Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100)

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Background: Androgen receptor (AR) signalling remains critically important in metastatic castration-resistant prostate cancer (mCRPC) as confirmed by recent phase III trials, showing a survival advantage for abiraterone acetate and enzalutamide (MDV3100). The antitumour activity of abiraterone and prednisolone in patients pre-treated with enzalutamide is as yet unknown.

Patients and methods: We investigated the antitumour activity of abiraterone and prednisolone in patients with mCRPC who had progressed following treatment with docetaxel (Taxotere) and enzalutamide. Clinical data were retrospectively analysed for prostate-specific antigen (PSA) and RECIST responses, clinical benefit and survival.

References

Results: Thirty-eight patients were included in the analysis. The median age was 71 years (range 52–84); metastatic sites included bone disease in 37 patients (97%), lymph nodes in 15 patients (39%) and visceral disease in 10 patients (26%). Abiraterone was well tolerated. Three patients (8%) attained a PSA response, defined as ≥50% decline in PSA confirmed after ≥4 weeks, while seven patients (18%) had a ≥30% PSA decline. The median progression-free survival (PFS) was 2.7 months (95% CI 2.3–4.1). Of the 12 patients assessable radiologically, only 1 (8%) attained a confirmed partial response.

Conclusion: Abiraterone and prednisolone have modest antitumour activities in patients with mCRPC pretreated with docetaxel and enzalutamide.

Key words: CRPC, enzalutamide; abiraterone, hormonal manipulations

introduction
Prostate cancer is the most prevalent cancer in men in the western world and the second leading cause of male cancer-related deaths [1, 2]. Several studies have now confirmed that androgen-based pathways and androgen receptor (AR) signalling remain key drivers in metastatic castration-resistant prostate cancer (mCRPC), including the recent clinical studies of abiraterone, enzalutamide [3, 4] and other compounds in development [5].

Abiraterone is a potent and selective small-molecule inhibitor of CYP17A1 (cytochrome P450 17 α-hydroxysteroid dehydrogenase), a key enzyme for androgen and oestrogen synthesis. The recently reported phase III trial in men who had previously received docetaxel (Taxotere) reported a 4.6-month improvement in overall survival (OS) for patients receiving 10 mg prednisone daily and abiraterone when compared with prednisone alone [6, 7]. A PSA decline ≥50% was achieved in 29% patients treated with abiraterone and the median progression-free survival (PFS) was 5.6 months. Abiraterone is now an approved agent for the treatment of docetaxel-pretreated mCRPC patients.

Enzalutamide is a specific inhibitor of the AR, blocking testosterone binding to the AR, impeding nuclear translocation and inhibiting AR binding to DNA [4, 8]. In the phase III AFFIRM trial, 1199 men with CRPC who had received prior docetaxel-based chemotherapy were randomly assigned to either enzalutamide (160 mg/day) or placebo. Based upon a planned interim analysis after 520 deaths, OS, the primary end point of the trial, was significantly increased in patients assigned to enzalutamide (median 18.4 versus 13.6 months, hazard ratio 0.63) [9].

However, we still need to fully determine the optimal way of using these novel agents. Abiraterone and enzalutamide target androgen signalling pathways albeit through different mechanisms of action; therefore, common mechanisms of resistance may occur. However, data with regard to the efficacy of abiraterone treatment in patients previously treated with enzalutamide have not been reported yet. This study aims to provide the first data on the question of clinical efficacy and tolerability of abiraterone and prednisolone treatment in patients previously treated with docetaxel, prednisolone and enzalutamide.

patients and methods
eligible population
Patients with mCRPC enrolled in the phase III clinical study AFFIRM [9] at the Institut Gustave Roussy (IGR) and the Royal Marsden NHS Foundation Trust (RM) were identified and their records accessed through the respective hospital electronic databases (supplementary Figure S1, available at Annals of Oncology online). Using information available following study unblinding, patients who received enzalutamide were identified. Patients with disease progression on enzalutamide who subsequently received abiraterone were selected for final analysis. All patients enrolled in the phase III AFFIRM study had castrate levels of testosterone and medical castration was maintained during subsequent therapies.

study procedures
Initiation of treatment with abiraterone followed standard clinical practice guidelines, including the requirement for adequate haematological, hepatic and renal function. Abiraterone was given orally at 1000 mg once daily, co-administered with 5 mg prednisone bid. Clinical and biological tolerance was assessed monthly, and all grade 3 and grade 4 toxicity events were recorded. PSA response was evaluated every month using the Prostate Cancer Working Group 2 (PCWG2) criteria [10]. As recommended by the PCWG2, PSA response was defined as ≥50% decline from baseline and PSA progression as a 25% increase (and a minimum of 2 ng/ml), confirmed with a second PSA reading a minimum of 3 weeks later. PSA declines of <30% and 50% from baseline with or without confirmation were also evaluated. Progression was defined as either PSA progression, radiographic progression, clinical progression or a combination of the above.

Objective responses were measured according to RECIST [11]. Bone progression based on bone scans was assessed according to the PCWG2 criteria

PFS was estimated from the time of treatment start to the date of confirmed progression or the date of last follow-up. OS was calculated from the date of start of abiraterone treatment to the date of death or date of last follow-up. Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 3.0.

statistics
Descriptive statistical methods were pursued. In line with PCWG2 criteria, waterfall plots with maximum PSA change were constructed. Survival and progression were calculated using Kaplan–Meier estimates and compared using a log-rank test. Patients who did not achieve a 50% fall in PSA on enzalutamide were designated enzalutamide-non-sensitive, and patients with a ≥50% decline in PSA on enzalutamide were designated enzalutamide-sensitive. Statistical analysis was used to test the null hypothesis that response to abiraterone in previously enzalutamide-non-sensitive patients was 29%, equal to the observed proportion in enzalutamide-naïve patients [6]. Statistical analyses were conducted using the R statistical software.
enzalutamide within the AFFIRM phase III clinical trial at IGR and RM. At the time of analysis (July 2012), nine patients continued with enzalutamide. Among the 95 patients who stopped enzalutamide, 38 patients subsequently received abiraterone (1000 mg/day) plus prednisone (10 mg/day). Ten patients had received prednisone before or during enzalutamide therapy. The characteristics of the latter 38 patients are reported in Table 1. The median age before starting abiraterone was 71 years (range 52–84 years) and the majority of patients had bone-only metastases. The median duration of enzalutamide therapy was 8 months (range 1–24). Seventeen patients (45%) who did not have a 50% decline in PSA on enzalutamide were designated as enzalutamide-sensitive. Overall, the median value of maximal PSA change on enzalutamide was −55% (range −100, +40) (supplementary Figure S2, available at Annals of Oncology online). On enzalutamide 24 (63%) and 21 patients (55%) had achieved a ≥30% and ≥50% PSA decline, respectively. Eight patients (21%) discontinued enzalutamide within the first 3 months for progressive disease. Thirty-three patients (84%) progressed by PSA while on enzalutamide, two patients had solely evidence of radiological disease progression and four had solely clinical progression. Only 4 patients out of 38 were rechallenged with docetaxel before starting abiraterone. One patient received cabazitaxel before abiraterone.

Table 1. Patients’ characteristics

<table>
<thead>
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<th>Patients’ characteristics</th>
<th>Number of patients (%)</th>
</tr>
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<tr>
<td>Age</td>
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<tr>
<td>Median</td>
<td>71</td>
</tr>
<tr>
<td>Range</td>
<td>52–84</td>
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<tr>
<td>Gleason score</td>
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<td>≤6</td>
<td>3 (8)</td>
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<tr>
<td>=7</td>
<td>13 (34)</td>
</tr>
<tr>
<td>≥8</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Not available</td>
<td>8 (21)</td>
</tr>
<tr>
<td>PS score</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>26 (68)</td>
</tr>
<tr>
<td>≥2</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Not available</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (58)</td>
</tr>
<tr>
<td>Not available</td>
<td>2 (5)</td>
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<tr>
<td>Bone metastasis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Yes</td>
<td>37 (97)</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (74)</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (26)</td>
</tr>
<tr>
<td>PSA (µg/l)</td>
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<td>Median</td>
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<td>Range</td>
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<td>Haemoglobin (g/dl)</td>
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<td>Albumin (g/l)</td>
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<tr>
<td>Median</td>
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<td>Range</td>
<td>20–45</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; PSA, prostate-specific antigen.

Figure 1. Maximum PSA change on abiraterone.

Abiraterone antitumour activity post-enzalutamide

Abiraterone was started mainly for PSA progression (in 37 patients, 97%), for clinical progression (in 19 patients, 50%) and for progression on bone imaging (in 14 patients; 37%). The median duration on abiraterone was 3 months (range 1–13). Overall, a ≥50% PSA fall in abiraterone was observed in three patients (8%, 95% confidence interval (CI): 2% to 21%). A ≥30% PSA decline in abiraterone was observed in seven patients (18%, 95% CI 8% to 34%) (Figure 1). Out of 38 patients, 31 patients had progression at the time of analysis. Among these 31 patients, 27 had PSA progression, 19 a clinical progression, 13 a bone progression and 8 patients had PD by a RECIST criteria progression. The median PFS was 2.7 months (95% CI 2.3–4.1) (Figure 2A). The median OS was 7.2 months (95% CI 5.0–NR) (Figure 2B).

Among the 17 patients (45%, Table 2) who failed to achieve a 50% PSA fall on enzalutamide, only one patient had a subsequent ≥50% PSA decline on abiraterone (6%, 95% CI: 0% to 29%). Of the remaining 21 patients who had a ≥50% PSA decline with enzalutamide (55%, Table 2), 2 had a ≥50% PSA decline with abiraterone (10%, 95% CI: 1% to 30%) and 19 did not (90%) (supplementary Figure S3, available at Annals of Oncology online). The PSA response rates (≥50% decline in PSA) were 8% (95% CI 2% to 21% for abiraterone).
Furthermore, the >50% PSA response rate on abiraterone in patients having discontinued enzalutamide within 3 months (1/8, 13%, 95% CI 0% to 53%) was not significantly different from the PSA response on abiraterone observed in patients treated with enzalutamide >3 months (2/30, 7%, 95% CI 1% to 22%; P = 0.52, Fisher’s exact test). The null hypothesis that response to abiraterone in previously enzalutamide-treated patients is 29% was rejected with significance (two-sided P = 0.003455, exact binomial test). Of the 12 patients assessable radiologically, only 1 (8%) attained a confirmed partial response.

Among patients treated with placebo, 16 patients (36%) received abiraterone. The PFS was 6.5 months (95% CI 3.7–19.4) and the OS was 11.4 months (95% CI 7.3 – NR).

A PSA decline of ≥30% and ≥50% was observed in 5 (36%) and 4 (29%) out of 14 assessable patients, respectively.

**abiraterone tolerability post-enzalutamide**

Abiraterone was overall well-tolerated with no unexpected toxicity. The majority of reported side-effects were grade 1 and 2. One patient developed grade 2 hot flushes and one patient reported grade 1 loss of memory. One patient required discontinuation of abiraterone–prednisone due to oedema and hypokalaemia.

**discussion**

To our knowledge, this is the first study reporting the antitumour efficacy of abiraterone following progression on enzalutamide in patients with mCRPC using PSA-based and survival criteria. We have shown that in 38 patients progressing on enzalutamide, abiraterone resulted in ≥50% PSA declines in only 3 patients (8%, 95% CI 2% to 21%) and a median PFS of 2.7 months (95% CI 2.3–4.1). These results are lower than those expected from the COU-AA-301 study of post-docetaxel abiraterone, suggesting the possibility of cross-resistance between abiraterone and enzalutamide [6, 7]. Although our data are consistent with those reported by Noonan et al. [12], we cannot recommend to use abiraterone after resistance to enzalutamide so far because our data are only hypothesis-generating and warrant further specific studies.

Only a few studies have reported insights into the mechanisms of potential cross-resistance between abiraterone and enzalutamide. A recent preclinical study on human CRPC xenografts treated with abiraterone demonstrated that resistance to abiraterone and enzalutamide may occur through mechanisms that include induction of AR and AR splice variants that confer ligand-independent AR transactivation [13–14].

Cross-resistance might also involve steroidogenesis activation as preclinical data support the role of steroidogenesis as a mechanism of resistance to enzalutamide [15]. A recent study also showed an increase in bone marrow (BM) testosterone in patients treated with enzalutamide [16]. Plasma and BM testosterone and plasma dihydrotestosterone (DHT) assessed by mass spectrometry were consistently increased after 8 weeks of enzalutamide when compared with baseline levels. Similar data were observed with abiraterone in some preclinical models.
of abiraterone-resistant CRPC [13, 17]. In a clinical study aimed to evaluate testosterone and DHT in blood and BM of 58 patients with CRPC treated with abiraterone, BM aspirate and blood DHT were undetectable on treatment discontinuation but pretreatment BM aspirate DHT was undetectable in the BM and blood too in most samples [18]. This selection for tumour cells with activation of steroidogenesis in response to abiraterone or enzalutamide treatment indicates that steroid production may provide a growth advantage and could be a contributing mechanism for both abiraterone and enzalutamide resistance. The lack of significant biochemical activity with abiraterone and prednisolone following enzalutamide progression does, however, indicate that increased steroidogenesis alone is unlikely to be the sole mechanism of resistance to enzalutamide. The agonistic activity of iatrogenic prednisone/prednisolone on promiscuous AR variants needs to be further evaluated as one potential resistance mechanism [15].

Ligandless activation of AR by oncogenic pathways such as phosphatidylinositol 3-kinases (PI3K)-AKT signalling pathway may represent an alternative mechanism of resistance as several studies have demonstrated crosstalk between the AR pathway and PI3K signalling in prostate cancer models [19]. Several phase I/II trials assessing the combination of either abiraterone or enzalutamide plus PI3K/AKT/TOR inhibitors are now ongoing.

Concomitant treatment with enzalutamide and abiraterone might be more clinically useful than the sequential use of abiraterone followed by enzalutamide or vice versa to reverse some mechanisms of drug resistance. Clinical data on the antitumour activity of enzalutamide after progression on abiraterone are not yet available so far, but may further guide the optimal sequencing of these agents.

The lower antitumour activity of abiraterone following enzalutamide may result from patients having a more advanced disease in our study when compared with enzalutamide-naïve patients. However, an imbalance in most clinical or biological prognostic factors was not observed when considering the COU-AA-301 cohort. Although the baseline median PSA was lower in the COU-AA-301 cohort than in our study (129 compared with 232 ng/ml) and the Eastern Cooperative Oncology Group performance status (ECOG PS) was poorer in our cohort (10% versus 29%), other prognostic features (haemoglobin, ALP, LDH, albumin, visceral disease) were similar. Furthermore, this would not explain the lack of impact of abiraterone on PSA, a pharmacodynamic measure of AR signalling blockade in prostate cancer. Among patients treated with placebo who further received abiraterone, PSA response and PFS were much better than that of enzalutamide-treated patients supporting the hypothesis of cross-resistance between enzalutamide and abiraterone. However, in our pooled database, nine enzalutamide responders were excluded because they remained on therapy. These patients might have a molecular phenotype supportive of response to another AR-directed therapy. Their inclusion may have increased the PSA response to abiraterone in the group of enzalutamide-treated patients closer to the postulated 29% observed in COU-AA-301. Docetaxel exposure might also affect the response to abiraterone as some studies suggested cross-resistance between taxanes and AR-directed therapy [20]. A retrospective study has also supported the hypothesis of cross-resistance between docetaxel and abiraterone with lower than expected PSA response rate observed in patients treated with docetaxel following abiraterone [21]. However, a recent retrospective study reported a high response rate to cabazitaxel in patients previously treated with docetaxel and abiraterone [22]. Taken together, these data underscore the need for a thorough evaluation of sequence administration to design rational clinical trials, as well as the development of personalized medicine protocols based on the genomic analyses of tumour cells.

In conclusion, this study indicates that abiraterone has modest antitumour activity in patients with mCRPC pretreated with docetaxel and enzalutamide in both enzalutamide-refractory and -sensitive subgroups. This suggests that blockade of increased hormone synthesis alone post-enzalutamide imparts limited clinical benefit. Further prospective evaluation of these agents administered in combination is now warranted.

**Disclosure**

YL: Consultant, Entity: Sanofi-Aventis, Relationship: Myself, Compensation: Compensated

Honoraria, Entity: Sanofi-Aventis, Relationship: Myself, Research Funding, Entity: Astellas, Relationship: Myself

DB, EI, SS, AP, CP: none

CP: Employment or Leadership Position, Entity: ICR, Relationship: Myself, Title/Role Held: Employee, Compensation: Compensated

LA: Consultant or Advisory Role; Entity: Astellas; Relationship: Myself; Compensation: Compensated, Entity: Sanofi-Aventis, Relationship: Myself, Compensation: Compensated

GA: Consultant or Advisory Role, Entity: Janssen, Relationship: Myself, Compensation: Compensated

Honorary, Entity: Janssen, Relationship: Myself, Entity: Sanofi-Aventis, Relationship: Myself

Other Remuneration, Entity: I am on The ICR rewards to inventors list of abiraterone acetate; Relationship: Myself

KF: Consultant or Advisory Role; Entity: Astellas, Relationship: Myself, compensation: Compensated

EI: Consultant or Advisory Role, Entity: Janssen, Relationship: Myself

SS: Consultant or Advisory Role, Entity: Janssen, Relationship: Myself

AP: Consultant or Advisory Role, Entity: Janssen, Relationship: Myself

CM: Consultant or Advisory Role, Entity: Sanofi-Aventis, Relationship: Myself, Compensation: Compensated

Honoraria, Entity: Sanofi-Aventis, Relationship: Myself, Compensation: Compensated

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