Enzalutamide in Castration-resistant Prostate Cancer Patients Progressing After Docetaxel and Abiraterone

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Abstract

Background: Abiraterone, an androgen synthesis inhibitor, has been successfully used in the treatment of castration-resistant prostate cancer (CRPC) for 2yr. Enzalutamide is a second-generation nonsteroidal antiandrogen that has recently been approved for the same indication.

Objective: This is the first study to evaluate the effectiveness of enzalutamide after failure of abiraterone.

Design, setting, and participants: Thirty-five patients were identified as having received sequential therapy with abiraterone followed by enzalutamide. All patients had undergone prior docetaxel chemotherapy, and no patient had received ketoconazole.

Outcome measurements and statistical analysis: Posttreatment changes in prostate-specific antigen (PSA) were used to determine the activity of enzalutamide in patients who had received prior abiraterone.

Results and limitations: The median duration of abiraterone treatment was 9.0 mo (range: 2.0–19.0 mo). Of the 35 patients, 16 (45.7%) achieved a >50% decline in PSA, and 14 (40%) had a rising PSA as the best response. The median duration of subsequent enzalutamide treatment was 4.9 mo (Kaplan-Meier estimate; 95% confidence interval [CI], 2.4–7.4). Seven of 16 CRPC patients who were initially abiraterone-sensitive (43.8%) and 3 of 19 CRPC patients who were initially abiraterone-insensitive (15.8%) showed a >50% PSA decline while taking enzalutamide. Of the 35 patients, 17 (48.6%) were primarily enzalutamide-resistant and showed a rising PSA as the best response. Median time to progression was 4.0 mo (95% CI, 2.0–6.0) for 18 of 35 patients with at least one declining PSA value while taking enzalutamide (51.4%). Of the 17 patients who were assessable radiologically, only 1 (2.9%) attained a confirmed partial response. Small sample size was the major limitation.

Conclusions: Enzalutamide treatment achieved only a modest response rate in patients progressing after abiraterone. Although cross-resistance between abiraterone and enzalutamide was a common phenomenon, it was not inevitable, and a small but significant number of patients showed significant benefit from sequential treatment.

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1. **Introduction**

Almost all prostate cancer (PCa) patients in the Western world who die of their disease have received androgen-deprivation therapy (ADT). Although the majority of PCa responds to initial ADT, PCa cells usually acquire the ability to survive and grow under low levels of circulating testosterone (<50 ng/dl) within 12–48 mo of treatment. This state of the disease, also known as castration-resistant prostate cancer (CRPC), is almost invariably fatal [1].

Until recently, taxanes such as docetaxel and cabazitaxel were the only antineoplastic agents with significant activity against CRPC [2,3]. Consequently, there was an urgent need for additional new therapeutic approaches.

In contrast to previous beliefs, the progression from androgen-sensitive PCa to CRPC is rarely due to the loss of the androgen receptor (AR); in fact, in CRPC, the cells’ AR signaling remains active even under castration levels of serum testosterone [4]. Two novel drugs (abiraterone and enzalutamide) targeting the AR-signaling pathway have shown efficacy with mild toxicity in CRPC patients: Abiraterone is an oral CYP17A1 inhibitor that is able to block intracellular androgen synthesis in CRPC tissue (Fig. 1), thereby blocking a major mechanism of resistance to first-line ADT [5–7]. Enzalutamide is a nonsteroidal antiandrogen that binds to the ligand-binding domain (LBD) of the AR with 8–10 times higher affinity than bicalutamide [8]. On binding to the LBD, enzalutamide diminishes AR nuclear translocation, DNA binding, and recruitment of AR coactivators [8,9]. Because of their efficacy and favorable toxicity profiles, these drugs have become a standard treatment of CRPC.

Unfortunately, the clinical effectiveness of both compounds is limited. Phase 3 trials including docetaxel-refractory CRPC patients described a median time to prostate-specific antigen (PSA) progression of only 8.5 mo for abiraterone and 8.3 mo for enzalutamide [6,10].

To date, there is only limited information regarding the sequential use of both drugs. Two small studies showed only a limited efficacy of a sequential enzalutamide–abiraterone treatment [11,12]. To assess the potency of an enzalutamide treatment in abiraterone-refractory CRPC, we performed a pilot study analyzing biochemical response during sequential abiraterone–enzalutamide treatment.

2. **Patients and methods**

2.1. **Patients**

Since June 2012, 35 consecutive CRPC patients have been included in the MDV3100 (enzalutamide [Xtandi]) compassionate use program at three German university medical centers (Ulm, n = 11; Muenster, n = 19; Homburg/Saar, n = 5); at the time of their inclusion, these patients showed disease progression after or during treatment with docetaxel (Taxotere) and abiraterone (Zytiga). Implementation of the compassionate use program was approved by the respective local ethics commissions; all patients gave written informed consent prior to third-line enzalutamide therapy.

Patient- and tumor-specific data were obtained from the patients’ medical records. Under enzalutamide therapy (160 mg/d), patients had follow-up clinical examinations and PSA tests at least every 3 wk (weeks 1–12) and then every 6 wk. Inclusion criteria included, particularly, the presence of actively progressive CRPC as defined by the Prostate Cancer Clinical Trials Working Group 2, continuation of primary ADT, status after docetaxel treatment, absence of metastases to the central nervous system, and a general condition of Eastern Cooperative Oncology Group 0–2.

2.2. **Statistical methods**

The Fisher exact and χ² tests were conducted to assess correlations of nominal covariate distributions and response groups. The Mann-Whitney U test was applied to compare metric variables among different subgroups. Kaplan-Meier estimates of time on enzalutamide therapy, time to progression, and overall survival from the start of enzalutamide were calculated, and subgroups were compared by the log-rank test. A two-sided p < 0.05 was considered to indicate significance in all tests. SPSS 19.0 was used for statistical assessment.

3. **Results**

3.1. **Patient-specific characteristics**

The study included 35 CRPC patients treated sequentially with docetaxel, abiraterone, and enzalutamide. Patient- and tumor-specific characteristics are listed in Table 1.

3.2. **Response to the different lines of androgen-deprivation therapy**

Of the 35 patients, 33 (94.3%) showed a significant initial biochemical response to primary ADT (PSA decline >50%) (Table 2). Only two PCa patients were primarily refractory to conventional ADT.

At least one decline in PSA (5–99%) was observed in 21 of 35 patients who subsequently received abiraterone in the state of castration resistance (60.0%) (Table 2). PSA responses of >50% were achieved by 16 of 35 patients (45.7%) (Fig. 2). The median duration of abiraterone therapy was 9 mo (interquartile range [IQR]: 5–13 mo) in the entire cohort and 13.5 mo (range: 7–19 mo) in patients with a >50% PSA decline. None of the patients had significant adverse effects leading to premature termination of treatment.

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**Fig. 1** – Pathways involved in castration resistance of prostatic neoplasms. During hormonal therapy, most castration-resistant prostate cancer cells continue to depend on androgen receptor signaling but bypass the requirements for physiologic levels of circulating androgens. PCa = prostate cancer; CPRC = castration-resistant prostate cancer; AR = androgen receptor; LBD = ligand-binding domain; RTK = receptor tyrosine kinase.
After progression while taking abiraterone, all 35 patients received enzalutamide (Table 3). The median interval between termination of abiraterone and initiation of enzalutamide was 14 d (IQR: 1–119 d). Of the 35 patients, 18 (51.4%) had a PSA decline (range: 19–99%) on at least one occasion while taking enzalutamide. A PSA decline of >50% was observed in 10 patients (28.6%). At the time of the analysis, 13 patients were still receiving ongoing enzalutamide therapy, in many cases for clinically stable disease and/or lack of further treatment options despite primary or secondary PSA progression. The calculated median and mean duration of enzalutamide treatment for all patients was 4.9 and 5.1 mo, respectively (95% confidence interval [CI], 2.4–7.4; Kaplan-Meier estimate). The calculated mean duration differed significantly between patients with a <50% and >50% PSA decrease: 3.8 vs. 7.8 mo (p = 0.001; log-rank test). Patients with at least one PSA regression while taking enzalutamide (n = 18) had a median time to progression of 4.0 mo (95% CI, 2.0–6.0; Kaplan-Meier estimate).

The number of patients who failed to achieve a >50% PSA decline tended to be higher among patients who had poorly differentiated tumors (Gleason score 8–10) while taking both ADT therapies. Patients with at least one PSA decline while taking enzalutamide (n = 18) had a median time to progression of 4.0 mo (95% CI, 2.0–6.0; Kaplan-Meier estimate).

**Table 1 – Characterization of the study cohort**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>Age, yr, median (range)</td>
<td>70 (57–81)</td>
</tr>
<tr>
<td>Prior local treatment, no. (%)</td>
<td>Radical prostatectomy and/or irradiation 20 (57.1) None 15 (42.9)</td>
</tr>
<tr>
<td>Gleason score in biopsy/surgical specimen, no. (%)</td>
<td>6 1 (2.8) 7 9 (25.7) 8 7 (20.0) 9 10 (28.6) 10 2 (5.7) Unknown 6 (17.2)</td>
</tr>
<tr>
<td>Primary ADT treatment, no. (%)</td>
<td>LHRH analogues with/without first-generation AR blockers 32 (91.4) Orchiectomy 3 (8.6)</td>
</tr>
<tr>
<td>Duration of primary ADT, mo, median (IQR)</td>
<td>40 (18–71)</td>
</tr>
<tr>
<td>Chemotherapy, no. (%)</td>
<td>Docetaxel 35 (100) Cabazitaxel 1 (2.8)</td>
</tr>
<tr>
<td>Duration of chemotherapy</td>
<td>Docetaxel, cycles, median (IQR) 8 (4–12) Cabazitaxel, cycles, median 4</td>
</tr>
<tr>
<td>Duration of abiraterone, mo, median (IQR)</td>
<td>9 (5–13)</td>
</tr>
<tr>
<td>Duration of subsequent enzalutamide, mo, median</td>
<td>4.9</td>
</tr>
</tbody>
</table>

ADT = androgen-deprivation therapy; IQR = interquartile range; LHRH = luteinizing hormone-releasing hormone.

Thirty-five patients were sequentially treated with primary ADT (LHRH analogs, orchiectomy), second-line abiraterone, and third-line enzalutamide.

a Additional treatment after docetaxel chemotherapy.

b Kaplan-Meier estimates.

**Table 2 – Response to androgen-deprivation therapy**

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ADT</td>
<td>Significan response (PSA decline &gt;50%) 33 (94.3) Biochemical progression 2 (5.7)</td>
</tr>
<tr>
<td>Abiraterone in CRPC</td>
<td>Any PSA decline 21 (60.0) PSA decline &gt;30% 17 (48.6) PSA decline &gt;50% 16 (45.7)</td>
</tr>
<tr>
<td>Enzalutamide following abiraterone</td>
<td>Any PSA decline 18 (51.4) PSA decline &gt;30% 13 (37.1) PSA decline &gt;50% 10 (28.6)</td>
</tr>
</tbody>
</table>

ADT = androgen-deprivation therapy; CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen.

![Fig. 2 – Waterfall plot showing the maximum percentage reduction of prostate-specific antigen from baseline in 35 evaluable patients who received abiraterone and subsequent enzalutamide. PSA = prostate-specific antigen.](image-url)
abiraterone (13 of 19 patients [68.4%] vs 4 of 10 patients [40.0%]; \textit{p} = 0.24) and enzalutamide (16 of 19 patients [84.2%] vs 5 of 10 patients [50.0%]; \textit{p} = 0.08).  

### 3.3. Cross-resistance between different types of androgen-deprivation therapy

Two patients (6%) did not show a significant biochemical response (PSA decline >50%) to first-line ADT with luteinizing hormone-releasing hormone analogs and bicalutamide. The tumor of the first patient (Gleason score 9, PSA prior to abiraterone 105 ng/ml) proved to be also resistant to both abiraterone and enzalutamide. The second patient (Gleason score 7, PSA prior to abiraterone 670 ng/ml), although unresponsive to primary ADT, responded very well to second-line therapy with abiraterone (PSA decline of 99%). This patient had a time to progression of 14 mo and a treatment duration of 17 mo. Unfortunately, subsequent therapy with enzalutamide was no longer effective, as shown by PSA progression.

A significant biochemical response (>50% PSA decline) to enzalutamide was observed in 7 of 16 patients who had previously achieved a >50% decline with abiraterone (43.8%). However, only 3 of 19 patients who showed no significant response to abiraterone (15.8%) were sensitive to enzalutamide (\textit{p} = 0.13; Fisher exact test) (Table 3 and Fig. 2).  

### 3.4. Clinical response and survival

Of the 17 patients assessable radiologically, only 1 (2.9%) attained a confirmed partial response. A second patient showed a minor response. Nineteen patients (54.3%) responded clinically to enzalutamide or achieved at least a stabilization of their general condition, six of these 19 patients despite biochemical failure. Mean overall survival (Kaplan-Meier estimate) from the time of enzalutamide treatment initiation to death for the entire group was 7.1 mo (95% CI, 6.2–8.1) (Fig. 3).  

### 4. Discussion

Despite high initial response rates, the benefits from primary ADT are only transitory because of the emergence of CRPC cells in which AR reactivation occurs and tumor cells grow despite subphysiologic levels of circulating testosterone [4,13]. In 2001, Feldman and Feldman [4]
defined several potential pathways to independence from circulating androgens: AR signaling in CRPC cells was characterized by combinations of AR gene amplification, enhanced sensitivity through upregulation of cofactors, increased receptor stability (hypersensitive pathway), AR point mutations broadening the ligand specificity of the receptor (promiscuous pathway), and ligand-independent activation of the AR by peptide growth factor and cytokine signaling pathways (outlaw pathway). In many cases, these pathways act in concert to drive CRPC, suggesting that the AR still remains a key target in novel CRPC therapies.

During the last decade, a more profound analysis of AR signaling led to the identification of two additional mechanisms allowing the AR to circumvent its need for circulating androgens in CRPC: (1) the intracellular synthesis of androgens in PCA cells (steroidogenic pathway) [13] and (2) the formation of C-terminally truncated, constitutively active AR variants (AR-Vs) lacking the ligand-binding domain (LBD) (ARΔLBD pathway) [14–16]. ARΔLBDs are predominantly products of alternative splicing (AR-Vs), but point mutations leading to premature stop codons (eg, AR-Q640X), as well as truncated AR forms as a product of intracellular proteolytic cleavage, have also been described [14,16–18]. Although AR-Vs can be found in normal and benign prostate hyperplasia tissue, they tend to be overexpressed in advanced PCa [15,19].

The pivotal role of the steroidogenic pathway is apparent in daily clinical practice owing to the effectiveness of the oral CYP17A1 inhibitor abiraterone. Fizazi et al. [6] were able to show that abiraterone significantly prolonged overall survival (15.8 mo vs 11.2 mo); 29.5% of patients in the verum arm and only 5.5% of patients in the control arm showed a significant PSA decline. Despite mild toxicity and a good initial response, the median treatment duration was short (8.3 mo).

A second promising new drug is the nonsteroidal high-affinity AR inhibitor enzalutamide [8]. In 2012, Scher et al. [10] published the results of a phase 3 study testing enzalutamide against placebo in CRPC patients after docetaxel failure. Enzalutamide also significantly prolonged survival (18.4 mo vs 13.6 mo); 54% of the enzalutamide group and 2% of the placebo group achieved a serum PSA decline >50%. However, like abiraterone, median treatment duration was short (8.3 mo).

Only few data are available on the sequential application of these treatments. Recently, Loriot et al. [11] published a study in which 38 patients received abiraterone plus prednisone after enzalutamide failure. Twelve patients (32%) had a PSA decrease on abiraterone, but only three patients (8%) achieved a >50% PSA response. The median progression-free survival and overall survival were 2.7 and 7.2 mo, respectively. Among those patients who had failed to achieve a 50% PSA fall on enzalutamide, only one patient (6%) had a subsequent >50% PSA decline on abiraterone.

A similar study was recently presented by Noonan et al. [12] that included 27 patients who received abiraterone after both docetaxel and enzalutamide had become ineffective. In this study, three patients (11%) and one patient (3%) showed a biochemical response of >30% and >50%, respectively. The median duration of abiraterone treatment was only 3 mo in the total population of enzalutamide-pretreated patients. It is interesting to note that again, two of three patients who responded to abiraterone with a PSA decline >30% had previously shown primary resistance to enzalutamide [12].

The present study is the first to analyze the effects of the reverse sequential application, abiraterone followed by enzalutamide. Although the number of patients in our study is relatively small, our data clearly show that enzalutamide is only moderately effective after abiraterone failure. Of the 35 patients in the study, 25 (71.4%) did not respond to subsequent enzalutamide therapy with a PSA decrease >50%. This low response rate indicates high levels of cross-resistance between abiraterone and enzalutamide. Indeed, preliminary in vitro studies suggest that the induction of ARΔLBD is responsible for the rapid development of resistance to abiraterone and enzalutamide in clinical practice. In a PCa xenograft model, Mostaghel et al. [20] demonstrated that abiraterone not only significantly reduces androgen levels in CRPC tissue but also is associated with a rapid increase of ARΔLBD, leading to abiraterone resistance [20]. A similar resistance mechanism involving ARΔLBD has recently been described for enzalutamide [21,22] (Fig. 4). These experimental data are in line with the assumption that in the majority of patients, abiraterone and enzalutamide

![Fig. 4 – Simplified model summarizing all currently known androgen receptor (AR)-dependent mechanisms involved in abiraterone and/or enzalutamide resistance of castration-resistant prostate cancer cells. However, the fact that promiscuous AR mutations and ARΔLBD are not mutually exclusive [14] reveals a more complex interplay between the different resistance mechanisms. LBD = ligand-binding domain.](image-url)
induce resistance mechanisms common to both types of drugs, particularly the enhanced formation of AR-LBD.

However, in our study, three of nine patients had been abiraterone-insensitive and nevertheless responded to enzalutamide. This observation demonstrates that in addition to AR-LBD, there are alternative mechanisms that can lead to abiraterone resistance. Resistance to abiraterone and concomitant response to enzalutamide may, for example, be caused by AR gain of function mutants enabling the AR to be activated by nonandrogenic steroids that do not require CYP17A1 for synthesis (Figs. 1 and 4). This hypothesis is supported by experimental findings showing that, in contrast to abiraterone, enzalutamide is able to inhibit the progesterone-sensitive AR mutant T877A [8,23].

Evaluating the drugs in the reverse sequence (enzalutamide–abiraterone), both Noonan et al. [12] and Loriot et al. [11] demonstrated that few patients may respond to abiraterone even after primary progression while receiving enzalutamide therapy. It is known from previous studies that AR mutations in the LBD can convert steroidal and nonsteroidal antiandrogens such as cyproterone acetate, hydroxyflutamide, or bicalutamide from an antagonist to an agonist [24–27]. In agreement with these data, there is evidence from a recent in vitro study that mutated AR F876L can be activated by enzalutamide in an androgenic manner [28]. It is tempting to speculate that such a mutation could cause enzalutamide resistance in abiraterone-sensitive cases.

Unfortunately, no reliable markers predicting the clinical effectiveness of abiraterone and/or enzalutamide treatment have been identified so far. To perform a more individual-targeted approach directed against the AR, a thorough analysis of AR signaling in circulating tumor cells, as recently initiated by Miyamoto et al. [29], might help to guide therapy in CRPC patients.

Our study has some limitations. It is a small pilot study with a relatively short follow-up and limited information about both primary ADT and potential effects of antiandrogen withdrawal in the patients included. Radiologic progression was not systemically evaluated and thus could not serve as a reliable second parameter of CRPC progression, in addition to effective inhibition of AR signaling. The patients included in this analysis could be a selected group that tended to respond poorly to ADT, since abiraterone has only recently become available. Thus, it could be conjectured that our analysis included predominantly patients who quickly became abiraterone-resistant or were primarily resistant, whereas all patients who responded well to abiraterone still continue the treatment. However, an argument against this assumption is the median abiraterone treatment duration of 9 mo in our patient population, which approximately corresponds to that observed in the phase 3 study that led to approval of the drug for the same indication (7.4 mo) [6].

Our results show that the efficiency and duration of enzalutamide in abiraterone-refractory patients are limited, and only a small subset of patients will experience long-term benefit from a sequential abiraterone–enzalutamide treatment. So far, markers predicting the clinical effectiveness of abiraterone and/or enzalutamide, thereby allowing the initiation or monitoring of the optimal therapeutic sequence, have not been identified. To overcome aberrant AR signaling in CRPC cells, small molecules able to inhibit the AR transactivation domain (common to normal or mutated full-length AR, as well as AR-LBD) are currently being developed [30]. In concert with new markers, these compounds will probably give rise to a more effective new (“third”) generation of antihormonal therapy.

5. Conclusions

Treatment with enzalutamide was associated with a low response rate in patients progressing after abiraterone treatment. Various experimental findings suggest that the expression of AR-LBD mutants or AR-LBD in CRPC might be responsible for the failure of both abiraterone and enzalutamide. Although cross-resistance between abiraterone and enzalutamide is a common phenomenon, it is not inevitable, and a small but significant number of patients can benefit from sequential treatment. Therefore, a more detailed and integrated analysis of AR signaling is necessary.

Author contributions: Andres Jan Schrader had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Boegemann, Krabbe, Schnoecker, Jentzmik, Ohlmann, Hajili, Schrader AJ.

Analysis and interpretation of data: Schrader AJ, Cronauer, Boegemann, Ohlmann, Herrmann.

Drafting of the manuscript: Schrader AJ, Cronauer, Boegemann, Krabbe.

Critical revision of the manuscript for important intellectual content: Cronauer, Schrader M, Herrmann, Stoeckle, Ohlmann.

Statistical analysis: Schrader AJ, Cronauer.

Obtaining funding: Bögemann, Schrader AJ, Ohlmann.

Administrative, technical, or material support: Bögemann, Schrader AJ, Ohlmann, Herrmann.


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References


