Enzalutamide in the Treatment of Patients with Metastatic Castrate-Resistant Prostate Cancer

Adegoke O. Adeniji, BPharm, PhD; David A. Kaland, PhD; Launa M.J. Lynch, PhD; Vicky M. Mody, PhD

BACKGROUND: Androgen-deprivation therapy (ADT) remains the mainstay for the treatment of advanced prostate cancer. The use of ADT usually involves a period of clinical improvement after which the tumor progresses to a form of prostate cancer that grows despite castrate levels of testosterone in most patients. This progressive state is called castrate-resistant prostate cancer (CRPC). CRPC is uniformly fatal and, historically, was managed with docetaxel-based chemotherapy as initial therapy. Enzalutamide is a potent second-generation androgen receptor antagonist approved for the treatment of men with CRPC or without previous exposure to docetaxel.

OBJECTIVE: To review the development of enzalutamide, including its safety and efficacy outcomes in clinical trials, the challenges to its optimal efficacy in the clinic, and efforts to overcome them.

DISCUSSION: Enzalutamide continues to be an effective therapeutic agent for the treatment of CRPC. However, cases of tumor resistance to enzalutamide and enzalutamide withdrawal syndrome have now been reported. Enzalutamide-resistant tumors continue to depend on androgen receptor signaling for growth, which suggests that newer drugs targeting the androgen receptor or other alternate pathways that impinge on the androgen axis may be effective against these tumors.

CONCLUSION: The approval of enzalutamide for the treatment of patients with CRPC represents a significant milestone. This compound showed good activity in patients who had been exposed to chemotherapy, as well as in chemotherapy-naïve patients. As with all other anti-androgen therapies, resistance remains a significant challenge. Elucidating the mechanisms of resistance, and therapeutic modalities that may delay or prevent the onset of resistance, are essential to optimize the use of this drug and other drugs targeting the androgen axis.
Testosterone is primarily produced in the Leydig cells of the testes, which account for approximately 90% of the testosterone production in the body, with the adrenal gland contributing the remainder. Testosterone can be converted into the more potent androgen, DHT, in the tissues by 5α-reductases. ADT targets testicular production of androgens and produces a dramatic reduction in systemic levels of testosterone (<50 ng/dL). Despite the castrate level of systemic testosterone and DHT, intratumoral levels of these androgens in CRPC are increased relative to non-CRPC tumors, and are sufficient to activate the androgen receptor and drive tumor proliferation. The testosterone and DHT levels within the tumors are maintained by an upregulation of enzymes that catalyze important steps in androgen biosynthesis (Figure 1). These enzymes include cytochrome (CY)P45017A1, aldo-keto reductase 1C3 (AKR1C3), and 3β-hydroxysteroid dehydrogenase (3β-HSD). 5,7 These enzymes catalyze the conversion of adrenal precursors—dehydroepiandrosterone (DHEA) and 4-androstene-3,17-dione (Δ4-Adione)—to testosterone and DHT, as well as the denovo biosynthesis of androgens from cholesterol (Figure 1). Recently, Chang and colleagues reported a gain of function mutation in type 1 3β-HSD (3β-HSD1) in CRPC cells. 8 This point mutation increases the stability and half-life of the protein, which leads to increased DHT biosynthesis.

The importance of renewed androgen biosynthesis in CRPC and the potential therapeutic utility of inhibitors of androgen biosynthesis are underscored by the remarkable clinical efficacy and subsequent US Food and Drug Administration (FDA) approval of abiraterone acetate, a CYP17A1 inhibitor, for the treatment of patients with CRPC. CYP17A1 catalyzes the 2 consecutive reactions that convert pregnenolone to DHEA and progesterone to Δ4-Adione. Δ4-Adione is subsequently reduced to testosterone by AKR1C3. This has spurred intensive efforts into the discovery and development of other compounds that target CYP17A1, AKR1C3, and other androgen biosynthetic enzymes. 9-11

The androgen receptor is a ligand (androgen)-activated transcription factor that belongs to the nuclear receptor superfamily. In the absence of agonist occupancy, the androgen receptor is resident in the cytoplasm bound to chaperone proteins, such as heat shock proteins. Binding of an agonist induces a conformational change in the receptor that causes it to dissociate from the inactive complex. The bound receptor homodimerizes and trans-
locates into the nucleus, where it binds specific DNA sequences known as androgen response elements, and facilitates the transcription of androgen-responsive genes that bring about the plethora of physiologic effects associated with androgens.

Adaptive genetic changes in the androgen receptor represent another route through which the tumor escapes the growth-suppressive effect of ADT. These changes alter androgen receptor transcriptional activity by affecting the androgen receptor and/or its binding partners within the cell, and include androgen receptor upregulation, androgen receptor mutation, development of constitutively active androgen receptor splice variants (AR-Vs), and alteration in androgen receptor co-factors.12

The androgen receptor has 3 functional domains corresponding to the N-terminal domain, the DNA-binding domain, and the carboxy-terminal ligand-binding domain (LBD).13 Androgen receptor upregulation has been consistently observed in CRPC samples after ADT. Androgen receptor upregulation causes an increase in androgen receptor mRNA and protein, which results in androgen receptor ligand hypersensitivity.13-15 The androgen receptor ligand hypersensitivity reduces the androgen threshold required for significant androgen receptor activation, which allows for androgen receptor signaling in the presence of the significantly reduced levels of androgens brought about by ADT. Chen and colleagues showed that a 3- to 5-fold increase in androgen receptor mRNA was sufficient for the tumor to bypass the growth-inhibitory effects of ADT.16

Most of the androgen receptor mutations seen in prostate cancer after ADT occur in the androgen receptor LBD and lead to relaxation of the androgen receptor ligand specificity. These mutated androgen receptors are usually characterized by an increased responsiveness to weak androgens, such as DHEA, Δ4-Adione, or 5α-Adione, as well as to nonandrogen steroid hormones, such as estrogens, progesterone, or cortisol.17-22 Antagonist to agonist conversion was also observed with some of these mutated androgen receptors. A notable example is the androgen receptor T877A mutation (AR7877A), which involves the replacement of a threonine residue with an alanine residue at position 877. The AR7877A is activated by estrogen, progesterone, and anti-androgens, such as bicalutamide or flutamide.23-26 The activation of mutated androgen receptors by anti-androgens is consistent with the reduction in prostate tumor markers and clinical improvement in some patients after cessation of anti-androgen therapy, a phenomenon that is often referred to as anti-androgen withdrawal syndrome.27,28

Development of Enzalutamide

Enzalutamide was discovered in a screen that evaluated the androgen receptor antagonism of compounds in a setting of elevated androgen receptor expression designed to mimic CRPC.34 Enzalutamide is a 3-ringed thiohydantoin derivative; the rings are labeled A, B, and C, as shown in Figure 2.
Enzalutamide was derived after modification of a nonsteroidal androgen receptor agonist, RU59063, which showed excellent androgen receptor affinity and was more potent than DHT (Figure 2). The binding of the nonsteroidal agonist with higher potency triggered the search for a nonsteroidal androgen receptor antagonist. The aim was to modify RU59063 to produce an androgen receptor antagonist. Activities of these RU59063 analog were compared with the androgen receptor antagonist bicalutamide. Different analog of RU59063 were prepared with different substituents at N1 to provide adequate binding at the androgen receptor. This led to the development of N1-phenyl ring-substituted analog.

The presence of dimethyl groups at C5 of the thiohydantoin ring also resulted in better antagonist activity. Other modifications—such as the thiocarbonyl at C2 in enzalutamide compared with a carbonyl group at the same position in RU59063—created a more potent antagonist. These modifications of RU59063 led to the development of enzalutamide. Compared with bicalutamide, enzalutamide displayed excellent androgen receptor antagonist activity (IC50: 122 nM) and a desirable pharmacokinetic and toxicologic profile.

**Absorption and Distribution**

The pharmacokinetics of enzalutamide were studied in patients and in healthy volunteers. Enzalutamide is well-absorbed after oral administration, with approximately 85% of the administered dose being absorbed. The extent of absorption of enzalutamide after oral administration is not affected by the presence of food. Enzalutamide undergoes extensive extravascular distribution with a volume of distribution of 110 L. When patients with metastatic CRPC took the 160-mg oral dose of enzalutamide, the median time to reach the maximum plasma concentration (Cmax) was 1 hour, with a range from 30 minutes to 3 hours. Steady-state levels are achieved when enzalutamide is taken daily for 28 days and the accumulation of enzalutamide is approximately 8.3-fold greater than a single dose. Once the steady-state level is reached, the mean Cmax level is 16.6 µg/mL for enzalutamide and 12.7 µg/mL for N-desmethyl enzalutamide, the active metabolite of enzalutamide. Enzalutamide and N-desmethyl enzalutamide are 97% to 98% and 95%, respectively, plasma protein bound. The mean peak-to-trough ratio is 1.25, demonstrating a low fluctuation in daily plasma concentrations of enzalutamide.

**Metabolism and Elimination**

The primary route of elimination of enzalutamide is hepatic, with the 2 main enzymes involved being CYP2C8 and CYP3A4. CYP2C8 converts enzalutamide to N-desmethyl enzalutamide, an active metabolite for the drug. There is conversion to an inactive carboxylic acid metabolite as well. In patients with metastatic CRPC, the mean apparent clearance was 0.56 L hourly, and the mean terminal half-life was 5.8 days. The half-life for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

**Special Populations**

The patient’s age or body weight does not have a clinically significant impact on the pharmacokinetics of enzalutamide. Likewise, the clearance of enzalutamide is not changed in patients with mild or moderate renal or hepatic impairment. However, not enough data are available to determine how severe renal or hepatic impairment or end-stage renal disease affects the clearance of the drug. Enzalutamide is pregnancy category X, and women who are or may become pregnant should not ingest or handle the drug.

**Mechanism of Action**

Enzalutamide is a second-generation anti-androgen. The second-generation anti-androgens were developed because the first-generation anti-androgens acted as partial agonists in advanced-stage prostate cancer caused by the overexpression of the androgen receptor and the mutations in androgen receptor LBD. Enzalutamide has a high binding affinity for the carboxy-terminal LBD of the androgen receptor, and is active in the presence of androgen receptor overexpression and mutations that render other androgen receptor antagonists ineffective. Enzalutamide competes with testosterone and DHT binding to the androgen receptor LBD, and consequently inhibits androgen receptor signaling. Unlike bicalutamide, enzalutamide also inhibits nuclear translocation and transcription.

**Drug Interactions**

Data from clinical trials indicate that enzalutamide is a strong CYP3A4 inducer and a moderate inducer of CYP2C9 and CYP2C19. Time-dependent inhibition of CYP1A2 has been observed with enzalutamide treatment. Enzalutamide and N-desmethyl enzalutamide are
2 inhibitors of P-glycoprotein.\textsuperscript{36,37} Therefore, caution should be used when co-administering enzalutamide with substrates of P-glycoprotein, CYP2C9, CYP2C19, and CYP3A4. The pharmacokinetics of drugs that are substrates of P-glycoprotein (eg, loperamide, vinblastine) may be affected when administered with enzalutamide. Use of drugs that have a narrow therapeutic index and are substrates of CYP2C9, CYP2C19, and CYP3A4 enzymes should be avoided with enzalutamide (Table 1).\textsuperscript{17}

### Enzalutamide Pharmacotherapy

Enzalutamide was approved by the FDA for the treatment of men with metastatic CRPC based on the results of the AFFIRM clinical trial.\textsuperscript{39} In this randomized, phase 3, placebo-controlled study, 1199 men with CRPC were randomized to enzalutamide 160 mg (four 40-mg capsules) once daily or to placebo in a 2:1 ratio. All participants had received ≥1 docetaxel-containing chemotherapy regimens before enrollment in the study. The study design was almost identical to that of the COU-AA-301 trial, which led to the FDA approval of abiraterone acetate, except for the use of prednisone or other glucocorticoids with the latter.\textsuperscript{40}

Abiraterone acetate is a potent inhibitor of androgen synthesis in the adrenal gland, testes, and prostate tumor. It requires concomitant steroid use to prevent the hypokalemia, fluid retention, and hypertension from mineralocorticoid excess caused by adrenal blockade.\textsuperscript{40} In contrast, enzalutamide does not lower androgen levels; rather, it inhibits androgen receptor signaling by competitively inhibiting the binding of androgens, without stimulating the receptor. Tumor growth requires androgen binding to the receptor, followed by nuclear translocation. Thus, inhibition of androgen receptor signaling is important in preventing disease progression.

The primary end point in AFFIRM was overall survival (OS), which was 18.4 months in the treatment group and 13.6 months in the placebo group.\textsuperscript{39} This correlated to a significant 37% mortality risk reduction with enzalutamide versus placebo. This benefit was seen across all subgroups, even after adjustment for baseline prognostic factors. Secondary end points, including quality of life, were also significantly improved. After the interim analysis, the study was unblinded, and the placebo group was offered enzalutamide.

Although adverse events were more common in the enzalutamide group, they were generally mild and included fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache. These effects could be caused by the further inhibition of androgen receptor signaling in normal tissues. Interestingly, the AFFIRM study also demonstrated reduced incidence of grades 3 and 4 adverse events with enzalutamide compared with placebo. In addition, the median time to first grade 3 or 4 adverse event was lengthened by 8.4 months in the enzalutamide group. The most common of such events were fatigue and diarrhea. This finding suggests that the toxicity associated with placebo was mainly caused by the underlying disease.

No differences in cardiac disorders or in development of metabolic syndrome were reported. Convulsions have been reported as a dose-dependent toxic effect in animal studies, and seizures were seen at doses >360 mg in the phase 1 and 2 clinical trials of enzalutamide.\textsuperscript{39,41} Of the 5 patients in the treatment group of the AFFIRM trial who reported seizures, 4 had identifiable seizure causes, predisposing them to a heightened seizure risk.\textsuperscript{39} Regardless, the prevailing recommendation is to use enzalutamide with caution in patients with a history of seizure disorders or other predisposing factors.

The results of the AFFIRM trial, as well as the reported survival benefit of abiraterone plus prednisone, underscore the notion that androgen receptor signaling contributes to disease progression, even in the presence of castrate levels of testosterone.\textsuperscript{39,40} However, although enzalutamide reduced the rate of disease progression compared with placebo, there was still a large proportion (42%) of patients who required additional antineoplastic therapy after cessation of the study drug.\textsuperscript{39} In addition, PSA levels were increased in the majority of patients whose disease progressed after enzalutamide treatment. This suggests that tumor growth in these patients continues to be driven by the androgen receptor, and they may benefit from further hormonal interventions. It was also reasoned that if the androgen receptor is still driving the development and progression of CRPC, enzalutamide would be active in these patients regardless of previous exposure to docetaxel.\textsuperscript{45}

This reasoning proved to be correct, based on the results of another phase 3 clinical trial, the PREVAIL study, which led to the FDA approval of enzalutamide for the treatment of metastatic CRPC in chemotherapy-naive patients. The PREVAIL study included 1717 chemotherapy-naive patients with metastatic CRPC and compared enzalutamide with placebo.\textsuperscript{45} Patients were required to continue ADT but had not received

### Table 1: Drugs to Avoid Concomitantly with Enzalutamide

<table>
<thead>
<tr>
<th>CYP2C9 substrates</th>
<th>CYP2C19 substrates</th>
<th>CYP3A4 substrates</th>
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<tbody>
<tr>
<td>Phenytoin</td>
<td>Omeprazole</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Warfarin</td>
<td>S-mephénytoïn</td>
<td>Fentanyl</td>
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<tr>
<td>Sirolimus</td>
<td>Midazolam</td>
<td>Fosinopril</td>
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chemotherapy or abiraterone acetate before the study. The patients were randomly assigned to receive enzalutamide 160 mg or placebo once daily, with or without food. Primary end points were OS and progression-free survival (PFS).

At 1 year, PFS was significantly better with enzalutamide, at 65% compared with 14% with placebo, resulting in an 81% risk reduction for disease progression or death (95% confidence interval [CI], 0.15-0.23; P <.001). At a median 22-month follow-up, significantly fewer deaths were reported in the active treatment group compared with the placebo group (28% vs 35%, respectively), resulting in a 29% reduction in mortality risk (95% CI, 0.60-0.84; P <.001). This correlated to a median OS of 32.4 months for enzalutamide compared with 30.2 months for placebo. This improvement was seen across all subgroups.

As was done in the AFFIRM trial, the PREVAIL study was halted early and was unblinded at this point, and the placebo group was offered the study drug. In addition, subsequent antineoplastic therapy, most often docetaxel or abiraterone acetate, was given to 40% of patients in the enzalutamide group versus 70% in the placebo group, and enzalutamide delayed the time to chemotherapy initiation by 17 months. The delay of initiating active treatment in the placebo group may account for some of the benefits of enzalutamide. This point is supported by the finding that abiraterone acetate also was associated with a more pronounced delay of disease progression when it was used before than after chemotherapy. However, no studies to date have directly looked at the effect of the timing of therapy in patients with metastatic CRPC. The PREVAIL trial demonstrated that the safety profile of enzalutamide was consistent with previous data. Enzalutamide was again shown to prolong the time to first grade 3 or 4 adverse event by 9 months. However, unlike the AFFIRM study, grade 3 or 4 adverse events were more common in the enzalutamide group than in the placebo group (43% vs 37%, respectively). Even after adjustment for a longer exposure for the treatment group, the rate of adverse events was higher with enzalutamide than with placebo, most notably hypertension, although this was not attributed to mineralocorticoid excess. Notably absent was a risk for seizures in the PREVAIL trial, with 1 patient in each study group having a seizure. Both of these patients had an unreported history of seizures at the time of enrollment.

In the COU-AA-302 clinical trial, abiraterone acetate plus prednisone was found to benefit chemotherapy-naïve patients with CRPC, which led to its FDA approval in this setting. Although the results reported at 27.2 months showed a trend toward improved OS for the treatment group compared with prednisone alone, the study failed to reach significance at the time. However, in the final OS analysis at 4 years, the clinical and statistical survival advantage of abiraterone acetate was confirmed.

It is worth noting, however, that COU-AA-302 had excluded patients with visceral metastases, whereas the AFFIRM and the PREVAIL studies did not. Visceral metastases confer a poorer prognosis than nonvisceral sites; therefore, exclusion of such patients may inflate the results for abiraterone acetate compared with enzalutamide.

In late 2014, the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) updated their respective prostate cancer guidelines to reflect the new data regarding enzalutamide. Both guidelines now recommend abiraterone acetate plus prednisone or enzalutamide as first-line therapy in patients with metastatic CRPC, regardless of previous chemotherapy status. In addition, enzalutamide carries the benefit of a first-line recommendation for those with visceral metastases.

Despite establishing enzalutamide among the various standards of care for patients with metastatic CRPC, the AFFIRM and PREVAIL studies demonstrated only approximately an 8- to 11-month time frame before disease progression with enzalutamide. A similar time to progression was noted with abiraterone acetate in its respective studies. This has raised concerns regarding resistance to enzalutamide. Indeed, the issue of resistance, even to newer androgen and androgen receptor–targeted therapies, remains a continuing challenge in the treatment of patients with CRPC. Such concerns have led to the suggestion that resistance to enzalutamide can be overcome by subsequent therapy with abiraterone acetate and vice versa, given the nonoverlapping mechanisms of action of the 2 drugs. Similarly, it is generally believed that combination therapy should reduce the incidence of resistance to either drug.

Enzalutamide and abiraterone acetate have been included in the NCCN recommendations for subsequent therapy after disease progression with each drug. However, this is based on several small studies examining the sequencing of abiraterone acetate and enzalutamide. When abiraterone acetate was given after disease progression with enzalutamide, few patients achieved a ≥50% PSA reduction, and the time to progression was only approximately 3 to 4 months. Likewise, when enzalutamide was given after disease progression with abiraterone acetate, the PSA response rate was low, and the median time to progression with enzalutamide was 2.8 to 4 months. The blunted response to enzalutamide in patients with resistance to abiraterone acetate was without regard to previous exposure to docetaxel. These data, although limited, would suggest significant...
cross-resistance between the 2 agents as a result of similar or overlapping mechanisms of acquired tumor resistance. Theoretically, combination therapy may be effective in overcoming or delaying resistance mechanisms in the same fashion that highly active antiretroviral therapy is effective in HIV/AIDS treatment. Clinical trials are currently underway to examine this theory, and interim results are promising. In one such study, PSA decline of \( \geq 50\% \) was reported in approximately 76% of patients, and disease progression in approximately 12%. In addition, a favorable side-effect profile has been reported thus far.53

Several resistance mechanisms have been elucidated in enzalutamide-resistant prostate tumors. It is well-established that androgens and androgen receptor activation continue to drive tumor growth in patients with CRPC, which explains the efficacy of anti-androgen therapy, such as abiraterone acetate or enzalutamide. Indeed, it is these mechanisms of resistance that abiraterone acetate and enzalutamide target. As observed in the phase 3 studies discussed earlier, of the patients with CRPC who initially respond to hormonal therapy, nearly all will acquire secondary resistance.40,43,44,51

Much like the resistance to ADT, bicalutamide, and other first-generation androgen receptor antagonists, an increase in androgen biosynthesis enzymes, presence of androgen receptor mutations, and constitutively active androgen receptor splice variants lacking the C-terminal–binding domain have been observed after treatment with enzalutamide.54,57 The presence of a spontaneous F876L mutation on the androgen receptor (AR\(^\text{F876L}\)) was observed in preclinical models of prostate cancer cells and xenografts that developed resistance to enzalutamide.55,56

Genetically engineered prostate cancer cells expressing this androgen receptor mutation were also resistant to enzalutamide. AR\(^\text{F876L}\) occurs in the hypermutable androgen receptor LBD and confers androgen receptor agonist properties on enzalutamide, which allows for sustained growth of the treated cells. This indicates the possibility of an enzalutamide withdrawal syndrome, although few cases have been reported.56,57 Notably, this mutation, although resistant to enzalutamide, increases tumor cells’ sensitivity to bicalutamide, which underscores the need for an evaluation of the specific mutation present in an individual patient to determine the best course of therapy.

Another mechanism that has been implicated in enzalutamide resistance in preclinical models is an increased expression of AKR1C3.57 Patients receiving enzalutamide have been reported to have elevated testosterone levels in the bone marrow, and enzalutamide-resistant prostate cancer cells were found to produce several-fold increased levels of testosterone and DHT.57,60,61 This is consistent with the prostate cancer cells’ adaptive response to the inhibition of androgen receptor activation. AKR1C3 is an important enzyme in androgen biosynthesis that is highly upregulated in CRPC.5,7,62,63 It catalyzes the conversion of weak androgens—Δ\(^4\)-Adione and 5α-Adione—to testosterone and DHT, respectively.64,65 Liu and colleagues showed that an increase in AKR1C3 expression and activity was a critical mechanism that drives enzalutamide resistance in prostate cancer cells and xenografts.57 Enzalutamide sensitivity was restored after AKR1C3 knockdown or inhibition by small molecules. This suggests that AKR1C3 inhibitors could potentially be used independently for the treatment of metastatic CRPC, or in addition to enzalutamide, to reverse or limit the resistance to enzalutamide.5,10,36

Increased expression of AR-Vs, particularly AR-V7, has also been associated with enzalutamide resistance. The clinical relevance of AR-V7 on the efficacy of abiraterone acetate and enzalutamide was tested in a small, prospective study of men with metastatic CRPC who were beginning therapy with enzalutamide or with abiraterone acetate.67 Antonarakis and colleagues measured a baseline AR-V7 status in circulating tumor cells to predict response or resistance to anti-androgen therapy. The 62 patients with detectable circulating tumor cells were equally randomized to receive enzalutamide or abiraterone acetate. Twelve of the 31 patients in the enzalutamide group and 6 of the 31 patients in the abiraterone group had detectable AR-V7 mRNA (Table 2).67

A total of 50% of patients with previous enzalutamide exposure had detectable AR-V7 compared with 15% who had no previous exposure. Similarly, 55% of the patients who had previous exposure to abiraterone acetate had detectable AR-V7 compared with 9% who never received the drug. In addition, 6 patients in the en-

### Table 2

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>Patients with AR-V7 detected (n = 18)</th>
<th>Patients with AR-V7 not detected (n = 44)</th>
<th>P value</th>
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</thead>
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<tr>
<td>Enzalutamide</td>
<td></td>
<td></td>
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<tr>
<td>Baseline status (n = 31)</td>
<td>12 (39%)</td>
<td>19 (61%)</td>
<td></td>
</tr>
<tr>
<td>PSA response</td>
<td>0 (0%)</td>
<td>10 (53%)</td>
<td>.004</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline status (n = 31)</td>
<td>6 (19%)</td>
<td>25 (81%)</td>
<td></td>
</tr>
<tr>
<td>PSA response</td>
<td>0 (0%)</td>
<td>17 (68%)</td>
<td>.004</td>
</tr>
</tbody>
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AR-V7 indicates androgen receptor splice variant 7; CRPC, castrate-resistant prostate cancer; PSA, prostate-specific antigen.

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Enzalutamide group and 2 in the abiraterone acetate group) had converted from negative AR-V7 status to positive AR-V7 status during the course of treatment.6 This supports the involvement of AR-V7 as a mechanism of resistance to the drugs. Although 53% of the AR-V7-negative patients achieved a PSA response, defined as ≥50% PSA reduction, during treatment with enzalutamide, none of the AR-V7-positive patients achieved the same threshold after treatment with enzalutamide.67

Similarly, none of the AR-V7-positive patients had a PSA response to abiraterone acetate. In addition, the patients who became AR-V7-positive after treatment initiation, only 17% achieved a PSA response; this is in contrast to the 68% of patients who remained AR-V7-negative throughout treatment and had a PSA response. These observations translated to a significant reduction in OS in AR-V7-positive patients.67

These results demonstrate a strong association between AR-V7 status and resistance to enzalutamide and abiraterone acetate. However, as indicated by the authors, it is possible that AR-V7 is simply a marker of higher disease burden.67 These findings need to be replicated in a larger cohort of patients to establish the role of AR-V7 in enzalutamide resistance, and potentially use it as a biomarker to facilitate individualized treatment of CRPC.

Should AR-V7 be validated as a mechanism of resistance, drugs that target the N-terminal domain would theoretically inhibit the full-length androgen receptor, as well as the AR-Vs. Indeed, inhibitors of androgen receptor N-terminal domain, such as EPI-001, are in the early stages of development and may represent another step forward in the treatment of CRPC.68,69 EPI-001 binds covalently to the androgen receptor N-terminal domain and irreversibly inhibits androgen receptor transcriptional activity.68,70 Because it does not bind to the androgen receptor LBD, EPI-001 cannot be outcompeted by androgens, and is able to inhibit full-length androgen receptors and AR-Vs, which are correlated with resistance to enzalutamide and abiraterone acetate.

Conclusion

Enzalutamide is a rationally designed, second-genera-
tion anti-androgen that has been approved by the FDA for the treatment of patients with metastatic CRPC without regard to previous docetaxel therapy. Despite the initial efficacy, resistance to enzalutamide eventually occurs. This may be the result of selective pressure on the tumor after enzalutamide therapy. Although the mechanisms of resistance to enzalutamide have not been completely elucidated, these adaptive changes involve reactivation of the androgen axis. The continued dependence on androgen receptors and androgens by prostate cancers that have progressed with enzalutamide provides opportuni-
ties for newer agents that target the androgen axis to be used concurrently with enzalutamide, or after resistance develops. However, these drugs are likely to be effective for a limited time, as the tumor will invariably progress. The findings of the combined use of abiraterone acetate and enzalutamide will be critical to optimizing the use of these agents. The outcome of this study will also have implications for the development and use of new agents targeting the androgen receptor axis.

Author Disclosure Statement

Dr Adeniji, Dr Kaland, Dr Lynch, and Dr Mody have no conflicts of interest to report.

References