

# SEQUENTIAL ANDROGEN RECEPTOR PATHWAY INHIBITOR IN PROSTATE CANCER: PILING-UP THE BENEFITS OR A CASE FOR CROSS-RESISTANCE?

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## ABSTRACT

In the last 10 years, there has been accumulating evidence that, even in a low serum testosterone environment, the androgen receptor (AR) remains the main driver of prostate cancer progression. This has led to the discovery and clinical development of new anti-androgens and androgen biosynthesis inhibitors. Enzalutamide and abiraterone acetate are the lead compounds of this new generation of agents, but multiple other agents are on their way. Because they both target the ligand-dependent regulation of AR activity, it is plausible that cross-resistance may exist when both drugs are used sequentially, and that the benefit of these agents may fade away when sequencing them. As the exact mechanisms for cross-resistance between AR-targeted agents remain unclear at this point, additional clinical studies are crucial to define the exact combination or sequencing order that could yield highest clinical benefits. Moreover, new molecular targets are needed in order to address these resistances, as well as establishing biomarkers to improve patient selection that could most benefit from AR-targeted therapies, but also help develop novel agents to improve and optimise the management of castration-resistant prostate cancer and metastatic, castration-resistant prostate cancer.

Keywords: Enzalutamide, abiraterone, androgen receptor, anti-androgens, cross-resistance.

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## INTRODUCTION

The treatment of metastatic castration-resistant prostate cancer (mCRPC) has been profoundly modified with the discovery of new androgen receptor (AR) pathway inhibitors. Until 2010, docetaxel-based chemotherapy was indeed the only option to improve overall survival (OS) of patients progressing under androgen-deprivation therapy. However, for diverse reasons including age and comorbidities, it appears now that many patients do not receive docetaxel, and more options are needed.<sup>1</sup>

In the last 10 years, there has been accumulating evidence that, even in a low serum testosterone environment, the AR remains the main driver of prostate cancer (PrCa) progression. This has led to

the discovery and clinical development of new anti-androgens and androgen biosynthesis inhibitors (ABIs). Enzalutamide and abiraterone acetate are the lead compounds of this new generation of agents, but many others are on their way (ARN-509, ODM-201, TOK-001).<sup>2-7</sup> In contrast to docetaxel, these new AR pathway inhibitors are orally available and easy to manage with a very favourable toxicity profile. It is not surprising then that these agents have been widely adopted by physicians as soon as they became available. Because they both target the ligand-dependent regulation of AR activity, it is plausible that cross-resistance may exist when both drugs are used sequentially.

Indeed, the development programmes of abiraterone and enzalutamide were conducted quasi in parallel, therefore not addressing that

important question for the clinician. One of the main inclusion criteria of these four pivotal clinical trials, supporting indication approval for either abiraterone or enzalutamide, is that the patients enrolled in the studies could not have previously received the other agent. Enzalutamide has recently been approved by the FDA and EMA in the pre-docetaxel setting,<sup>8,9</sup> similarly to abiraterone, which means that a patient can sequentially receive abiraterone or enzalutamide, then docetaxel, and finally the other one of these two AR-targeted agents. This is an important factor as it means that should a cross-resistance exist, it could not have been unveiled by these trials; this was raised in an editorial by Goldkorn et al.,<sup>10</sup> and up until last year, the issue remained unaddressed.

Understanding the level of cross-resistance between these drugs is crucial for the clinicians but also for regulators and reimbursement authorities. Most importantly, this may severely hamper the development of the newer generation of AR pathway inhibitors. Repeating agent versus placebo in a setting where enzalutamide or abiraterone will be used later is unlikely to produce positive trials as demonstrated by the recent failure of the TAK-700 programme, in which TAK-700 therapy failed due to a high degree of cross-over to abiraterone, enzalutamide, and chemotherapy.<sup>11</sup> To date, there has been no direct head-to-head trial comparing abiraterone and enzalutamide.

While other cross-resistances have also been identified between AR-targeted agents and taxane chemotherapy, this review will investigate the potential mechanisms for cross-resistance between AR-targeted agents and their impact on clinical implications in CRPC and mCRPC management within this therapeutic class.

## THE AR SIGNALLING PATHWAY FOR CRPC

In the last few years, novel agents targeting AR signalling have been developed to address the unmet medical needs generated by CRPC and mCRPC.

### ABIs: Abiraterone Acetate

A few years ago, several research groups demonstrated that, in the absence of exogenous testosterone, PrCa cells were capable of expressing enzymes, encoding androgen-synthesising enzymes, and maintaining intratumoural androgens

at concentrations capable of activating AR target genes, as well as maintaining tumour cell survival. One of these important enzymes is CYP17A1, or 17 $\alpha$ -hydroxylase/17,20 lyase/17,20 desmolase, a key enzyme in the androgen pathway.<sup>12</sup> Abiraterone acetate (Zytiga<sup>®</sup>, Janssen) is the prodrug of abiraterone that is a selective and irreversible inhibitor of CYP17A. Oral administration of abiraterone increases levels of adrenocorticotrophic hormone (ACTH) and steroids upstream of CYP17A, and suppresses serum testosterone, downstream androgenic steroids, and estradiol. Through feedback mechanisms, ACTH increases, potentially resulting in a syndrome of secondary mineralocorticoid excess, hence justifying the association with low-dose daily prednisone.

The Cougar 301 (COU-AA-301) Phase III trial was a pivotal clinical trial conducted in 1,195 mCRPC patients who had failed docetaxel therapy.<sup>13</sup> At the final analysis, with median follow-up of 20.2 months, median OS was 15.8 months for abiraterone/prednisone and 11.2 months for prednisone (HR, 0.74; 95% CI, 0.64-0.86;  $p < 0.0001$ ; [Table 1](#)).<sup>14</sup> These results led to the approval of abiraterone by the FDA in April 2011 and by the EMA in September 2011.

The Cougar 302 (COU-AA-302) trial was conducted in 1,088 mCRPC patients who had not previously received chemotherapy, thus challenging docetaxel as a primary modality.<sup>15</sup> At a median follow-up duration of 27.1 months, radiological progression-free survival (rPFS) was significantly improved from 8.2 months in the prednisone group to 16.5 months in the abiraterone/prednisone group (HR, 0.52; 95% CI, 0.45-0.61;  $p < 0.0001$ ). For the patients, however, one of the most relevant benefits was that abiraterone delayed the time to administration of cytotoxic chemotherapy by 9.7 months (HR 0.61; 95% CI, 0.51-0.72;  $p < 0.0001$ ).<sup>16</sup> When the results were initially released, the predefined endpoints for OS were not met ( $p = 0.01$ ). However, the results were considered strong enough to grant label-extension for pre-chemotherapy clinical settings in December 2012, both by the FDA and the EMA.

The final OS results were released at the latest European Society of Medical Oncology meeting.<sup>17</sup> With median follow-up of 49.4 months at final analysis, abiraterone/prednisone significantly prolonged OS versus prednisone alone (median OS, 34.7 versus 30.3 months; HR, 0.80; 95% CI, 0.69-0.93;  $p = 0.0027$ ).

**Table 1: Main findings from key clinical studies on abiraterone and enzalutamide.**

Study	Population	Active therapy arm containing	Median follow-up	OS (versus comparator arm)	PSA response rate*
COU-AAA-301	1,195 CRPC patients with previous docetaxel therapy	Abiraterone	12.8 months <sup>13</sup>	14.8 versus 10.9 months; HR, 0.65; 95% CI, 0.54-0.77; p<0.001	29% versus 6% in the placebo arm; p<0.0001
			20.2 months <sup>14</sup>	15.8 months versus 11.2 months; HR, 0.74, 95% CI 0.64-0.86; p<0.0001	29.5% versus 5.5 in the placebo arm %; p<0.0001
COU-AAA-302	1,088 mCRPC patients chemotherapy-naïve	Abiraterone	22.2 months <sup>15</sup>	OS was improved with abiraterone-prednisone (median not reached, versus 27.2 months for prednisone alone); HR, 0.75; 95% CI, 0.61-0.93; p=0.01	-
			27.1 months <sup>16</sup>	35.3 versus 30.1 months; HR, 0.79; 95% CI, 0.66-0.95; p=0.0151	-
			49.4 months <sup>15</sup>	34.7 versus 30.3 months; HR, 0.80; 95% CI, 0.69-0.93	-
Loriot et al. <sup>30</sup>	38 mCRPC patients who had received treatment with docetaxel and enzalutamide in the AFFIRM trial	Abiraterone	-	-	8% (triple sequential therapy) and 29% (abiraterone without prior enzalutamide)
Noonan et al. <sup>31</sup>	30 patients with progressing disease following treatment with docetaxel and enzalutamide	Abiraterone	-	11.8 months (Cougar 301 study, 14.8 months)	3% (triple sequential therapy) and 60% (enzalutamide only)
AFFIRM <sup>20</sup>	1,199 CRPC patients with previous docetaxel therapy	Enzalutamide	14.4 months	18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR, 0.63; 95% CI, 0.53-0.75; p<0.001)	54% versus 2% in the placebo arm, p<0.001
PREVAIL <sup>21</sup>	1,717 mCRPC patients chemotherapy-naïve	Enzalutamide	49.4 months	-	78% versus 3%; p<0.001

Table 1 continued.

Study	Population	Active therapy arm containing	Median follow-up	OS (versus comparator arm)	PSA response rate*
Schrader et al. <sup>33</sup>	35 mCRPC patients who had received abiraterone and received enzalutamide after failure	Enzalutamide	-	-	43.8% (patients who were initially abiraterone-sensitive) and 15.8% (patients who were initially abiraterone-insensitive) versus 45.7% (abiraterone only)

\*PSA response rate: proportion of patients with a decrease of  $\geq 50\%$  in the PSA concentration from baseline.

CI: confidence interval; HR: hazard ratio; (m)CRPC: (metastatic) castration-resistant prostate cancer; OS: overall survival; PSA: prostate-specific antigen.

## Second-Generation AR Antagonist: Enzalutamide

Enzalutamide (Xtandi®, Medivation and Astellas Pharma) is a second-generation nonsteroidal anti-androgen that retains activity in the setting of increased AR expression, one of the most common features of mCRPC.<sup>18,19</sup> In contrast to abiraterone, enzalutamide does not require steroid protection, so a placebo was chosen as the comparator in the clinical trials. Consequently, this hampers the comparison between the relative benefit of abiraterone and enzalutamide versus their chosen comparator.

The FDA approved enzalutamide in August 2012 following the promising results of the Phase III AFFIRM trial.<sup>20</sup> The study was conducted in 1,199 CRPC patients who had previously failed chemotherapy treatment with docetaxel. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR, 0.63; 95% CI, 0.53-0.75;  $p < 0.001$ ). A subsequent Phase III clinical trial, the PREVAIL study,<sup>21</sup> aimed to evaluate the efficacy and safety of enzalutamide in 1,717 mCRPC patients who were chemotherapy-naïve. Median OS (risk of death, HR=0.71;  $p < 0.0001$ ) was significantly improved in the enzalutamide group compared with placebo. This trial led to an extension of indication in chemotherapy patients by the FDA and the EMA, in September and October 2014 respectively.<sup>8,9</sup>

As for abiraterone, the main benefit of enzalutamide in chemotherapy-naïve patients is to delay radiographic progression and time to chemotherapy. At 12 months, median rPFS was not reached in the enzalutamide group, as compared with 3.9 months in the placebo group; the rate of rPFS was significantly improved in the enzalutamide group compared to the placebo group (65% versus 14%; HR, 0.19; 95% CI, 0.15-0.23;  $p < 0.001$ ). The median time to initiation of cytotoxic chemotherapy was 28.0 months in the enzalutamide group, as compared with 10.8 months in the placebo group (HR 0.35; 95%CI, 0.3-0.40;  $p < 0.001$ ).<sup>21</sup>

### THE POTENTIAL FOR CROSS-RESISTANCE AMONG ANDROGEN-BLOCKING AGENTS

#### Molecular Evidence of Cross-Resistance between Anti-Androgens and Steroidogenesis Inhibitor

The most prominent rationale for enzalutamide resistance is the F867L mutation, a missense mutation in the ligand-binding domain of the AR receptor, which acts like an antagonist-to-agonist switch, thus converting enzalutamide into an AR agonist in preclinical models.<sup>22,23</sup> Furthermore, the AR F876L mutant encoding DNA was found in the plasma of patients progressing on ARN-509, a novel AR antagonist.<sup>23</sup>

Efstathiou et al.<sup>24</sup> recently reported the results of a very interesting prospective Phase II study on bone marrow biopsies of 60 mCRPC patients, obtained before and after 8 weeks of treatment with enzalutamide. In most patients, enzalutamide was effective in blocking nuclear translocation of AR, but interestingly enough, testosterone increased following 8 weeks of treatment in the majority of patients with evaluable paired samples in both blood (40 of 51, 78%) and bone marrow aspirate plasma (34 of 44, 77%). This suggests an adaptive physiologic feedback mechanism that could contribute to enzalutamide resistance.

In a previous work by Efstathiou et al.,<sup>25</sup> conducted in a cohort of 57 patients with CRPC, the same group showed that abiraterone depleted blood and bone marrow aspirate testosterone, the latter remaining suppressed at progression, thus indicating the strong action of abiraterone in inhibiting intratumoural production of androgen. The authors suggested that in patients progressing in the presence of a depleted environment, persistent androgen signalling could be explained by native ligand-independent mechanisms or by altered steroid biosynthesis.

While it is still unclear what drives resistance to abiraterone, preliminary results show that it could be explained by the reactivation of intratumoural androgen synthesis through upregulation of CYP17A1 transcripts, or other transcripts encoding enzymes involved in androgen synthesis within tumour cells. Other investigated mechanisms include the involvement of the glucocorticoid receptor<sup>26</sup> and the induction of AR splice 7 variant with a ligand-independent AR transactivation ability, as detected in circulating tumour cells from CRPC patients with resistances to enzalutamide or abiraterone.<sup>27-29</sup>

### **Current Clinical Evidence for Cross-Resistance between Abiraterone and Enzalutamide**

#### **Abiraterone therapy following docetaxel plus enzalutamide treatment**

Loriot et al.<sup>30</sup> reported the results of a French study evaluating the efficacy and safety parameters of abiraterone in 38 mCRPC patients following treatment with docetaxel and enzalutamide in the context of the AFFIRM trial (triple sequential therapy arm).<sup>20</sup> The control arm (n=16) comprised patients from this trial who had been originally assigned to the placebo arm, which means they

received abiraterone without prior enzalutamide. Main results revealed that patients who had received both active therapies had shorter and poorer responses than patients who had only received abiraterone. Median PFS was 2.7 and 6.5 months in the triple sequential therapy arms and the control arm, respectively. Similar results were observed in terms of median OS (7.2 and 11.4 months, respectively), prostate-specific antigen (PSA) response >30% (18% and 36%, respectively), and PSA response >50% (8% and 29%, respectively) decrease from baseline.

In a Canadian study, Noonan et al.<sup>31</sup> also evaluated 30 patients receiving abiraterone for progressing disease following treatment with docetaxel and enzalutamide. Median PFS (time to progression [TTP]) with abiraterone was 3.6 weeks (Cougar 301 study, 5.6 months), while median OS was 11.8 months (Cougar 301 study, 14.8 months).<sup>13</sup> PSA responses as >30% and >50% decreases from baseline were 11% and 3%, respectively (Cougar 301 no available data, and 29%, respectively).

Both of these studies highlighted the fact that abiraterone therapy following docetaxel and enzalutamide could be associated with shorter and poorer responses to therapy, as well as weaker PSA responses. While the safety of abiraterone following enzalutamide appears to be acceptable, the underlying mechanism to explain poorer responses for sequential use of novel therapies could be acquired cross-resistances. However, larger cohort data are required to firmly establish a link between prior enzalutamide therapy and abiraterone resistance, as these studies lacked in statistical power and presented selection bias. In the meantime, these findings are the only clinical data that physicians can rely on to select and choose appropriate therapy for mCRPC.

#### **Enzalutamide therapy following docetaxel plus abiraterone treatment**

As abiraterone was approved sooner than enzalutamide, a large majority of patients received sequential enzalutamide following abiraterone in the context of expanded-access programmes and compassionate use, and were therefore involved in many clinical studies. The clinical benefits and safety of enzalutamide in patients with mCRPC (n=61) who failed docetaxel and abiraterone therapy were evaluated in a retrospective study.<sup>32</sup> Enzalutamide had a modest clinical activity, as demonstrated by a median PFS of 12.0 weeks.



Median time to PSA progression was 17.4 weeks and the OS was 31.6 weeks. The safety profile of enzalutamide was consistent with those of previous clinical trials.

In a retrospective study conducted at a German centre, 35 mCRPC patients who had received abiraterone for a median duration of 9.0 months were evaluated.<sup>33</sup> 45.7% of them had achieved a  $\geq 50\%$  PSA decline. Then, after failure of abiraterone, they received enzalutamide for a median duration of 4.9 months. Enzalutamide achieved a modest response, with 43.8% of the patients who were initially abiraterone-sensitive and 15.8% of patients who were initially abiraterone-insensitive having a  $\geq 50\%$  PSA decline. Median TTP was 4.0 months among patients with at least one declining PSA value while taking enzalutamide. A similar retrospective study in the UK also suggested limited activity for enzalutamide as second-line in mCRPC (n=39) following failure of abiraterone and docetaxel therapy.<sup>34</sup> 41% of patients achieved a  $\geq 30\%$  PSA decline and, among patients who were refractory to abiraterone, only 9% of patients achieved a  $\geq 50\%$  PSA decline with enzalutamide.

At the 2014 Genitourinary Cancers Symposium held on 30<sup>th</sup> January-1<sup>st</sup> February, 2014 in San Francisco, USA, many new findings were made available on this pathway. Roeder et al.<sup>35</sup> presented the results of a study on 24 mCRPC Danish patients who received enzalutamide following disease progression with docetaxel and abiraterone in the setting of a compassionate use program. Median OS (minimum follow-up of 3 months) was 4.8 months, 46% of patients had a PSA response  $>30\%$  decrease from baseline, and the best median PSA response was -22%. These results were less marked than those in the AFFIRM study,<sup>20</sup> therefore being consistent with the possibility of a cross-resistance for this sequential order as well. At the same meeting, Cheng et al.<sup>36</sup> presented the results of a retrospective study on 195 mCRPC patients from 7 centres. A marked difference was observed in terms of PSA response as 39% of previously treated patients with abiraterone experienced a  $\geq 30\%$  PSA decline, compared to 55% of abiraterone-naïve patients (odds ratio 2.3; 95% CI 1.0-5.5; p=0.06).

A retrospective study from 7 UK centres evaluated the sequential use of enzalutamide following abiraterone and taxane chemotherapy failure in 79 mCRPC patients.<sup>37</sup> Preliminary results revealed a TTP for abiraterone of 37.44 weeks and a TTP

of 15.87 weeks for enzalutamide (at the time of the abstract presentation, 55% of patients had discontinued enzalutamide therapy because of disease progression). In another study, 23 mCRPC patients received enzalutamide therapy as part of an expanded access programme, following failure to docetaxel and abiraterone therapy.<sup>38</sup> Median biological PFS was 11.9 weeks, while 39% of patients showed enzalutamide sensitivity, as defined by a PSA response  $>50\%$  decrease from baseline.

A Canadian study reviewed the cases of 26 patients with mCRPC and who received the same sequential therapy.<sup>39</sup> 27% of patients had a PSA response  $>50\%$  decrease from baseline, and an additional 27% had a PSA response  $>30\%$  decrease from baseline. Median time to treatment failure was 4.9 months. A retrospective chart review was conducted on 63 patients progressing on abiraterone and docetaxel, in order to determine the PSA response rates of enzalutamide.<sup>40</sup> After a median follow-up of 12.5 weeks,  $\geq 30\%$  PSA decline was observed in 29% of patients.

At the 2014 American Society of Clinical Oncology Annual Meeting held 30<sup>th</sup> May-3<sup>rd</sup> June in Chicago, USA, Zhang et al.<sup>41</sup> presented the results of a prospective study conducted at Duke University on mCRPC patients (n=20) who had received pre-chemotherapy abiraterone, and then went on to receive either enzalutamide or docetaxel therapy. Median PFS was 3.6 and 5.1 months for the enzalutamide and docetaxel groups, respectively. Median OS was 8.5 months for the enzalutamide group, while the median OS for the docetaxel was not reached. A  $\geq 50\%$  PSA decline was observed in 12.5% and 50% of patients, respectively. These findings also highlight the high probability for cross-resistance between both novel agents, while confirming the higher additional radiographic and clinical benefits of docetaxel following first-line abiraterone.

## The Current Consensus on Sequential Monotherapy

In April 2014, a European Expert Consensus Panel<sup>42</sup> published some recommendations on the management of mCRPC, including guidance in the selection and sequencing of available therapeutic options. The advisors worked according to a modified Delphi method; a strong consensus (90% of the votes) was made as the advisors agreed on the fact that there are cross-resistances between

approved AR-targeted agents, and that patients with disease progression on either abiraterone or enzalutamide should not be prescribed the other novel agent (85-86% agreed) due to cross-resistance, or should be prescribed the novel agent only if a 'durable' response to the first agent had occurred (76% agreed).

## CONCLUSION

As the exact mechanisms for cross-resistance between AR-targeted agents remain unclear at

this point, additional clinical studies are crucial to define the exact combination or sequencing order that could yield highest clinical benefits. Moreover, new molecular targets are needed in order to address these resistances, as well as establishing biomarkers to improve patient selection that could most benefit from AR-targeted therapies but also help develop novel agents to improve and optimise the management of CRPC and mCRPC.

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