Optimizing the sequence of metastatic castration-resistant prostate cancer treatment options

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Chapter 2

Clinical activity and Tolerability of Enzalutamide (MDV3100) in Metastatic Castration Resistant Prostate Cancer Patients progressing after Docetaxel and Abiraterone Treatment

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ABSTRACT

Background

Both Enzalutamide (Enz) and Abiraterone acetate (AA) are hormonal treatments, which have shown survival advantage in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with docetaxel (Doc). Recently limited activity of AA after Enz treatment was shown, however, there are no clinical data on the activity of Enz in patients progressing after AA and Doc treatment.

Methods:

The efficacy and tolerability of Enz in men with progressive metastatic castrate resistant prostate cancer previously treated with Doc and AA was investigated. Toxicity and progression free survival (PFS), time to PSA progression (TTPP) and overall survival (OS), were retrospectively evaluated.

Results

Sixty-one patients were included in the analysis. The median age was 69 years (IQR 64-74), 57 patients (93%) had an ECOG performance status 0-2, 48 patients (79%) had bone metastases, 33 patients (54%) had lymph-node metastases and 13 (21%) visceral metastases. Median duration of Enz treatment was 14.9 weeks (IQR 11.1 – 20.0) and 13 patients (21%) had a maximum PSA decline of ≥50%. The median PFS was 12.0 weeks (95% CI 11.1 – 16.0), the median TTPP 17.4 weeks (95% CI: >16.0) and median OS 31.6 weeks (95% CI: > 28.7). Enz was well tolerated, with fatigue and muscoskeletal pain as the most frequent ≥grade 2 adverse events. PSA response on Doc and AA did not predict for PSA response on Enz.

Conclusions

Enz has modest clinical activity in mCRPC patients previously treated with Doc and AA.

INTRODUCTION

Prostate cancer is the most prevalent cancer among men in the western world and the second leading cause of male cancer death [1, 2]. After an initial response to medical or surgical castration, the disease will progress into castration resistant prostate cancer (CRPC)[3]. CRPC, however, is still driven by androgen-receptor signaling, requiring lower than castration testosterone levels as a result of androgen receptor modulations [4-6]. Therefore, new drugs have been developed that more effectively inhibit androgen receptor signaling. Enzalutamide (Enz, MDV3100, Xtandi®), a novel nonsteroidal androgen-receptor (AR) signaling inhibitor, has shown survival advantage in metastasized CRPC (mCRPC) patients previously treated with Docetaxel (Doc) in combination with prednisone [7]. However, earlier, Abiraterone Acetate (AA, Zytiga®), an inhibitor of testosterone synthesis, has shown a comparable survival advantage in combination with prednisone in the same patient population [8]. It is suggested that Enz and AA actions are non-overlapping and therefore potentially synergistic [9]. However, only limited activity of AA was described in two cohort studies of patients previously treated with Enz [10, 11]. Reversely, there is no data on the antitumor activity of Enz following AA treatment in mCRPC patients. Knowledge of the clinical cross-resistance in both sequences of these anti-hormonal treatments is of value for future trial design.

Pending final registration of Enz in The Netherlands, Astellas Pharma Europe Ltd. established an Expanded Access Program (EAP) for patients with progressive disease and no satisfactory alternative treatments available. Therefore, Enz treatment was positioned after Doc and AA treatment. Here we report tolerability and efficacy of Enz in a cohort of mCRPC patients previously treated with Doc and AA.

PATIENTS AND METHODS

Patients and treatment

In this multicenter, observational study, we included patients with progressive mCRPC enrolled in the Dutch EAP for ENZ, treated earlier with Doc and AA. Patients all progressed on or did not tolerate AA treatment and consented to join the program. Inclusion criteria for the EAP included: effective surgical or medical castration, progressive disease, ECOG performance 0-2 and no satisfactory alternative treatment at the physician's discretion. The exclusion criteria of the EAP included: earlier treatment with- or participation in a clinical trial with ENZ, severe concurrent disease, inadequate bone marrow, liver, vascular, hart and kidney functions and prior chemotherapy, biologic therapy or radiation therapy within 3 weeks prior to treatment and radionucleotides treatment 8 weeks prior to treatment.

Enz was given as a once daily dose of 160 mg. All patients received at least one dose of Enz. Treatment was continued until clinical deterioration, disease progression and/or unacceptable adverse effects, all to physician discretion, or death.

Study procedures and data collection

Patient baseline characteristics were documented including age, ECOG performance status, disease characteristics (including Gleason score, involved metastatic sites, number of metastatic sites), blood test results (including hemoglobin concentration, liver chemistry tests, creatinine, testosterone and PSA), clinical signs of disease progression, previous anti-hormonal and chemotherapy treatments (including duration of Doc and AA treatment, best PSA response to Doc and AA treatment and reason for AA discontinuation) and use of concomitant medication with known interaction with Enz (macrolide antibiotics, benzodiazepines, immune modulators, anti-epileptics, coumarins, colchicine, digoxin).

Clinical and biochemical activity and toxicity, was assessed at Enz treatment initiation and every month according to the EAP protocol, including ECOG performance and toxicity recording using Common Toxicity Criteria (CTC v 4.0). Imaging studies were performed at the discretion of the physician. Prostate cancer progression and survival were followed up until April 2013.

PSA response was evaluated using the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations [12]. Progression Free Survival (PFS) was defined as the time of treatment start to the first date of confirmed progression or the date of last follow-up. Progression was defined as PSA progression and/or radiographic progression and/or clinical progression. 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. Where no decline from baseline was documented, PSA progression was defined as a 25% increase from baseline value along an increase in absolute value of at least 2 ng/ml after 12 weeks of treatment. PSA declines of < 30%, <50% and <90% from baseline after 12 weeks with or without conformation were also evaluated. Objective responses were measured according to RECIST [13]. Bone progression based on bone scans was assessed according to the PCWG2 criteria. Overall survival (OS) was calculated from the date of start of Enz treatment to the date of death or date of last follow-up. Informed consent was obtained from all patients prior to enrolment into the EAP and patient's outcomes were analyzed with ethics committee approval.

Statistical analysis

In line with PCWG2 criteria, waterfall plots with maximum PSA decline from baseline and PSA after 12 weeks of treatment were constructed. Survival and progression were evaluated using Kaplan-Meier (KM) estimates. Patients who did not achieve a 50% fall in PSA on Doc or AA were designated Doc or AA non-sensitive, respectively, and patients with a ≥50% decline in PSA on Doc or AA treatment were designated Doc or AA-sensitive, respectively. Best PSA responses on Enz were compared between subpopulations of patients according to Doc and AA sensitivities using a two sample t-test. Predictive power of best Doc and AA response and their interaction for maximum PSA decline on Enzalutamide was evaluated by means of linear regression using a log link. Statistical analyses were conducted using Statistical Analysis System (SAS) statistical software and R.[14]

RESULTS

Patients

Starting in June 2012, a EAP for Enz was established in the Netherlands. At the time of closing of the program in March 2013, 61 patients in 9 hospitals, previously treated with both Doc and AA, were evaluable for treatment outcome and tolerability. Patient characteristics at the time of Enz treatment initiation are summarized in Table 1. The median age before starting Enz treatment was 69 years (IQR 64 – 74), ECOG performance was 0-1 in 57% and 2 in 36% of patients, 79% of patients had bone metastases and 54% lymph node metastases and the majority (93%) had more than one metastatic site. With respect to laboratory results, the median hemoglobin concentration was 11.0 g/dL (IQR 9.9 – 12.5), Alkaline Phosphatase (ALP) 191 U/L (IQR 100 – 288) and Lactate Dehydrogenase (LDH) 241 U/L (IQR 191 – 385) at the time of Enz treatment initiation. Disease progression at the time of Enz treatment initiation presented in 95% as a PSA progression and in 87% of patients as clinical progression and could be confirmed in 57% by a bone scan and in 30% of patients as progression of measurable lesions.

Ninety percent of patients had one course of Doc treatment, while 10% had two or more courses. The median number of cycles of Doc in all courses combined was 8 (IQR 6 – 10). Thirty % of patients had at least one course of Cabazitaxel in combination with prednisone. The median duration of AA treatment was 26 weeks (IQR 13 – 37) and the reason for AA discontinuation was disease progression after initial response in 54% and no initial activity in 38% of patients. All patients were treated with an LHRH antagonist/agonist or had an orchidectomy, while 18% used steroid drugs as mono therapy at the time of Enz treatment initiation. Twenty % of patients used drugs with a known interaction with Enz.

Table 1. Patient and treatment characteristics

Patient demographics	**Number of patients (%), median values (IQR)**	
Age	*Median*	*IQR*
	69	64-74
ECOG performance status	*n*	%
0-1	35	(57%)
2	22	(36%)
3	4	(7%)
Gleason score		
≤6	10	(17%)
7	14	(23%)
≥8	26	(43%)
Not available	11	(18%)
Metastatic sites		
Bone	48	(79%)
Lymph nodes	33	(54%)
Visceral metastases	13	(21%)
Number of metastatic sites		
0	0	(0%)
1	1	(2%)
≥2	57	(93%)
Unknown	3	(5%)
Laboratory	*Median*	*IQR*
PSA (μg/L)	267	(79 – 687)
Haemoglobin (g/dL)	11.0	(9.9 – 12.5)
ALP (U/L)	191	(100 – 288)
LDH (U/L)	241	(191 – 385)
ALAT (U/L)	18	(14 – 26)
Creatinine (μmol/L)	74	(64 – 87)
Testosterone (nmol/L)	<0.5	(<0.2 – <0.7)
Disease progression	*n*	%
PSA increase	58	(95%)
Progression on bone scan	35	(57%)
Progression: Clinical progression	53	(87%)
Progression: Measurable lesions	18	(30%)
Docetaxel treatment	*Median*	*IQR*
Number of cycles (all courses)	8	(6 – 10)
Number of courses	*n*	%
One course	55	(90%)
Two courses	5	(8%)
Three courses	1	(2%)

Previous chemotherapy (other than docetaxel)		
Mitoxantrone	2	(3%)
Cabazitaxel	18	(30%)
Abiraterone treatment	*Median*	*IQR*
Duration of treatment (weeks)	26	(13 – 37)
Reason for discontinuation:	*n*	%
Intolerance	4	(7%)
Progression	33	(54%)
No activity	23	(38%)
Unknown	1	(2%)
Antihormonal treatment while on Enzalutamide		
LHRH antagonist/agonist	59	(97%)
Orchidectomy	2	(3%)
Dexamethasone/prednisone mono therapy	11	(18%)
Previous antihormonal treatment (other than Abiraterone)		
Ketoconazol	0	(0%)
Diethylstilbestrol	0	(0%)
Concomitant medication with known interaction with Enzalutamide	13	(22%)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; ALP: serum Alkaline Phosphatase; LDH: Lactate dehydrogenase; ALAT, Alanine-aminotransferase

Antitumor effects

Patients started Enz treatment a median of 60.7 weeks (IQR 36.6 – 78.2) after Doc discontinuation and 8.9 weeks (IQR 4.3 – 28.9) weeks after AA discontinuation (Table 2). The median duration of Enz treatment was 14.9 weeks (IQR 11.1 – 20.0) and median follow-up was 16.3 weeks (IQR 13.7 – 21.1). A ≥ 30% maximum PSA decline was observed in 28 patients (46%), a ≥50% PSA decline in 13 patients (21%) and a ≥90% PSA decline in 2 patients (3%)(Figure 1). The maximum PSA decline was reached after a median of 5.0 weeks (IQR 4.0 – 8.6). Eighteen patients (30%) had no PSA response at any time. For each patient we collected the PSA measurement at the time point closest to 12 weeks after Enz treatment initiation (median 12 weeks, IQR 10.7 – 13.6). A ≥ 30% PSA decline was observed in 17 patients (28%), a ≥50% PSA decline in 9 patients (15%) and a ≥90% PSA decline in 1 patient (2%). Reasons for Enz treatment discontinuation included no initial activity in 16 patients (26%), progressive disease in 22 patients (36%) and death in 2 patients (3%). One patient died of a hemorrhagic stroke and one patient died of disease progression while on Enz reatment. One (2%) patient was intolerant for Enz and experienced severe nausea and fatigue (Table 2). At the time of analysis, 19 patients (31%) were still on Enz treatment. PFS is depicted in Figure 2. The KM estimate for the median PFS is 12.0 weeks (95% C.I.:11.1 – 16.0) (Table 2), the estimated median Time To PSA Progression (TTPP) 17.4 weeks (95% confidence > 16.0)(Table 2) and median OS 31.6 weeks (95% confidence > 28.7)(Table 2; Figure 2). Of the eleven (18%) patients on steroid therapy at Enz initiation, 4 (36%) had a maximum PSA response

≥30%, 2 (18%) a maximum PSA response ≥50% and 1 (9%) patient had a PSA response ≥90%. Median time to maximum PSA response was 6.9 weeks (IQR 3.6– 10.5) in these patients.

Tolerability

No unexpected toxicity of Enz was reported. Of the 382 Adverse Events (AE) collected, the majority (247; 65%) was grade 1 (Table 2). Grade 2 (101; 26%) and grade 3 (34; 9%) AEs were less frequent. Hot flushes were all grade 1. Fatigue was the most frequent grade 2 and 3 AE, 60 (59%) and 16 (47%), followed by musculoskeletal pain 27 (27%) and 7 (20%), respectively.

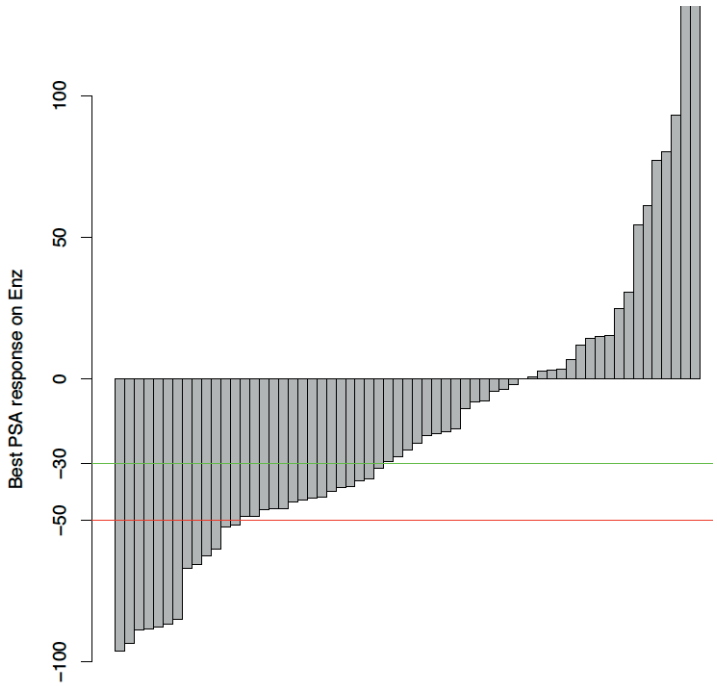

Figure 1. The best prostate-specific antigen (PSA) responses to Enzalutamide (Enz) are illustrated.

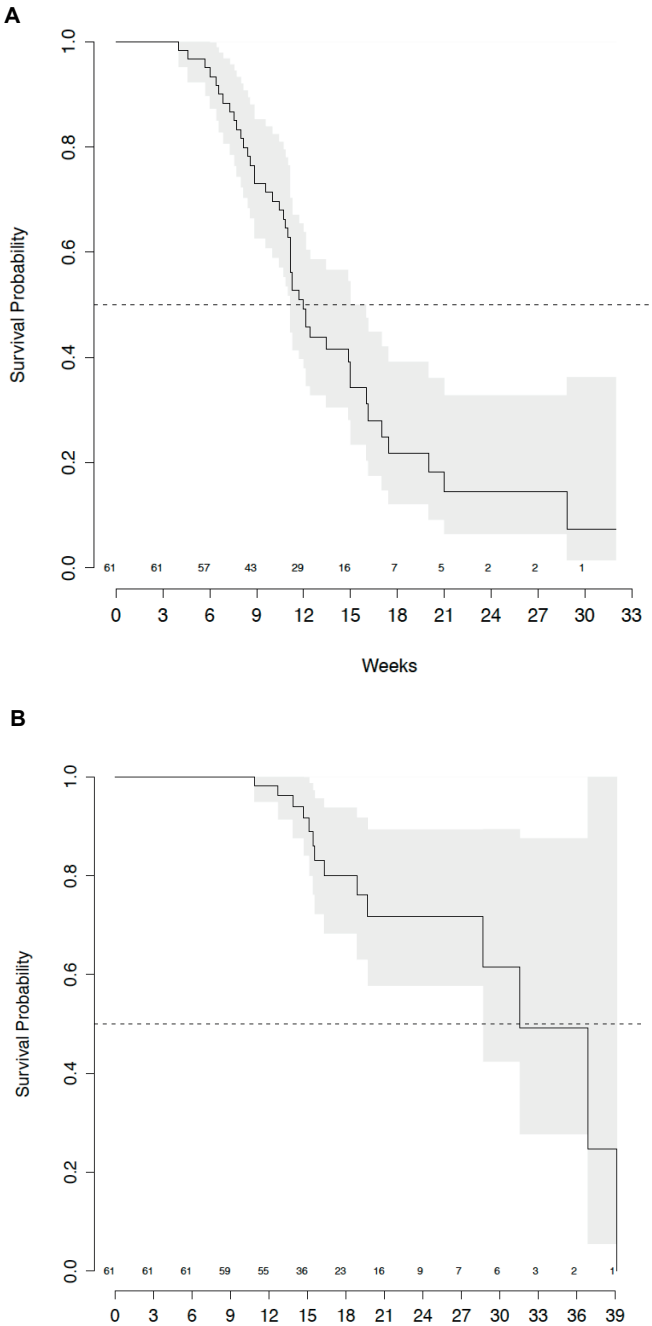

Figure 2. (Top) Progression-free survival and (Bottom) overall survival are illustrated.

Table 2. Outcomes of Enzalutamide Treatment After Abiraterone Treatment

Outcome Variable	Median [IQR] or No. of Patients (%)
Time after docetaxel discontinuation, wk	60.7 [36.6-78.2]
Time after Abiraterone discontinuation, wk	8.9 [4.3-28.9]
Duration of Enzalutamide treatment, wk	14.9 [11.1-20.0]
Follow-up, wk	16.3 [13.7-21.1
Time to maximum PSA decline, wk	5.0 [4.0-8.6]
PSA decline	
>30%	28 (46)
>50%	13 (21)
>90%	2 (3)
Reason for Enzalutamide discontinuation	
No initial activity	16 (26)
Progressive disease	22 (36)
Death	2 (3)
Intolerance	1 (2)
Reason unknown	1 (2)
Treatment ongoing on date of data collection	19 (31)
Survival	
PFS: Median/95% CI, wk	12.0/11.1-16.0
Time to PSA progression: Median/95% CI, wk	17.4/>16.0
OS: Median/95% CI, wk	31.6/>28.7
Adverse events	
Grade 1	247
Grade 2	101
Grade 3	34

Abbreviations Wk, weeks; PSA, prostate specific antigen; CI, Confidence interval; PFS, progression-free survival; OS Overall survival

Relation between Doc and AA response and response to Enz

Table 3 summarizes characteristics of patients that did not reach a ≥50% PSA response on Doc or AA treatment and were considered Doc or AA non-sensitive, respectively, and patients that reached a ≥50% PSA response on these treatments and were considered Doc or AA sensitive, respectively, and the entire population. The 24 patients considered Doc non-sensitive, received less cycles of Doc and had a lower median best PSA response to Doc treatment, compared to the 29 patients who were considered Doc sensitive and the entire population (6, 10, 8 cycles and -20.1%, -78.3%, -59.7%, respectively)(Table 3). Duration of AA treatment was not different between Doc non-sensitive and sensitive patients and the entire population (26.1, 21.9 and 25,9

weeks, respectively). Although not statistically significant, the median maximum response on AA treatment was better in the Doc non-sensitive then in the Doc sensitive population (-27.7% and -9.2%, respectively). Five (21%) Doc non-sensitive and 5 (18%) Doc sensitive patients had a ≥50% PSA response on AA treatment. However, there was no difference in maximum PSA response to Enz treatment (median -28.4%, -22.8% and -25.2%, respectively)(Table 3) and duration of Enz treatment (median 14.6, 14.9 and 14.9 weeks, respectively) between Doc non-sensitive and sensitive patients and the entire population. The 43 patients who were considered AA non-sensitive received AA treatment for a shorter period than patients considered AA sensitive (21.6 and 39.1 weeks, respectively). There was no difference in median maximum PSA response to Enz treatment (-31% and -20%, respectively)(Table 3) and duration of Enz treatment (median 15 and 17.4 weeks, respectively) between AA non-sensitive and sensitive patients. Best response on AA and Doc were not found to be predictive for response on Enz.

DISCUSSION

The response rates on Enz in men with mCRPC previously treated with Doc and AA and survival outcomes suggest a modest activity in this cohort of patients. Fourty-six % of patients had a PSA decline ≥30% on Enz, however, only 21% had a PSA decline ≥50%. These PSA response rates are comparable to PSA response rates reported in a smaller cohort of 35 mCRPC patients treated with Enz after previous AA treatment [15] Median TTPP on Enz, as estimated by the KM-method, was 17.4 weeks and median OS 31.6 weeks. These outcomes compare unfavorably with the outcomes of the AFFIRM study of Enz in the post-docetaxel setting, where 54% of patients were reported to have a ≥50% PSA response, median TTPP was 36.1 weeks and median OS 80 weeks. However, comparison is hampered by the more advanced stage of the disease of patients in the current analysis than patients in the AFFIRM study, which is reflected by a poorer performance score, lower hemoglobin concentration and a higher PSA at baseline [7]. A post-hoc analysis of the AFFIRM data, suggested a worse outcome of patients using corticosteroid while on Enz treatment [16]. Eighteen % of patients in the present cohort were using corticosteroids, however, maximum PSA response and time to maximum PSA response seemed not different from the total population. Enz treatment was well tolerated in these extensively pretreated patients with advanced disease and no unexpected AEs were reported. As in the AFFIRM study fatigue was the most frequent AE and hot flushes were all grade 1 [7]. However, in contrast, diarrhea was a non-frequent AE in the current study and musculoskeletal pain was more common than in the AFFIRM study.

Recently, Loriot *et al* and Noonan *et al* reported modest response rates and survival outcomes of AA treatment in cohorts of 38 and 30 patients, respectively, who progressed on Enz treatment [10, 11]. In these studies PSA response rates of ≥50% were reported in 8% and 4% of patients,

Table 3. Response on AA and Enz treatment in relation to Doc sensitivity and response on Enz treatment in relation to AA sensitivity

Doc treatment [a]	**Median (IQR)**		
	Doc non-sensitive (n=24)	**Doc sensitive (n= 29)**	**Entire population (n=61)**
Number of docetaxel cycles.[b]	6 (4 - 7.25)	10 (8-10)	8 (6 – 10)
Maximum PSA response (%) on Doc treatment. [c]	-20.1% (-43.3% – -5.1%)	-78.3% (-94.7% – -70.2%)	-59.7% (-78.9% – -39.8%)
Duration (weeks) of AA treatment.	26.1 (12.6 – 38.6)	21.9 (13.1 – 34.6)	25.9 (13.1 – 37.3)
Maximum PSA response (%) on AA treatment. [c]	-27.7% (-43% – 0.0%)	-9.2% (-38.9% – 0.0%)	-22.3% (-43.4% – 0.0%)
Duration (weeks) of Enz treatment.	14.6 (11.6 – 22)	14.9 (10.9 – 17.4)	14.9 (11.1 – 20)
Maximum PSA response (%) on Enz treatment. [c]	-28.4% (-44.0% – +1.1%)	-22.8% (-62.7% – +7.0%)	-25.2% (-46.4% – +3.0%)
AA treatment [a]	**Median (IQR)**		
	AA non-sensitive (n=43)	**AA sensitive (n= 13)**	**Entire population (n=61)**
Duration (weeks) of AA treatment	21.6 (13.1 – 30.4)	39.1 (30.4 – 43.7)	25.9 (13.1 – 37.3)
Maximum PSA response (%) on AA treatment. [c]	0.0% -28.1% - 0.0%	-87.4 (-98.6% – -80.0%)	-22.3% (-43% – 0.0%)
Duration (weeks) of Enz treatment.	15 (11.2 – 20.5)	17.4 (12.7 – 21.3)	14.9 (11.1 – 20.0)
Maximum PSA response (%) to Enz treatment. [c]	-31% (-56% – +5.1%)	-20% (-38.3 – -7.7)	-25.2% (-46.4% – +3.0%)

Abbreviations: AA, Abiraterone acetate in combination with prednisone; Doc, docetaxel in combination with prednisone; Enz, Enzalutamide; IQR, interquartile range; PSA, prostate-specific antigen.

[a] Patients were stratified according to their maximum PSA response, <50% or ≥50%, on Doc or AA treatment. The Doc response was not known in 8 patients, and the AA response was not known in 5 patients.

[b] This included only the first course of Doc treatment.

[c] The maximum PSA response is indicated as the percentage of the baseline value. A negative value reflects a PSA decrease.Doc and AA non-sensitive is defined as a maximum PSA response <50% and Doc and AA sensitive as a maximum PSA response ≥50%.

respectively, which is lower than the 21% of patients in the current cohort. However, the median PFS reported by Loriot *et al* and Noonan *et al* were in the same range as the median PFS of the current cohort, 11.7 weeks, 15.4 weeks and 12.0 weeks, respectively, as were the reported median OS of the three studies, 31.3 weeks, 50.1 weeks and 31.6 weeks, respectively.

Enz inhibits androgen-receptor signaling by competitively inhibiting the binding of androgens, inhibiting the translocation of ligand bound receptor to the nucleus and binding to its response elements in the DNA [17]. In contrast, AA inhibits CYP17A, which is crucial for testosterone synthesis, with potent suppression of extragonadal androgen production as a result [18]. Although by different means, both drugs target persistent AR signaling. Despite the differences in patient populations between the AFFIRM study and the studies into the sequence of AA and Enz, data from these studies suggest the possibility of cross-resistance. However, in the current study PSA response on AA treatment did not predict for PSA response on Enz treatment, which is in line with the non-statistically significant relation between PSA response on Enz and PSA response on AA in the study of Loriot *et al* [10].

There is limited data on the mechanism of resistance against AA and Enz. Since AA and Enz both target AR signaling, the mechanism of cross-resistance might be at the AR level, including AR modifications, complex interactions of AR with coactivators or correpressors and mutual regulation of miRNA and AR [19]. In xenografts of human mCRPC treated with AA, induction of AR expression and AR splice variants was demonstrated [20, 21], while in another study AR splice variants were identified as key mediators of persistent AR signaling and resistance to Enz [22]. Increased steroidogenesis activation might also mediate cross-resistance between AA and Enz [19]. Testosterone levels in blood and bone marrow of patients treated with AA were undetectable on treatment discontinuation [23], however, Enz treatment increased the testosterone levels in bone marrow of patients and decreased nuclear AR expression [24]. In a mouse model of human prostate cancer, the oncogenic AKt pathway was activated when the AR was inhibited [25]. This reciprocal activation of oncogenic pathways upon AR inhibition might represent a mechanism of resistance to AR receptor antagonists [19].

Combination treatment of Enz and AA might reverse some mechanisms of drug resistance. A study in human prostate cancer cell lines provided evidence that the glucocorticoid drugs administered with AA, to prevent side effects, and mineralocorticoid receptor antagonists could activate mutant AR, which was inhibited by Enz [26]. These findings provide a rationale for combination treatment. Currently a Phase II trial into the safety and tolerability of Enz in combination with AA is enrolling (NCT01650194).

In conclusion, patients in the current study who previously progressed on AA had a modest PSA response rate and limited survival on subsequent Enz treatment. PSA response on AA

treatment did not seem to predict for Enz treatment outcome. Although a higher PSA response rate was found in patients treated with Enz after progression on AA treatment, PFS and OS were in the same range as those described in two cohorts of men with mCRPC treated with AA after progression on Enz. Data from these three studies suggest limited activity and no preference for either sequence of treatments. However, recommendation on the sequencing of Enz and AA in the post-docetaxel setting cannot be concluded, since these data are only hypothesis generating. Further studies are needed to establish the sequence of treatments with these new drugs.

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DISCLOSURES

Drs. van Oort, van den Berg, and Bergman report personal fees from Astellas Pharma and Jansen Pharma outside the submitted work. Drs. Hamberg and de Jong report personal fees from Jansen Pharma outside the submitted work. Dr. van den Eertwegh reports personal fees from Astellas Pharma outside the submitted work.

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ENZALUTAMIDE