



Review

Enzalutamide and Cancer

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Abstract

Prostate carcinoma is androgen-dependent, and therefore the main target of treatment is lowering androgen levels. Medical or surgical castration, androgen receptor-blocking agents, androgen-synthesis inhibitors, chemotherapy, sipuleucel-T, and radium-223 are treatment options. Enzalutamide is a relatively new androgen-signaling inhibitor that has 5 to 8 times greater affinity for the androgen receptor (AR) than bicalutamide. Enzalutamide does not demonstrate agonistic activity on ARs. Enzalutamide induces apoptosis of prostate cancer cells. Enzalutamide is effective in metastatic castration-resistant prostate cancer in patients with progression after docetaxel treatment and in chemotherapy-naïve patients. Enzalutamide is also superior to the commonly used AR blocking agent bicalutamide in chemotherapy-naïve metastatic and non-metastatic castration-resistant prostate cancer patients. Its efficacy has been proven in hormone-naïve patients, and several trials are ongoing. Enzalutamide has a favorable side effect profile and improves quality of life and pain scores. There are ongoing studies examining the efficacy and safety of enzalutamide on other several AR-expressing tumors.

Keywords: Breast cancer, enzalutamide, prostate cancer

The normal development and functions of prostate tissue are androgen-dependent.^[1] Androgen maintains the continuity of epithelial secretory activity of normal prostate tissue. Testosterone and dihydrotestosterone (DHT) act via binding to the androgen receptor (AR). The binding of DHT or testosterone to an AR leads to the translocation of the AR to the nucleus. In the nucleus, AR regulates transcription of target genes by binding to androgen response elements of DNA. AR signaling provides the balance between proliferation and apoptosis of epithelial cells.^[1] This balance deteriorates in favor of proliferation when prostate cancer develops. The predominant driver of prostate carcinoma is androgen, which acts via AR signaling. At every stage of the disease, AR signaling pathways play a crucial role.

According to 2014 data, the incidence of prostate cancer in our country, standardized by age in male individuals, is 32.9 in 100.000; it is the second most common cancer after lung carcinoma. In 2014, a total of 24.601 people were diagnosed

with prostate cancer in Turkey.^[2] The primary treatment of metastatic prostate cancer is surgical or medical castration, AR blockers, and chemotherapy. The preferred first-line treatment for most patients with metastatic prostatic carcinoma is androgen-deprivation therapy (ADT). Ultimately, despite a castrate level of testosterone, during the treatment process, AR overexpression, AR mutation, the development of AR splice variants, cofactor upregulation of the AR, and extragonadal, mainly intratumoral androgen production, leads to progression of the disease.^[3-5] This phase is called castration-resistant prostate cancer (CRPC). Chemotherapy, antiandrogens, abiraterone acetate, sipuleucel-T, and radium-223 are treatment options for CRPC.

Enzalutamide is an AR inhibitor with a 5- to 8-fold greater affinity to bind AR than bicalutamide (Fig. 1).^[6] Bicalutamide has partial agonistic activity, especially in the case of AR overexpression, and acts as an AR agonist. Antiandrogen withdrawal syndrome is the clinical manifestation of this

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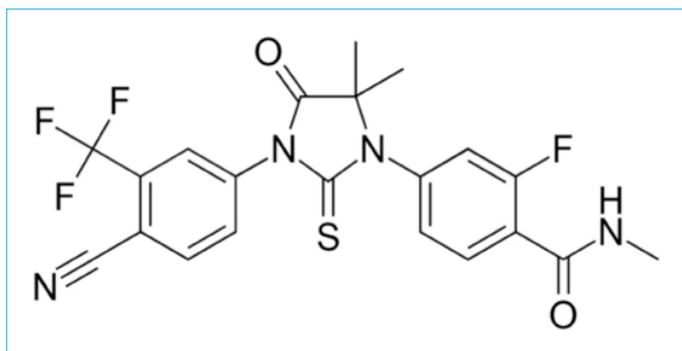


Figure 1. Molecular schema of enzalutamide.

agonistic affect. Enzalutamide was designed as a potent AR inhibitor without agonistic activity. Infact, enzalutamide is an AR signaling inhibitor. Unlike other antiandrogen therapies, enzalutamide also inhibits nuclear translocation of an activated AR to androgen response elements and coactivator recruitment. Enzalutamide also induces apoptosis while suppressing the growth of malignant prostate cells. These features differentiate enzalutamide from androgen-synthesis inhibitors and other first-generation AR inhibitors.^[6] The efficacy of enzalutamide in prostate cancer has been proven in several phase II and phase III trials that are discussed in this review.

Efficacy

Prostate Cancer

Metastatic Castration-Resistant Prostate Cancer after Chemotherapy

Subsequent to the proven efficacy of enzalutamide in prostate cancer in a phase I-II study, the phase III AFFIRM trial investigated the efficacy and safety of enzalutamide compared with a placebo in the post-chemotherapy setting in patients with metastatic CRPC.^[7, 8] A total of 1199 patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1 or 2 and who had progressed according to Prostate Cancer Clinical Trials Working Group 2 criteria were randomized 2:1. The primary endpoint of the study was overall survival (OS). The interim analysis indicated that there was a significant difference in OS between the enzalutamide arm (18.4 months) and in the placebo arm (13.7 months) (hazard ratio [HR]: 0.63; $p < 0.001$). Enzalutamide reduced the risk of death by 37% compared with the placebo.

This survival advantage was also observed in all subgroups. Enzalutamide was also found to be superior to the placebo in the secondary endpoints: the prostate-specific antigen (PSA) level response rate (54% vs. 2% $p < 0.001$), radiological progression-free survival (PFS) (8.3 months vs. 2.9 months; $p < 0.001$), time to PSA progression (8.3 months

vs. 3.0 months; $p < 0.001$), soft tissue response rate (29% vs. 4%; $p < 0.001$), and the length of time until the first skeletal-related event (16.7 months vs. 13.3 months; $p < 0.001$).

When the patients were stratified according to the baseline Gleason Scores, a median OS of patients who had Gleason Score of 7 or less was 18.4 months with enzalutamide and 14.8 months with the placebo (HR: 0.67; 95% confidence interval [CI]: 0.51-0.88). In patients with a Gleason Score of 8 or more, the median OS was 18.2 months in the enzalutamide arm and 11.3 months in the placebo arm (HR: 0.60; 95% CI: 0.47-0.76). According to these unpublished AFFIRM results, enzalutamide is effective in metastatic CRPC, independent of the Gleason Score.

Metastatic CRPC Before Chemotherapy

The PREVAIL study is a phase III trial that evaluated the efficacy and safety of enzalutamide compared with a placebo in patients with chemotherapy-naïve metastatic CRPC.^[9] A total of 1717 asymptomatic or mildly symptomatic metastatic prostate cancer (including visceral organ metastasis) patients were included in the study. The primary endpoints were the radiographic PFS and OS. At the 12-month follow-up, treatment with enzalutamide was observed to provide an 81% reduction in the risk of death or radiographic progression (HR: 0.19; 95% CI: 0.15-0.23; $p < 0.001$), and the rate of radiographic PFS was 65% in the enzalutamide group and 14% in the placebo group. The median duration of enzalutamide treatment was more than 3-times longer than the placebo (16.6 months vs. 4.6 months). The mortality rate was lower in the enzalutamide group than in the placebo group (28% vs. 35%). Treatment with enzalutamide demonstrated a survival advantage, with a 29% decrease in the risk of mortality (HR: 0.71; 95% CI: 0.60-0.84; $p < 0.001$). At a preplanned interim analysis after 22 months, the median OS was longer in the enzalutamide group than in the placebo group (32.4 months vs. 30.2 months; $p < 0.001$). The radiographic PFS and OS also favored enzalutamide in all of the previously described subgroups. At the end of this interim analysis, the study was terminated in order to allow the crossover of the patients from the placebo arm to the enzalutamide arm. Among patients who had a measurable visceral metastasis at baseline, the objective response rate was 59% in the enzalutamide group, and 5% in the placebo group ($p < 0.001$). Enzalutamide was also found to be superior to the placebo in measurements of secondary endpoints. Treatment with enzalutamide delayed the median time to the initiation of conventional chemotherapy (28.0 months vs. 10.8 months; $p < 0.001$). Enzalutamide also reduced the risk of a first skeletal-related event (32% vs. 37%; $p < 0.001$) at median 31 months of treatment.

Updated results of the PREVAIL study were published in

2017.^[10] The median radiographic PFS in the enzalutamide group was 20.0 months, while it was 5.4 months in the placebo group. Enzalutamide treatment reduced the risk of radiologic progression or death by 68% (HR: 0.32; $p < 0.0001$). In all, 81% of the patients in the placebo group received subsequent antineoplastic treatments (29.5% received enzalutamide), and enzalutamide treatment resulted in a 23% reduction in the risk of mortality (HR: 0.77; $p = 0.0002$). After 31 months of follow-up, the median OS was 35.3 months and 31.3 months in the enzalutamide and in the placebo group, respectively. In the enzalutamide arm, 52% of the patients received subsequent antineoplastic treatments. Despite the crossover and treatment after progression, it was demonstrated that enzalutamide maintained the survival benefit in comparison with the placebo. The AFFIRM and PREVAIL trials showed the clinical effectiveness of enzalutamide in patients groups treated with first-line chemotherapy and the chemotherapy-naïve.

Once the prostate cancer becomes castration-resistant, adding bicalutamide or other androgen receptor blockers to castration provides a minor clinical benefit for a short period of time.^[11, 12] Enzalutamide, which provides stronger androgen suppression than bicalutamide, has been compared with bicalutamide in patients with metastatic CRPC in 2 head-to-head phase II studies.

In the TERRAIN study, the efficacy of adding bicalutamide or enzalutamide to ADT was investigated in patients with metastatic CRPC.^[13] A total of 375 patients were randomized 1:1 and PFS was the primary endpoint. The median PFS was 15.7 months in the enzalutamide arm, and 5.8 months in the bicalutamide arm. There was a significant PFS improvement in the enzalutamide arm compared with the bicalutamide arm (HR: 0.44; 95% CI: 0.34–0.57; $p < 0.0001$). The median time to a PSA progression was longer in the enzalutamide group (19.4 months vs. 5.8 months; $p < 0.0001$). A PSA decline of at least 50% was noted in 82% and 21% of patients in the enzalutamide and bicalutamide arms, respectively. The median time to a 50% or greater PSA decline from the baseline was 2.8 months (95% CI: 2.8–2.8) in the enzalutamide arm. However, the median time was not reached in the bicalutamide arm because a few patients had a 50% PSA decrease or more (HR: 7.01; 95% CI: 4.83–10.16; $p < 0.0001$). Among the patients who had measurable soft tissue lesions at the initial assessment, the objective response rate was 37% (26 of 70 patients) in the enzalutamide arm, and 2 patients had a complete response. In the bicalutamide arm, the objective response rate was 7% (5 of 71 patients) ($p < 0.001$).

In the phase II STRIVE study, 396 patients were randomized 1:1 into bicalutamide and enzalutamide groups to

compare the efficacy and safety in patients with metastatic and non-metastatic CRPC.^[14] The primary endpoint was PFS. The median PFS was 19.4 months in the enzalutamide arm and 5.7 months in the bicalutamide arm. Enzalutamide treatment resulted in a 76% reduced risk of progression or death compared with bicalutamide (HR: 0.24; 95% CI: 0.18–0.32; $p < .001$). Among those with nonmetastatic CRPC, the median PFS was not reached with enzalutamide, and it was 8.6 months with bicalutamide (HR: 0.24; 95% CI: 0.14–0.42). The median PFS was 16.5 months for those with metastatic CRPC who received enzalutamide, and 5.5 months for those treated with bicalutamide (HR: 0.24; 95% CI: 0.17–0.34). Enzalutamide was also superior to bicalutamide in both patients with metastatic and nonmetastatic CRPC with respect to the secondary endpoints (PSA progression, PSA response). Among those with metastatic disease, the risk of radiographic progression or death decreased 68% with enzalutamide treatment compared with bicalutamide (HR: 0.32; 95% CI: 0.21–0.50; $p < 0.001$). In nonmetastatic patients, the risk decreased 76% (HR: 0.24; 95% CI: 0.10–0.56; $p < 0.001$).

These 2 studies demonstrated that the addition of enzalutamide to ADT in metastatic CRPC patients provided a significant PFS benefit compared with bicalutamide. In addition, the STRIVE study revealed that enzalutamide also prolongs PFS in patients without metastasis. The phase III PROSPER study also supports these results.^[15] Patients with nonmetastatic CRPC and a PSA doubling time ≤ 10 months and a PSA ≥ 2 ng/mL were randomized 2:1 into enzalutamide 160 mg and placebo groups while continuing ADT. The primary endpoint of the PROSPER trial was metastasis-free survival (MFS). The median MFS was significantly longer in the enzalutamide arm (36.6 months vs. 14.7 months; $p < 0.0001$). Enzalutamide also significantly prolonged the time to PSA progression (37.2 months vs. 3.9 months; $p < 0.0001$).

Hormone-naïve Prostate Cancer

The first-line treatment for advanced or metastatic prostatic carcinoma is ADT or ADT plus docetaxel. ADT is continued through subsequent treatments after the development of resistance to castration. ADT causes osteoporosis, sarcopenia, a decreased libido, fatigue, and abnormalities in glucose and lipid profiles. With new treatment modalities, the life expectancy of patients with prostate cancer is longer, and the safety and quality of life have become increasingly important. Anti-androgen treatment without ADT is an alternative with a different safety profile. Analysis of studies that compared bicalutamide with castration (medical or surgical) showed that there is no OS difference in nonmetastatic patients, whereas castration provides an

OS advantage in metastatic cases.^[16, 17]

Enzalutamide has also been tested in hormone-naïve prostatic cancer. A group of 67 hormone-naïve prostate cancer patients (26 metastatic) were enrolled in an open-label phase II trial to assess the efficacy and safety of enzalutamide. In 62 patients, a PSA response (decline of 80% or more by week 25) was noted.^[18] At the second year, 67% of the patients were on treatment, and 73% of these had a PSA level of 0.1 ng/mL or less. Of the 26 patients with metastatic disease, 50% achieved a complete tumor response and 15% a partial response.^[19] The antitumor activity of enzalutamide is maintained at the third year.^[20] Enzalutamide is highly active in hormone-naïve prostatic cancer, as well as in the castrate-resistant state.

The ENZAMET (NCT02446405), ARCHES (NCT02677896) and EMBARK (NCT02319837) studies to investigate the safety and efficacy of enzalutamide in different clinical conditions in cases of hormone-naïve prostate cancer are still ongoing.

Breast Cancer

Breast cancer, like prostatic carcinoma, is hormonally regulated. AR and estrogen receptors (ER) have some similar biologic properties.^[21] Androgens cause the proliferation of AR-positive breast cancer cells.^[22] Nearly 60% of early breast cancer is AR-positive. ER-positive early tumors had more AR-positivity than ER-negative tumors (74.8% vs. 31.8%). The OS improved in AR-positive early breast cancer.^[23] There are controversial reports about the prognostic impact of AR on triple-negative breast cancer (TNBC).^[24-26] One-third of TNBC cases demonstrate the expression of AR; therefore, the AR pathway may be a therapeutic target. In vivo and in vitro models have indicated that enzalutamide inhibited androgen-mediated growth in ER-negative tumors.

A single-arm phase II study evaluating the safety and antitumor activity of enzalutamide in AR-positive TNBC has been published.^[27] The primary endpoint was clinical benefit rate at week 16. The clinical benefit rate was 25% at week 16 in the intent-to-treat population (ITT) and 33% in patients whose tumor expressed 10% or more AR (evaluable group). The median PFS and OS was 2.9 months and 12.7 months, respectively, in the ITT group and 3.3 months and 17.6 months, respectively, in the evaluable group. The clinical benefit rate, disease-free survival and OS were numerically higher in the evaluable group. This study demonstrated the clinical activity of enzalutamide in advanced AR-positive TNBC.

Several cancers, including that of the bladder, pancreas, renal cell, ovaries, salivary gland tumors, and the endome-

trium, express AR. There are also ongoing studies examining the efficacy and safety of enzalutamide on these AR-expressing tumors.^[28]

Safety

Patient-Reported Outcomes

In most clinical studies, patient-reported outcomes are an important endpoint. In the practice of oncology, the aim while struggling for longer survival is to not reduce the quality of life (QoL) of the patients, and when possible, to improve it. It is becoming more important to protect or enhance the quality of life in prostate cancer cases, where survival is longer than some other malignancies. Health-related quality of life (HRQoL) parameters have prognostic significance for PFS and OS in metastatic CRPC.^[29] The Functional Assessment of Cancer Therapy-Prostate (FACT-P) has been used in major trials of enzalutamide to evaluate patient reported HRQoL.

In both the AFFIRM and the PREVAIL trials, enzalutamide significantly improved QoL and the median time to QoL deterioration. FACT-P deterioration was observed in 47% and 59% of the patients in the enzalutamide and the placebo arms, respectively, in the AFFIRM trial ($p=0.001$).^[8] In the 2 studies described here that compared enzalutamide with bicalutamide, the length of time to deterioration was longer in the TERRAIN trial. In the STRIVE study, which included non-metastatic patients, the median time to deterioration was not different in the 2 arms. In this study, approximately 1 of 3 patients was not metastatic and was less symptomatic, which may have contributed to the non-significant difference. (Table 1) The Brief Pain Inventory- Short Form (BPI-SF) is a tool used to determine pain intensity and interference with daily activity. In the AFFIRM study, enzalutamide treatment had significantly improved both pain interference scores and pain severity at week 13. Fewer patients at week 13 had pain progression in the enzalutamide arm compared with the placebo arm (28% vs. 38%; $p=0.0018$).^[29] In the PREVAIL trial, pain progression at week 13 was also low in the enzalutamide arm (29% vs. 42%; $p<0.001$). Enzalutamide treatment improves quality of life as well as the success of treatment in CRPC and provides a reduction in pain progression.

Adverse Events

The most frequently reported adverse events with enzalutamide were fatigue, musculoskeletal pain (back pain), and hot flushes. Despite the fact that the duration of treatment in the enzalutamide arm was longer than that of the placebo or the standard treatment arm, treatment withdrawal rates due to adverse events were almost the same (Table 2).

Table 1. Patient reported outcomes

Trial	Treatment	Median duration to QoL deterioration		Improvement in QoL	
Affirm	Enzalutamide	9 months		43 %	
	Placebo	3.7 months	p<0.001	18 %	p<0.001
Prevail	Enzalutamide	11.3 Months		40%	
	Placebo	5.6 Months	p<0.001	23%	p<0.001
Terrain	Enzalutamide	13.8 Months		33%	
	Bicalutamid	8.5 Months	p=0.006	22%	p=0.026
Strive	Enzalutamide	8.4 months			
	Bicalutamid	8.3 months	p=0.49	NR	

QoL: Quality of life.

Grade 3 or higher hypertension was more often observed in the enzalutamide group than in the placebo group in the PREVAIL trial (13% vs. 4%), and more often than in the bicalutamide group in the STRIVE trial (10 patients vs. 3 patients) and the TERRAIN trial (13 patients vs. 8 patients). In a meta analysis, side effects of enzalutamide and other alternative drug, abiraterone were assessed. All-grade (RR 1.28 - 95% CI 1.06-1.55) and grade ≥ 3 (RR 1.76 - 95% CI 1.12-2.75) cardiovascular event risk was higher with abiraterone however there was no increase in risk of all-grade (RR 1.06 - 95% CI 0.67-1.65) or grade ≥ 3 (RR 0.81 - 95% CI 0.28-2.33) cardiovascular events in enzalutamide treated patients. All-grade fatigue was significantly higher in the enzalutamide group (RR: 1.29; 95% CI: 1.15-1.44).^[30]

Since hypothalamohypophyseal system is not inhibited in patients with hormone-naïve disease, AR blockage causes elevated levels of testosterone, luteinizing hormone (LH) and sex hormone-binding globulin. LH and testosterone levels increased rapidly through the fifth week of treat-

ment. Therefore, different side effects from those usually seen emerged in patients without ADT. The main adverse events observed in these patients were gynecomastia (49%), fatigue (39%), nipple pain (21%), and hot flashes (21%).^[19]

After oral administration of enzalutamide, more than 84% was rapidly absorbed.^[31] It can be taken with or without food. It reaches steady-state concentration by 28 days of daily administration. Enzalutamide is mainly metabolized in the liver by CYP2C8 and CYP3A4; the major metabolites are active N-desmethyl enzalutamide and inactive carboxylic acid.^[7, 32] The primary elimination route of enzalutamide is through the liver. Carboxylic acid is excreted by the kidneys.^[7, 31] The analysis of two phase I studies conducted with patients with hepatic impairment (Child-Pugh class A: 6 patients, class B: 8 patients, and class C: 8 patients) but without prostatic carcinoma showed that enzalutamide was well tolerated and did not cause significant drug-related laboratory abnormalities. Single-dose pharmacokinetics were not different in patients with hepatic impairment and healthy controls. The authors suggested that no dose adjustment was necessary while treating these patients.^[33] In patients with severe hepatic impairment, the half-life of enzalutamide is 2 times longer than in healthy subjects, but the clinical significance of this is not known yet. Patients with severe hepatic impairment have not been included in the clinical trials, and since there is no clinical information related to long-term use, treatment decisions should be made considering the benefit-loss ratio. There is no need to reduce the dose in patients with a creatinine clearance level greater than 30mL/minute. There is insufficient data in cases where the creatine clearance level is less than 30 mL/minute. Enzalutamide and its metabolites are not dialyzable.^[34]

Enzalutamide has a similar efficacy in younger patients and in those 75 years of age and older. In the AFFRIM study, all-grade fatigue, diarrhea, and peripheral edema were

Table 2. Median treatment durations and drug discontinuation rates due to AE in enzalutamide trials

	Median duration on treatment	Drug discontinuation rate due to AE
Affirm		
Enzalutamide	8.3	7.6%
Placebo	3.0	9.8%
Prevail		
Enzalutamide	16.6	5.6%
Placebo	4.6	6.0%
Terrain		
Enzalutamide	11.7	7.6%
Bicalutamid	5.8	6.2%
Strive		
Enzalutamide	14.7	8.1%
Bicalutamid	8.4	6.1%

most common the most common adverse events in these patients.^[35] In the PREVAIL trial, the overall incidence of falls increased in patients older than 75 years.^[36] Grade 3 or greater cardiac events were more common in patients older than 75 years of age in both the enzalutamide and the bicalutamide arms.^[37]

Seizures

In a phase I-II study, there were 2 witnessed seizures at doses of 600 mg and 360 mg per day, and 1 possible seizure at 480 mg per day. The effect of enzalutamide on seizures is unclear; the patients who had seizures were concurrently using drugs that could lower the seizure threshold, and they also had comorbidities that could facilitate a seizure.^[7] Foster et al.^[38] found that as a class effect, an AR antagonist at high doses caused convulsions in laboratory animals. The seizure risk increases with a greater drug concentration in the brain. As an off-target effect, AR antagonists inhibit currents created by gamma-aminobutyric acid (GABA)-A. The authors proposed that GABA-A current inhibition was the cause of the seizures.

Patients with a history of seizures and who have any medical condition that pre-disposes them to seizures are not recruited in clinical trials. In the AFFIRM trial, 5 of 800 patients treated with enzalutamide (0.6%) had seizures. No patients in the placebo arm had seizures. The seizures occurred 31 to 603 days after initiation of enzalutamide.^[7] In the PREVAIL study, 1 of 871 patients (0.1%) treated with enzalutamide and 1 of 844 patients (0.1%) in the placebo arm had seizures.^[9] In addition, 1 patient in the STRIVE trial, and 2 patients in the enzalutamide arm and 1 in the bicalutamide arm of the TERRAIN trial had a seizure. When examined in detail, it can be seen that almost all of the patients in the studies had factors that may cause seizures. In patients with seizures, treatment was completely terminated and all recovered. The most important risk factor for the occurrence of a seizure in patients with metastatic CRPC is a seizure history.^[39] In contrast, the data results of the UPWARD trial demonstrated no increased risk of seizure in enzalutamide-treated patients who had potential risk factors for seizures.^[40]

Patients taking enzalutamide should avoid combination with medicines that reduce the seizure threshold and they should be closely monitored in the event of a history of neuropsychiatric disease, head trauma, cerebrovascular event, or brain metastasis.

Resistance to Enzalutamide

Acquired resistance to enzalutamide invariably emerges despite the impressive clinical activity in patients with prostate cancer. AR mutations, chiefly in the ligand-bind-

ing domain of the receptor, cause the development of anti-androgen resistance and progression of prostate cancer. Marcelli et al.^[41] reported that 21% of patients with advanced prostate cancer had an AR mutation, while none of the patients with early stage disease had a mutation. A T877A mutation is frequently detected in CRPC.^[42] Antagonistic activity of enzalutamide is maintained in the T887A-mutated AR.^[6, 42] Another important mutation in the ligand-binding domain of the androgen receptor is F876L. Enzalutamide-resistant, F876L mutations emerge when prostate cancer cells are cultured in the presence of enzalutamide. Enzalutamide demonstrates agonist activity at ARs containing this mutation.^[43, 44]

Alternative splicing of exons results in a truncated form of AR that lacks ligand-binding domains. There are many different AR splice variants (AR-V) that cause resistance to ADT.^[45] In CRPC, AR-V7 and AR-V1 are more frequently expressed.^[45] Overexpression of AR-V1 does not affect the treatment outcome. Particularly AR-V7 and other AR-Vs are associated with progression of prostate cancer and a poor prognosis.^[46] In the absence of androgens, AR-V7 is constitutively active.^[47] AR-V7 also has the ability to dimerize with itself, other AR-Vs, and full-length AR, independent from androgens, and dimerization activates target genes and contributes to tumor growth and the transition to CRPC.^[48]

A study investigating AR-V7 expression in circulating tumor cells (CTCs) of 62 metastatic CRPC patients treated with enzalutamide (31 patients) or abiraterone (31 patients) found that of all of the AR-V7-positive patients, neither those treated with enzalutamide (12 patients) nor those treated with abiraterone (6 patients) had a PSA response (50% or more decline). However in a patient treated with enzalutamide, a PSA decline of around 30% was noted. PSA progression-free survival was shorter in AR-V7-positive patients in both groups. Subsequently, during the course of treatment, 6 of 42 AR-V7-negative patients with available follow-up samples (4 receiving enzalutamide and 2 receiving abiraterone) converted to AR-V7-positive status.^[49] AR-V7-positive patients had an inferior OS compared with AR-V7-negative patients in both the enzalutamide (HR: 6.9; 95% CI: 1.7–28.1; $p=0.002$) and the abiraterone (HR: 12.7; 95% CI: 1.3–125.3; $p=0.006$) groups.^[50] The expansion phase of this study, which included 202 patients, confirmed the earlier finding of an association with a poorer PSA response and shorter OS in patients treated with enzalutamide or abiraterone.^[51] In contrast, Bernamann et al.^[52] analyzed 21 CRPC patients with AR-V7-positive CTCs, and 6 experienced a benefit from either enzalutamide or abiraterone treatment. Four of the 6 patients displayed a PSA decrease of more than 50%. When AR-V7 positivity is detected in the CTCs, this finding is extrapolated to the whole tumor. Miyamoto et al.^[53] analyzed CTCs on the single-cell level and

demonstrated the differences between CTCs and primary tumors, as well as heterogeneity within individual patients using RNA profiling. Therefore, AR-V7 detection with CTCs may not be a reliable method to decide treatment.

The glucocorticoid receptor pathway, cross-talk of the AR pathway, with other signaling pathways are other resistance mechanisms in prostate cancer.

Conclusion

Prostate cancer is a common and complex disease with a relatively longer survival than other cancer. Enzalutamide is an AR-signaling inhibitor with a 5- to 8-fold greater affinity to bind AR than bicalutamide. It also induces apoptosis of prostate cancer cells. The efficacy of enzalutamide in the treatment of prostate cancer has been demonstrated in various settings. It is also associated with improved survival and HRQoL, and has a favorable side effect profile.

Disclosures

Ethics Committee Approval: Ethics committee approval was not requested for this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – B.E.; Design – B.E.; Supervision – B.E.; Materials – B.E., O.K., B.H.; Data collection &/or processing – B.E., O.K., B.H.; Analysis and/or interpretation – B.E., O.K., B.H.; Literature search – B.E., O.K., B.H.; Writing – B.E., O.K.; Critical review – B.H.

References

1. Heinlein CA, Chang C. Androgen receptor in prostate cancer. *Endocr Rev* 2004;25:276–308. [CrossRef]
2. [Available from: https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/2014-RAPOR_uzuuun.pdf.
3. Schalken J, Fitzpatrick JM. Enzalutamide: targeting the androgen signalling pathway in metastatic castration-resistant prostate cancer. *BJU Int* 2016;117:215–25. [CrossRef]
4. Taplin ME, Balk SP. Androgen receptor: a key molecule in the progression of prostate cancer to hormone independence. *J Cell Biochem* 2004;91:483–90. [CrossRef]
5. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. *J Clin Oncol* 2005;23:8253–61.
6. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 2009;324:787–90.
7. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, et al; Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* 2010;375:1437–46. [CrossRef]
8. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012 27;367:1187–97. [CrossRef]
9. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–33. [CrossRef]
10. Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol* 2017;71:151–4. [CrossRef]
11. Kucuk O, Fisher E, Moinpour CM, Coleman D, Hussain MH, Sartor AO, et al. Phase II trial of bicalutamide in patients with advanced prostate cancer in whom conventional hormonal therapy failed: a Southwest Oncology Group study (SWOG 9235). *Urology* 2001;58:53–8. [CrossRef]
12. Manikandan R, Srirangam SJ, Pearson E, Brown SC, O'Reilly P, Collins GN. Diethylstilboestrol versus bicalutamide in hormone refractory prostate carcinoma: a prospective randomized trial. *Urol Int* 2005;75:217–21. [CrossRef]
13. Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol* 2016;17:153–63. [CrossRef]
14. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J Clin Oncol* 2016;34:209–106. [CrossRef]
15. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore ND, Demirhan E, et al. PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). *Journal of Clinical Oncology* 2018;36 Suppl 6:3. [CrossRef]
16. Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Van Poppel H, Tammela TL, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. *J Urol* 2000;164:1579–82. [CrossRef]
17. Tyrrell CJ, Kaisary AV, Iversen P, Anderson JB, Baert L, Tammela T, et al. A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. *Eur Urol* 1998;33:447–56. [CrossRef]
18. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol* 2014;15:592–600.
19. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Pop-

- pel H, Heidenreich A, et al. Long-term Efficacy and Safety of Enzalutamide Monotherapy in Hormone-naive Prostate Cancer: 1- and 2-Year Open-label Follow-up Results. *Eur Urol* 2015;68:787–94. [CrossRef]
20. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naive Prostate Cancer: 3-Year Open Label Followup Results. *J Urol* 2018;199:459–64. [CrossRef]
21. Fioretti FM, Sita-Lumsden A, Bevan CL, Brooke GN. Revising the role of the androgen receptor in breast cancer. *J Mol Endocrinol* 2014;52:R257–65. [CrossRef]
22. Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, et al; Translational Breast Cancer Research Consortium (TBCRC 011). Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. *Clin Cancer Res* 2013;19:5505–12. [CrossRef]
23. Vera-Badillo FE, Templeton AJ, de Gouveia P, Diaz-Padilla I, Bedard PL, Al-Mubarak M, et al. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106:djt319. [CrossRef]
24. Park S, Koo JS, Kim MS, Park HS, Lee JS, Lee JS, et al. Androgen receptor expression is significantly associated with better outcomes in estrogen receptor-positive breast cancers. *Ann Oncol* 2011;22:1755–62. [CrossRef]
25. Qu Q, Mao Y, Fei XC, Shen KW. The impact of androgen receptor expression on breast cancer survival: a retrospective study and meta-analysis. *PloS one* 2013;8:e82650. [CrossRef]
26. Kim Y, Jae E, Yoon M. Influence of Androgen Receptor Expression on the Survival Outcomes in Breast Cancer: A Meta-Analysis. *J Breast Cancer* 2015;18:134–42. [CrossRef]
27. Traina TA, Miller K, Yardley DA, Eakle J, Schwartzberg LS, O'Shaughnessy J, et al. Enzalutamide for the Treatment of Androgen Receptor-Expressing Triple-Negative Breast Cancer. *J Clin Oncol* 2018;36:884–90. [CrossRef]
28. Schweizer MT, Yu EY. AR-Signaling in Human Malignancies: Prostate Cancer and Beyond. *Cancers (Basel)* 2017;9:pii: E7.
29. Fizazi K, Scher HI, Miller K, Basch E, Sternberg CN, Cella D, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *Lancet Oncol* 2014;15:1147–56. [CrossRef]
30. Moreira RB, Debiase M, Francini E, Nuzzo PV, Velasco G, Maluf FC, et al. Differential side effects profile in patients with mCRPC treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials. *Oncotarget* 2017;8:84572–8.
31. Gibbons JA, Ouatas T, Krauwinkel W, Ohtsu Y, van der Walt JS, Beddo V, et al. Clinical Pharmacokinetic Studies of Enzalutamide. *Clin Pharmacokinet* 2015;54:1043–55. [CrossRef]
32. Tsao CK, Liaw B, Yee T, Galsky MD, Oh WK. Metabolic and toxicological considerations of newly approved prostate cancer drugs. *Expert Opin Drug Metab Toxicol* 2013;9:835–46.
33. Krauwinkel W, Noukens J, van Dijk J, Popa S, Ouatas T, de Vries M, et al. A comparison of the pharmacokinetics and safety of enzalutamide in subjects with hepatic impairment and matched healthy subjects. *J Clin Pharm Ther* 2017;42:268–75.
34. Tsang ES, de Haan M, Eigel BJ. A case report of enzalutamide administration in a dialysis-dependent patient with castration-resistant prostate cancer. *J Oncol Pharm Pract* 2018;24:143–5.
35. Sternberg CN, de Bono JS, Chi KN, Fizazi K, Mulders P, Cerbone L, et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *Ann Oncol* 2014;25:429–34. [CrossRef]
36. Graff JN, Baciarello G, Armstrong AJ, Higano CS, Iversen P, Flaig TW, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol* 2016;27:286–94. [CrossRef]
37. Siemens DR, Klotz L, Heidenreich A, Chowdhury S, Villers A, Baron B, et al. Efficacy and Safety of Enzalutamide vs Bicalutamide in Younger and Older Patients with Metastatic Castration Resistant Prostate Cancer in the TERRAIN Trial. *J Urol* 2018;199:147–54. [CrossRef]
38. Foster WR, Car BD, Shi H, Levesque PC, Obermeier MT, Gan J, et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *The Prostate* 2011;71:480–8. [CrossRef]
39. Dharmani C, Bonafede M, Krivoshik A. Risk Factors for and Incidence of Seizures in Metastatic Castration-Resistant Prostate Cancer: A Real-World Retrospective Cohort Study. *Clin Drug Investig* 2017;37:1183–90. [CrossRef]
40. Slovin S, Clark W, Carles J, Krivoshik A, Park JW, Wang F, et al. Seizure Rates in Enzalutamide-Treated Men With Metastatic Castration-Resistant Prostate Cancer and Risk of Seizure: The UPWARD Study. *JAMA Oncol* 2017. [CrossRef]
41. Marcelli M, Ittmann M, Mariani S, Sutherland R, Nigam R, Murthy L, et al. Androgen receptor mutations in prostate cancer. *Cancer Res* 2000;60:944–9.
42. Azad AA, Volik SV, Wyatt AW, Haegert A, Le Bihan S, Bell RH, et al. Androgen Receptor Gene Aberrations in Circulating Cell-Free DNA: Biomarkers of Therapeutic Resistance in Castration-Resistant Prostate Cancer. *Clinical Cancer Res* 2015;21:2315–24. [CrossRef]
43. Korpál M, Korn JM, Gao X, Rakiec DP, Ruddy DA, Doshi S, et al. An F876L Mutation in Androgen Receptor Confers Genetic and Phenotypic Resistance to MDV3100 (Enzalutamide). *Cancer Discov* 2013;3:1030–43. [CrossRef]
44. Joseph JD, Lu N, Qian J, Sensintaffar J, Shao G, Brigham D, et al. A Clinically Relevant Androgen Receptor Mutation Confers Resistance to Second-Generation Antiandrogens Enzalutamide and ARN-509. *Cancer Discov* 2013;3:1020–9. [CrossRef]

45. Hu R, Dunn TA, Wei S, Isharwal S, Veltri RW, Humphreys E, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. *Cancer Res* 2009;69:16–22. [\[CrossRef\]](#)
46. Hörnberg E, Ylitalo EB, Crnalic S, Antti H, Stattin P, Widmark A, et al. Expression of androgen receptor splice variants in prostate cancer bone metastases is associated with castration-resistance and short survival. *PLoS One* 2011;6:e19059.
47. Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. *Cancer Res* 2008;68:5469–77.
48. Xu D, Zhan Y, Qi Y, Cao B, Bai S, Xu W, et al. Androgen Receptor Splice Variants Dimerize to Transactivate Target Genes. *Cancer Res* 2015;75:3663–71. [\[CrossRef\]](#)
49. Antonarakis ES, Lu C, Wang H, Lubner B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med* 2014;371:1028–38. [\[CrossRef\]](#)
50. Antonarakis ES, Lu C, Wang H, Lubner B, Nakazawa M, Roeser J, et al. 7980 AR-V7 Splice variant and resistance to enzalutamide and abiraterone in men with metastatic castration-resistant prostate cancer (MCRPC): overall survival results. *Annals of Oncology* 2014;25:v1–4. [\[CrossRef\]](#)
51. Antonarakis ES, Lu C, Lubner B, Wang H, Chen Y, Zhu Y, et al. AR-V7 and efficacy of abiraterone (Abi) and enzalutamide (Enza) in castration-resistant prostate cancer (CRPC): Expanded analysis of the Johns Hopkins cohort. *Journal of Clinical Oncology* 2016;34 Suppl 15: 5012.
52. Bernemann C, Schnoeller TJ, Luedeke M, Steinestel K, Boegemann M, Schrader AJ, et al. Expression of AR-V7 in Circulating Tumour Cells Does Not Preclude Response to Next Generation Androgen Deprivation Therapy in Patients with Castration Resistant Prostate Cancer. *Eur Urol* 2017;71:1–3. [\[CrossRef\]](#)
53. Miyamoto DT, Zheng Y, Wittner BS, Lee RJ, Zhu H, Broderick KT, et al. RNA-Seq of Single Prostate CTCs Implicates Noncanonical Wnt Signaling in Antiandrogen Resistance. *Science* 2015;349:1351–6. [\[CrossRef\]](#)