamide 160 mg/day vs. placebo | • Metastatic<br>• Prior chemotherapy<br>• ECOG PS: 0–5<br>• BPI-SF Q3: 0–10 | 1199 | 69 (41-92) | OS | [32] |
| NCT00510718 | • Phase I/II | Enzalutamide 30–600 mg/day | • Metastatic, progressive | 140 | 68 (44-93) | Antitumor activity, safety | [28] |

†Coprimary end points.
‡Composite of radiographic progression, PSA progression and death.
§PSA doubling time of ≤ 10 months. ¶Phase I.
#Phase II.
††Interquartile range.
‡‡Radiographic or unequivocal clinical progression or death.
**Abbreviations**: AA: Abiraterone Acetate; ADT: Androgen Deprivation Therapy; BIC: Bicalutamide; BPI-SF Q3: Brief Pain Inventory Short Form question 3; CRPC: Castration-Resistant Prostate Cancer; DB: Double-Blind; ECOG PS: Eastern Cooperative Oncology Group Performance Status; M0: Nonmetastatic; OS: Overall Survival; PFS: Progression-Free Survival; PRED: Prednisone; PSA: Prostate-Specific Antigen; R: Randomized; rPFS: Radiographic Progression-Free Survival.

PFS was 15.7 months in the enzalutamide group versus 5.8 months in the bicalutamide group (HR: 0.44; 95% CI: 0.34–0.57; p<0.0001).

Strive was the first randomized trial to enroll men with nmCRPC (n=139) as well as mCRPC (n=257). Patients received enzalutamide (n=198) or bicalutamide 50 mg/day (n=198) until confirmed PSA or radiographic progression or until an AE that would lead to undue risk if dosing had continued [24]. Enzalutamide treatment extended PFS (primary end point) and reduced the risk of progression or death by 76% compared with bicalutamide. Enzalutamide significantly improved all key secondary end points, including rPFS in metastatic patients (not yet reached [NYR] vs. 8.3 months; HR: 0.32; 95% CI: 0.21-0.50; p<0.001). Prolongation in PFS by enzalutamide was consistently observed in both the nmCRPC and mCRPC subgroups, and in groups by baseline age, ECOG PS, Gleason score, use of bone-targeting agents, and PSA, LDH, and hemoglobin levels above versus below median values [24].

## Standard First Line Therapy in Metstatic Prostate Cancer

The benefits of adding docetaxel or abiraterone to testosterone suppression in men with metastatic, hormone-sensitive prostate cancer has been shown in several randomized trials [25]. Starting docetaxel early in the course of treatment, particularly in men with high-volume metastatic disease has shown survival benefits that are substantially larger than the survival benefits associated with using docetaxel later after castration resistance has developed [26]. Similarly, addition of abiraterone to testosterone suppression

also improved overall survival in hormone-sensitive prostate cancer, regardless of the burden of metastatic disease [14, 27-29].

Davis hypothesized that adding enzalutamide to first-line therapy would delay the emergence of castration resistance and thereby improve overall survival [25]. They reported their open-label, randomized, phase 3 trial, wherein patients were assigned to receive testosterone suppression plus either open-label enzalutamide or a standard no steroidal ant androgen therapy (standard-care group). The primary end point was overall survival. Secondary end points included progression-free survival as determined by the prostate-specific antigen (PSA) level, clinical progression-free survival, and adverse events. A total of 1125 men underwent randomization; the median follow-up was 34 months. There were 102 deaths in the enzalutamide group and 143 deaths in the standard-care group (hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.86; P=0.002). Kaplan–Meier estimates of overall survival at 3 years were 80% (based on 94 events) in the enzalutamide group and 72% (based on 130 events) in the standard-care group. The authors concluded that enzalutamide was associated with significantly longer progression-free and overall survival than standard care in men with metastatic, hormone-sensitive prostate cancer receiving testosterone suppression.

## Conclusion

Use of enzalutamide has resulted in a high level of disease control in different disease settings and in subgroups of patients with mCRPC and nmCRPC across several landmark clinical trials. In men with metastatic hormone-sensitive prostate cancer receiving testosterone suppression, the addition of enzalutamide has resulted in longer overall survival, PSA progression-free survival, and clinical progression-free survival within 3 years than the use of standard nonsteroidal antiandrogen therapy. Enzalutamide was associated with some additional toxic effects, including fatigue and a small risk of seizures. Overall, enzalutamide has been well tolerated both in young and elderly patients, with a safety profile that has been generally consistent across diverse clinical trial populations. All men treated with enzalutamide, particularly the elderly, require counselling on the risk of falls.

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**How to cite this article:**Nerli, Rajendra, Adarsh Sanikop, Shoubhik Chandra, Shridhar C. Ghagane, Shashank Patil and Pulkit Gupta. "Use of Enzalutamide in Carcinoma Prostate."*J Cancer Sci Ther* 13 (2021): 467