Enzalutamide: an evidence-based review of its use in the treatment of prostate cancer

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Introduction: Enzalutamide is an oral androgen receptor (AR) signaling inhibitor that was specifically engineered to overcome castration-resistant prostate cancer (CRPC) harboring AR amplification or overexpression. Enzalutamide has demonstrated significant activity in men with metastatic CRPC.

Aims: To update the evidence and provide an overview of the available data on enzalutamide.

Evidence review: Peer reviewed articles published and listed in Medline Search were reviewed. In addition, relevant ASCO and ESMO abstracts were searched. The activity of enzalutamide is mediated by potently antagonizing the full-length AR, impairing translocation of the AR from the cytoplasm into the nucleus, and inhibiting the transcriptional activity of the AR by modulating the interaction of the AR with androgen-response elements in gene promoter regions. Enzalutamide has a favorable safety profile and the most common adverse events include fatigue, hot flashes and headache; 1% of patients experienced seizure.

Place in Therapy: The AFFIRM phase III study evaluated the clinical utility of treatment with enzalutamide in men with docetaxel-refractory metastatic CRPC. Enzalutamide improved overall survival compared to placebo, with a median overall survival of 18.4 months versus 13.6 months respectively.

Conclusion: Enzalutamide has demonstrated impressive efficacy in men with metastatic CRPC, moving swiftly from a phase I/II study to two pivotal phase III trials testing this agent in both chemotherapy-pretreated as well as chemotherapy-naïve CRPC patients. Ongoing studies are aiming to explore the utility of enzalutamide in earlier stages of the disease, and to investigate the optimal sequencing and combination of enzalutamide with other standard and novel therapies for prostate cancer.

Keywords: castration-resistant prostate cancer, enzalutamide, MDV3100, antiandrogen, androgen receptor

Core evidence clinical impact summary for enzalutamide

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<th>Outcome measure</th>
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<tr>
<td>Disease-oriented evidence</td>
<td>Preclinical studies in castration-resistant prostate cancer cell lines and mouse xenograft models, including preclinical models harboring androgen receptor amplification.</td>
<td>Enzalutamide mediates its activity by potently antagonizing the androgen receptor, inhibits nuclear translocation of the androgen receptor, and impairs binding of the androgen receptor to promoter areas of androgen-regulated genes.</td>
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**Introduction**

The treatment of localized prostate cancer is most often curative. However, metastatic disease can arise in approximately 20%–30% of patients and accounts for over 28,000 deaths a year in the United States. Androgen-deprivation therapy (ADT) has been the standard treatment for advanced and metastatic prostate adenocarcinoma for decades and is achieved by medical castration (luteinizing-hormone releasing hormone [LHRH] agonist or antagonist) or surgical castration (bilateral orchiectomy). Although the disease is initially sensitive to ADT, resistance is inevitably acquired, leading to castrate-resistant prostate cancer (CRPC) which is incurable. However, there are several agents which can improve survival in such patients (see Table 1).

Antiandrogens are oral compounds that compete with endogenous ligands for the androgen receptor (AR), and when bound induce a conformational change that impedes transcription of key androgen-regulated genes. This inhibits the biological effects of testosterone and dihydrotestosterone. These antiandrogen agents can be categorized as steroidal or nonsteroidal. Steroidal antiandrogens were first developed in the late 1960s, can be distinguished by their physiologic progestational effects, and include agents such as cyproterone acetate, megestrol acetate and medroxyprogesterone. The nonsteroidal antiandrogens, including flutamide, nilutamide and bicalutamide, act only at the androgen receptors and are generally better tolerated by patients. Bicalutamide is perhaps the most extensively investigated antiandrogen. The addition of bicalutamide to standard care, either as monotherapy or as adjuvant treatment, improved progression-free survival (PFS) in men with locally-advanced prostate cancer, but not in patients with clinically localized disease.

In the setting of metastatic prostate cancer, survival in men treated with bicalutamide monotherapy was found to be inferior when compared to castration. The combination of medical or surgical castration with an antiandrogen, known as combined androgen blockade, may possibly improve five-year overall survival when compared to LHRH monotherapy (Hazard Ratio [HR] = 0.87; 95% Confidence Interval [CI], 0.81–0.94), although the significance of this finding has been debated. Intriguingly, an “antiandrogen withdrawal” effect can be observed in up to 25% of patients after discontinuation of these agents following clinical or biochemical progression. In this situation, bicalutamide can undergo an antagonist-to-agonist switch, thereby paradoxically stimulating AR activity and promoting prostate tumor cell growth.

### Enzalutamide for CRPC

Castrate-resistant prostate cancer (CRPC) is defined as cancer progression in the setting of “castrate levels” of serum androgens (generally <50 ng/dL). However, a number of such individuals with castrate-resistant disease will continue to respond to secondary hormonal manipulations such as other antiandrogens, estrogen agonists, corticosteroids and steroidogenesis inhibitors (eg, ketoconazole). Unfortunately, these responses are often short-lived and may be associated with significant toxicities. However, advances in our understanding of CRPC biology have now demonstrated that the AR pathway is still active at the molecular level in the majority of these cases, meaning that the tumor often remains androgen-driven. This may be attributed to AR gene amplification, AR gene mutation, increased AR expression, or increased androgen biosynthesis in prostate tumors. This

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<td><strong>Patient-oriented evidence</strong></td>
<td>Phase III clinical trial in men with chemotherapy-naive and chemotherapy-pretreated metastatic castration-resistant prostate cancer (NCT00510718). Phase III randomized-controlled trial in men with chemotherapy-pretreated metastatic castration-resistant prostate cancer (NCT00974311).</td>
<td>Enzalutamide improved overall survival compared to placebo. Enzalutamide was also superior to placebo with respect to all secondary clinical endpoints, as well as quality-of-life endpoints. The safety profile of enzalutamide is favorable and common adverse events include fatigue, headache, and hot flashes; 1% of patients experienced seizure. Enzalutamide was approved by the US Food and Drug Administration on August 31, 2012 for men with docetaxel-pretreated metastatic castration-resistant prostate cancer.</td>
</tr>
<tr>
<td><strong>Economic evidence</strong></td>
<td>Pharmacoeconomic studies have not yet been conducted.</td>
<td>The current market price for enzalutamide is approximately $7000 per month.</td>
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continued reliance on AR signaling has allowed for renewed opportunities to develop novel AR-targeted agents.\(^6\)

With this rationale in mind, second-generation antiandrogens began to be developed by the Sawyers/Jung groups based upon the non-steroidal agonist RU59063 through screening for potent antiandrogens lacking agonistic activity in context of AR-overexpressing tumors. Two molecules (RD162 and MDV3100) were initially chosen for further investigation. Ultimately, MDV3100 (now known as enzalutamide) was selected for clinical development because of its activity in CRPC xenograft models and its favorable drug-like properties. Ultimately, MDV3100 attacks multiple nodes in the AR signaling pathway. It is a competitive inhibitor of AR ligand binding, has a greater affinity for the AR, and has greater potency than other antiandrogens. Additionally, MDV3100 prevents nuclear translocation of the AR, and induces a conformational change that inhibits the receptor-complex binding to androgen-response elements of DNA, thereby preventing activation of target genes necessary for prostate cancer growth.

MDV3100 was shown to bind AR in castration-resistant LNCaP/AR human prostate cancer cells with fivefold greater affinity than bicalutamide. Importantly, MDV3100 did not have agonistic activity in a castration-resistant setting. Tumor activity was demonstrated in both in vitro and in vivo models, and MDV3100 administration resulted in tumor responses in several castration-resistant xenograft models. In mice with LNCaP/AR xenograft tumors, for example, MDV3100 induced tumor regression whereas bicalutamide only slowed growth. Furthermore, MDV3100 did not activate mutated ARs or wild-type AR receptors. More recent investigations have demonstrated that resistance to enzalutamide may develop via AR transcriptional splice variants.\(^7\) AR gene rearrangement is one potential mechanism of CRPC progression, by promoting synthesis of constitutively-active truncated AR splice variants (AR-Vs) that lack the AR ligand-binding domain. Because the ligand-binding domain is missing in these AR-Vs, none of the currently available antiandrogens would be expected to have any activity against these truncated AR forms. To this end, tumors containing high levels of these AR-Vs (and lower levels of the full-length AR) have been demonstrated to be both androgen-independent and enzalutamide-resistant.

**Phase I/II studies**

Enzalutamide, the clinical formulation of MDV3100, is a once-daily oral agent that does not require concurrent administration of corticosteroids. Early trials showed encouraging results for enzalutamide that seemed to improve upon the efficacy of earlier antiandrogens such as bicalutamide, nilutamide or flutamide. In an important Phase I/II study, 140 men with progressive CRPC were enrolled at multiple centers across the United States.\(^8\) The majority (78%) had metastatic disease and approximately half of patients had received prior chemotherapy.\(^8\) Cohorts received increasing doses of enzalutamide, ranging from 30 mg to 600 mg daily. The primary objective was to assess the safety and tolerability profile of the agent. Impressively, anti-tumor activity was observed at all doses. The maximum tolerated dose of enzalutamide was determined to be 240 mg, and no additional anti-tumor effects were observed at greater doses.
toxicities of enzalutamide included fatigue, hot flashes and headache. Three patients developed seizures.

More than 50% of patients had serum PSA declines of 50% or greater, and this effect was more pronounced in the chemotherapy-naïve group than in the chemotherapy-pretreated group. The median time to radiological progression in the whole population was 47 weeks. Better outcomes were seen in the chemotherapy-naïve group, with the median time to radiological progression being >60 weeks in these patients (compared with 29 weeks in chemotherapy-pretreated men). There were soft tissue responses reported in 22% of patients with measurable disease, while 56% of men had stabilized bone disease lasting 12 weeks or more. In addition, there was conversion from unfavorable (>5/7.5 mL) to favorable (<5/7.5 mL) circulating tumor cell counts in 49% of treated patients.

After longer follow-up, enzalutamide continued to demonstrate durable tumor responses. At the time of the updated analysis, 18 patients were still on study with a median time on treatment of 131 weeks. The median time on treatment for all patients was 51 weeks for those who had not yet received chemotherapy and 17 weeks for those who had received prior chemotherapy. The median time to PSA progression (by PCWG2 criteria) was 41 weeks in the chemotherapy-naïve group and 20 weeks in the chemotherapy-pretreated group. Median radiographic PFS was 56 weeks and 24 weeks for pre- and post-chemotherapy groups, respectively.

**Phase III studies**

Following from these encouraging early-phase data, the AFFIRM trial (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was designed to definitively evaluate the safety and efficacy of enzalutamide in patients with CRPC. AFFIRM was an international Phase III double-blind placebo-controlled trial in men with metastatic CRPC who had failed a previous docetaxel-based regimen. The study randomized 1199 men with metastatic CRPC across 166 sites in a 2:1 manner to receive either enzalutamide (5/7.5 mL) circulating tumor cell counts in 49% of treated patients. Enzalutamide was shown to be superior to placebo in all secondary endpoints examined. Treatment with enzalutamide was associated with an improved time to PSA progression (8.3 vs 3.0 months; HR 0.25, P < 0.001), as well as radiographic progression-free survival (8.3 vs 2.9 months; HR 0.40, P < 0.001). Patients assigned to enzalutamide had a ≥50% PSA reduction in 54% of cases compared with only 1.5% in the placebo group (P < 0.001), and had a ≥90% PSA decline in 25% and 1% of patients respectively (P < 0.001). In addition, approximately 30% of patients with measurable disease receiving enzalutamide had complete or partial responses compared with 4% on placebo (P < 0.001). Skeletal-related events (SREs) were also reduced in the enzalutamide arm. SREs were defined as radiation therapy, surgery to bone, pathologic bone fracture, spinal cord compression or change in antineoplastic therapy. The median time to first SRE was 16.7 months for patients receiving...
Enzalutamide versus 13.3 months for patients receiving placebo (HR 0.69, \( P < 0.001 \)).

Pain palliation was defined as a \( \geq 30\% \) reduction in median pain score after 12 weeks compared to baseline without a \( >30\% \) increase in analgesic use, and was determined by the mean of worst pain over seven days and analgesic use by the patients for disease-related pain.\(^{11}\)

Pain palliation as defined above was achieved in 45\% of those on enzalutamide compared to 7\% of those receiving placebo (\( P = 0.008 \)). The investigators reported that 28\% of patients in the enzalutamide arm had pain progression compared to 39\% of patients on placebo (\( P = 0.002 \)). On the FACT-P scale, median time to pain progression was not yet reached for patients receiving enzalutamide compared with 13.8 months for patients on placebo, representing a risk reduction of 44\% (HR = 0.56; \( P = 0.0004 \)). There was also a mean reduction in pain severity (average of 4 severity items on the Brief Pain Inventory-Short Form) of 0.65 in favor of patients receiving enzalutamide (\( P < 0.001 \)). The total quality-of-life (QoL) score on the FACT-P showed that QoL was dramatically improved in patients taking enzalutamide: 43\% had improvement in QoL versus 18\% in the placebo arm.\(^{11}\)

While the AFFIRM study did not mandate concurrent corticosteroid use given together with the study drug, the concomitant administration of steroids was not prohibited either. To this end, approximately 30\% of the patients in the AFFIRM trial received corticosteroids at baseline and 48\% were initiated on steroid therapy during the trial.\(^{12}\) A post-hoc analysis demonstrated that men who were taking corticosteroids (in both the enzalutamide and the placebo groups) had inferior survival compared to those who did not take steroids. There are two potential explanations for this paradoxical finding. The first is that patients requiring the introduction of steroids may have had more advanced disease with the presence of disease-related symptoms which mandated steroid use. An alternative explanation is that corticosteroids may have inadvertently stimulated aberrant androgen receptors through promiscuous binding to the AR, inducing a more rapid disease progression. Importantly, the beneficial effect of enzalutamide was maintained regardless of whether or not steroids were also co-administered. Patients on enzalutamide had improved outcomes in terms of overall survival, radiographic PFS, and time to PSA progression compared to individuals on placebo regardless of their steroid use, further confirming the benefit of this agent.\(^{12}\)

Based on the positive results of the AFFIRM study, the US Food and Drug Administration approved enzalutamide on August 31, 2012 for men with metastatic castration-resistant prostate cancer who have already received prior docetaxel-containing chemotherapy. As a result of this product label, enzalutamide cannot currently be recommended for men with metastatic CRPC who have not yet received chemotherapy, although the off-label use of this agent in the pre-chemotherapy setting is an attractive prospect. Indeed, a role for enzalutamide in all patients with metastatic CRPC is hinted at by the data from the Phase I/II studies, where enzalutamide appeared efficacious (and potentially even more efficacious) in chemotherapy-naïve patients.

To conclusively ascertain whether enzalutamide has a role in the pre-chemotherapy space, a second randomized Phase III study of enzalutamide versus placebo in men with chemotherapy-naïve metastatic CRPC was designed (NCT01212991), and has completed accrual of 1680 patients. The primary endpoints of this trial (PREVAIL) are overall survival and progression-free survival, considered as co-primary endpoints. Secondary endpoints include time to initiation of cytotoxic chemotherapy, and time to first SRE. A number of additional trials are currently underway that are evaluating enzalutamide in a diverse set of patient populations, as well as in novel combinations with other agents (discussed below). A selected list of these studies is shown in Table 2.

### Adverse effects

Enzalutamide is generally very well tolerated. In the Phase I/II study, the most common grade 3–4 adverse event was dose-dependent fatigue (11% patients), which was only observed at doses of 240 mg or greater, and generally resolved after dose reduction.\(^{8}\) In the AFFIRM study, there were very few toxicities that were more common in the enzalutamide arm, and these included fatigue (all grades, 33.6\% vs 29.1\%), diarrhea, musculoskeletal pain, headache, hypertension and hot flashes. Overall, the enzalutamide group had a lower incidence of grade 3–4 adverse events (45.3\% vs 53.1\%).\(^{10}\) The most common adverse reactions (occurring in \( \geq 5\% \) of patients) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flashes, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. A large number of these adverse events were probably related to disease progression rather than the study drugs, since their incidence was similar in both treatment arms. In addition, it should be noted that enzalutamide is a strong inducer of CYP 3A4 and a moderate inducer of CYP
Table 2 Selected ongoing studies of enzalutamide in men with prostate cancer

<table>
<thead>
<tr>
<th>Study population</th>
<th>Therapy</th>
<th>Phase</th>
<th>Study title</th>
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<tr>
<td>Localized prostate cancer, planning to undergo prostatectomy</td>
<td>Enzalutamide</td>
<td>Phase II</td>
<td>A Randomized Open-Label Phase II Study of Enzalutamide as Neoadjuvant Therapy for Patients Undergoing Prostatectomy for Localized Prostate Cancer</td>
<td>NCT01547299</td>
</tr>
<tr>
<td>Recurrent hormone-naive asymptomatic prostate cancer</td>
<td>Enzalutamide monotherapy</td>
<td>Phase II</td>
<td>A Phase II Open-label Single-arm Efficacy and Safety Study of Enzalutamide in Patients With Hormone-naive Prostate Cancer</td>
<td>NCT01302041</td>
</tr>
<tr>
<td>CRPC with progression despite LHRH agonist; Non-metastatic patients included</td>
<td>Enzalutamide versus bicalutamide</td>
<td>Phase II</td>
<td>A Multicenter Phase II Double-Blind Randomized Efficacy and Safety Study of Enzalutamide in Men With Prostate Cancer Who Have Failed Primary Androgen Deprivation Therapy (STRIVE)</td>
<td>NCT01664923</td>
</tr>
<tr>
<td>Metastatic CRPC; chemotherapy-naive</td>
<td>Enzalutamide versus bicalutamide</td>
<td>Phase II</td>
<td>A Randomized Double-Blind Phase II Efficacy and Safety Study of Enzalutamide Versus Bicalutamide in Castrate Men With Metastatic Prostate Cancer (TERRAIN)</td>
<td>NCT01288911</td>
</tr>
<tr>
<td>Metastatic CRPC; chemotherapy-naive</td>
<td>Enzalutamide + docetaxel</td>
<td>Phase I</td>
<td>A Phase Ib Open-label Safety and Tolerability Study of Enzalutamide in Combination With Docetaxel in Men With Advanced Prostate Cancer</td>
<td>NCT01565928</td>
</tr>
<tr>
<td>Bone-metastatic CRPC; ≥2 Prior chemotherapy regimens</td>
<td>Enzalutamide + abiraterone</td>
<td>Phase II</td>
<td>A Phase II Study Determining Safety and Tolerability of Enzalutamide in Combination With Abiraterone in Bone-Metastatic Castration-Resistant Prostate Cancer</td>
<td>NCT01650194</td>
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Abbreviations: CRPC, castration-resistant prostate cancer; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer.

2C9 and CYP 2C19. These combinations can alter the plasma exposure of enzalutamide and should be avoided if possible. Conversely, concomitant use of strong CYP 2C8 inhibitors can increase the plasma exposure to enzalutamide.

Enzalutamide belongs to a class of antiandrogens that carry a risk of seizures. This is likely related to inhibition of the γ-aminobutyric acid (GABA)-gated chloride channels by enzalutamide, which lowers the seizure threshold. In the Phase I/II study, seizures were reported in three out of 140 patients, all of whom were taking doses above 360 mg and were also concurrently being treated with other medications that may have contributed to a lower seizure threshold. All subsequent studies used 160 mg as the dose of enzalutamide. In the AFFIRM trial, patients with a history of seizures or with other risk factors for seizures were excluded from trial entry. In addition, patients who were on medications that were known to lower seizure threshold (ie, insulin, antiarhythmics) were also excluded. During the AFFIRM study, 5 of 800 patients receiving enzalutamide (0.6%) had seizures compared to 0% in the placebo arm. Of those individuals, two had brain metastases, one had received lidocaine, and one had brain atrophy associated with alcohol use. Each of these characteristics could increase the risk of seizures. Patients who experienced a seizure discontinued therapy permanently and all seizures resolved and did not recur. Longer follow-up of AFFIRM identified two additional patients who experienced seizures, and thus the overall seizure risk when combining data from all completed enzalutamide studies is approximately 1.0% (10 of 940 total patients).

Finally, there was an increased incidence of headaches in patients who received enzalutamide, and it is unclear whether this could be classified as migraine. Both androgen use and seizure activity have been associated with migraine and therefore an improved understanding as to the exact mechanism of this side effect is warranted.

### Potential mechanisms of resistance to enzalutamide

Unfortunately, resistance to antiandrogens emerges invariably over time, and enzalutamide is no exception. AR gene rearrangement is a mechanism of CRPC progression which can result in constitutively active truncated AR splice variants that lack the AR-ligand binding domain. AR splice variants have been suggested to be associated with resistance to enzalutamide in prostate cancer cell lines. In addition, treatment with enzalutamide may result in elevations of testosterone and dihydrotestosterone in plasma and bone marrow, suggesting that overexpression of CYP17 and increased intracrine/paracrine androgen synthesis may also promote continued growth of CRPC. Alternatively, it has been proposed that enzalutamide resistance may be associated with cellular Fas-associated death domain-like interleukin...
1β-converting enzyme inhibitory protein (c-FLIP) expression, which is a key regulator of caspase-8 (FLICE)-promoted apoptosis. However, the exact mechanism of resistance to enzalutamide in human CRPC is largely unknown and is currently being investigated as this could influence both future treatment and outcomes in the individual patient.

**ARN-509**

The success of enzalutamide has prompted investigators to explore additional next-generation AR signaling inhibitors for the treatment of prostate cancer. ARN-509 is a competitive AR inhibitor with similar activity to enzalutamide and is antagonistic to AR overexpression. It inhibits AR nuclear translocation and DNA binding resulting in tumor growth inhibition and apoptosis. Preclinical activity demonstrated that ARN-509 binds AR with five-fold greater affinity than bicalutamide. In a CRPC xenograft model, ARN-509 showed greater efficacy than enzalutamide. Notably, the maximal therapeutic response was attained at a lower relative dose compared to enzalutamide and achieved higher steady-state plasma concentrations. This would suggest that ARN-509 may have a higher therapeutic index and might possibly be more effective than current antiandrogens including enzalutamide. Similarly to enzalutamide, ARN-509 also binds GABA receptors weakly. However, it appears to exhibit less central nervous system penetration, which could suggest a lower seizure-inducing potential. In a Phase I study, the drug was found to be well tolerated with ≥50% PSA declines observed in 42% of patients. With longer follow-up, the PSA response rate increased to 55%. Up to 90 men with CRPC will be enrolled onto the Phase II portion of the study. The Phase II trial has a unique design, in that it allows three separate patient populations: men with non-metastatic CRPC, men with metastatic CRPC, and men with abiraterone-refractory CRPC. Results will be reported at the 2013 Annual ASCO meeting. A placebo-controlled Phase III trial of ARN-509 (SPARTAN) is currently being planned for patients with non-metastatic CRPC with a PSA doubling time of <10 months. The primary endpoint of this trial will be metastasis-free survival.

**Ongoing and future studies**

In addition to the PREVAIL trial in men with chemotherapy-naïve CRPC, enzalutamide will continue to be investigated in earlier disease settings. For example, there is a randomized double-blind Phase II study comparing enzalutamide to bicalutamide in men with CRPC who have progressed after LHRH agonist monotherapy, a Phase II study of single-agent enzalutamide in men with recurrent hormone-naïve prostate cancer, and a neoadjuvant study of enzalutamide combined with leuprolide and dutasteride in patients scheduled to undergo radical prostatectomy (Table 2).

Enzalutamide is also an attractive therapeutic option to combine with other standard or novel agents. The combination of enzalutamide and docetaxel is currently under investigation (NCT01565928). The combination of enzalutamide and a selective CYP450c17 inhibitor (such as abiraterone) has also been proposed. Enzalutamide is effective in the presence of low levels of circulating androgens, whereas increased adrenal-derived androgen levels have been found to predict likelihood of response to ketoconazole with improved survival compared to patients with lower levels. Similar findings have been reported with abiraterone, where it has been shown that higher baseline levels of circulating adrenal androgens predict abiraterone responses while undetectable androgen levels predict abiraterone resistance. In addition, another proposed mechanism of resistance with the use of abiraterone has been activation of the mutated androgen receptor induced by glucocorticoid use, which is a necessary treatment to prevent the mineralocorticoid side effects of abiraterone. The addition of enzalutamide could inhibit such AR activation. In men with CRPC treated with enzalutamide, levels of plasma testosterone, bone marrow testosterone and plasma DHT do not decrease, whereas nuclear AR expression is reduced or unchanged. Abiraterone acetate has been demonstrated to decrease plasma testosterone and increase AR copy number, and therefore one could suggest evaluation of the combination of enzalutamide and abiraterone. Currently a Phase II study to determine the safety and tolerability of abiraterone combined with enzalutamide is underway (NCT01650194), and a large intergroup study is also being designed to compare the efficacy of enzalutamide monotherapy versus enzalutamide plus abiraterone in men with chemotherapy-naïve CRPC.

**Conclusion**

The last few years have seen a bounty of new therapeutic options in the treatment of advanced prostate cancer due to improvements in our understanding of this disease. It is now abundantly clear that the androgen receptor in CRPC continues to play a crucial role in driving the disease, which has led to the development of novel androgen signaling inhibitors. Enzalutamide is a second-generation nonsteroidal antiandrogen that has demonstrated significant activity in metastatic CRPC, improving both the length, as well as the quality of life. In addition, due to its very favorable safety profile, it is likely to become an increasingly important drug in the treatment of various stages...
of prostate cancer moving forward. Enzalutamide will likely be used earlier in the disease, and the results from the PREVAIL study are eagerly anticipated. The questions as to how best to sequence therapy and whether to combine therapies remain challenges to overcome over the next several years. Finally, understanding mechanisms of primary and acquired resistance to enzalutamide will be critical if we are to design future therapies for men with enzalutamide-refractory disease.

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Disclosure
The authors report no conflicts of interest related to this work.

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