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

Badrising, S.K.

Chapter 3

Prognostic Parameters for Response to Enzalutamide after Docetaxel and Abiraterone Treatment in Metastatic Castration-Resistant Prostate Cancer Patients; a Possible Time Relation

Sushil K. Badrising, MD[#]; Vincent van der Noort, PhD[#]; Alfons J. M. van den Eertwegh, MD, PhD; Paul Hamberg, MD, PhD; Inge M. van Oort, MD, PhD[5]; H. Pieter van den Berg, MD; Maartje Los, MD, PhD; Maureen J.B. Aarts, MD; Jules L.L.M. Coenen, MD, PhD; Hans Gelderblom, MD, PhD; Igle J. de Jong, MD, PhD; Emile D. Kerver, MD; Suzan Vrijaldenhoven, MD; Theo van Voorthuizen, MD; Fabienne Warmerdam, MD; John B. Haanen, MD, PhD; Andries M. Bergman, MD, PhD. On behalf of the Dutch Uro-Oncology Studygroup (DUOS)

#These authors contributed equally

The Prostate. 2016 Jan; 76(1); 32-40

ABSTRACT

Background

Abiraterone Acetate (AA) and Enzalutamide (Enz) are effective hormonal treatments in mCRPC patients. Retrospective studies suggested clinical cross-resistance between Enz and AA. However, 12.8-39.1% of patients previously treated with docetaxel (Doc) and AA do respond to Enz. These responders have not been characterized.

Methods

102 Enz treated mCRPC patients after AA and Doc treatment were included in this study. Differences in patient characteristics and previous treatment outcomes between PSA responders and non-responders on Enz were evaluated.

Results

Median Progression-Free Survival was 12.2 weeks (95%CI 11.7-14.3) and Overall Survival 43.5 weeks (95%CI 37.4-61.2). There were 26 (25%) Enz-responders and 76 (75%) non-responders. Significant higher percentages of Gleason scores ≥8 and PSA doubling times (PSA-DT) <3 months were found in Enz responders than in non-responders. The interval between end of AA and start of Enz treatment (IAE) for responders was 24.6 weeks (IQR 4.0-48.1) and 8.9 weeks for non-responders (IQR 3.7-25.9) ($p=0.08$). In an IAE <40 days subgroup (34 patients), Enz responses were related to AA non-responsiveness, while univariate and logistic regression analysis of baseline criteria of a subgroup of patients with an IAE≥40 (68 patients) revealed significant differences in baseline PSA levels, PSA-DT <3 months, Gleason scores ≥8 and IAE's between Enz responders and non-responders.

Conclusions

PSA response to Enz after previous AA and Doc treatment was associated with a longer IAE, a higher Gleason score and a PSA-DT <3 months. Identification of these patients might be of value for sequencing of treatment options.

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is a prevalent and incurable disease, associated with high morbidity and mortality[1]. In recent years multiple drugs have become available that showed an increased quality of life and overall survival (OS) of mCRPC patients. Abiraterone acetate in combination with prednisone (AA) and Enzalutamide (Enz) both target the androgen receptor and both have proven efficacy in patients with mCRPC[2–5]. Enz inhibits Androgen-Receptor (AR) signaling through inhibition of androgen binding to the AR, reducing the efficiency of the AR complex nuclear translocation, preventing the AR complex from binding to response elements in the DNA and recruitment of its coactivators[3], while AA inhibits the synthesis of testosterone[6]. Several retrospective studies evaluated the efficacy of Enz in mCRPC patients previously treated with Docetaxel (Doc) and AA. The rate of PSA responses (≥50% PSA decline) varied between 12.8% and 39.1%[7–13], OS and Progression Free Survival (PFS) varied between 4.8 – 8.5 months[7, 9, 11] and between 2.9 – 4.0 months[7–9, 12], respectively. The reported PSA response rates, OS and PFS of Enz after Doc and AA treatment were all lower than the 54%, 18.4 months and 8.3 months, respectively, reported in mCRPC patients previously treated with Doc only[3]. These results suggest a significant clinical cross-resistance, however, a proportion of patients treated with Enz previously treated with Doc and AA did have a PSA response. Here we report the characteristics of these patients. This information might be of value for optimal sequencing of treatment options for mCRPC patients.

PATIENTS AND METHODS

Patients, study procedures and data collection

Recently, we reported on the efficacy of Enz in 61 mCRPC patients previously treated with Doc and AA in a retrospective multicenter study[7]. These patients were included in the Dutch Expanded Access Program (EAP) for Enz. For the current analysis, all 36 Dutch Uro-Oncology Study group (DUOS) hospitals were approached for updated records of patients included in the EAP and for new patients treated with the drug sequence of interest. Data from 9 hospitals on all 61 patients in the EAP could be updated and 14 hospitals indicated to hold records of 41 additional patients treated with Enz after previous Doc and AA not in the EAP.

Institutional Review Board (IRB) approval for retrospective collection and analysis of patient data was obtained from the Netherlands Cancer Institute, which covered all participating hospitals. Personal data were encoded and no informed consent was required.

Prior to Enz treatment (160mg orally daily) baseline characteristics were documented. Patients were assessed every 4-6 weeks during Enz treatment. Radiologic assessment was at the

discretion of the physician. Progression Free Survival and Overall Survival were followed up until May 2014 and assessed according to PCWG2 criteria[14]. PSA response was defined as a PSA decline of ≥50% from baseline, PSA doubling time (PSA-DT) was calculated for patients with at least three PSA measurements within the three months prior to Enz treatment according to PCWG2 criteria[14]. Duration of Enz response (DER) was defined as time from first PSA response (≥50% PSA decline) on Enz until PSA progression as defined by PCWG2[14]. Only patients who had an PSA response were included into the calculation. Patients with no PSA progression were censored at last follow-up. Radiologic responses were assessed according to RECIST[15] and PCWG2 criteria[14]. Interval between AA and Enz treatment (IAE), Interval between Doc and Enz (IDE) and Interval between last treatment and Enz (ILTE) were defined as time between last dose of AA, last dose of Doc treatment and end of last systemic therapy and start of Enz, respectively. Duration of Enz treatment (Enzdur) was defined as start of Enz through last day of treatment.

Patients were designated Doc or AA sensitive if they had a PSA decline of at least 50%. Those patients who did not achieve a 50% PSA decline were designated Doc or AA non-sensitive.

Statistical analysis

Follow-up time, OS , PFS and DER were evaluated using Kaplan-Meier (KM) estimates. Univariate comparisons of patient and treatment characteristics between Enz-responders and non-responders were assessed using a t-test or Wilcoxon-Mann-Witney test for continuous variables and by Fisher's exact test for categorical variables. Effect of IAE on response was evaluated graphically, as well by means of logistic regression. Effects of other patient and treatment characteristics on Enz-response were subsequently evaluated in bivariate logistic regressions using IAE as a covariate. The univariate comparisons above were repeated for the subgroup of patients with IAE<40 and the IAE≥40. For response to AA we tested for a statistical interaction with IAE as a predictor of Enz-response – both in the continuous setting (logistic regression) as in the dichotomized setting (using 40 days as cut off point). Aike's Information Criterion was used to decide whether or not to include a quadratic term (of the IAE) in the logistic regressions. Based on this it was decided to do so only for the subpopulation of patients with IAE≥40. All analyses were repeated for the subpopulation of patients receiving AA for at least 12 weeks. All p-values were two-sided and considered significant if $p<0.05$. No correction was made for multiple significance testing. Statistical Analysis System (SAS) statistical software and R were used for statistical analysis[16].

RESULTS

Patients

A total of 102 patients were included from 14 medical centers located in the Netherlands. All patients treated with Enz after AA and Doc in the participating centers have been included. Patient and tumor specific characteristics and previous treatments are listed in table 1 and supplementary table 1. For 6 patients (6%) the Enz dose was reduced as a result of adverse events (data not shown). Ninety patients (88%) had one course of Doc treatment prior to Enz treatment, while 12% had more than one course. Sixty-four % of the patients were considered Doc sensitive (≥50% PSA decline). The median AA treatment duration was 26 weeks (IQR 14 – 38). Twenty-eight % of the patients were considered AA-sensitive (≥50% PSA decline).

PSA response on Enz treatment and survival

Enz treatment was initiated a median of 60.6 weeks (IQR 40.9 – 87.9) and 9.7 weeks (IQR 3.7 – 31.4) after Doc (IDE) and AA discontinuation (IAE), respectively (Table 1). Twenty-six patients (25%) had a PSA response on Enz treatment (Table 1). The Kaplan-Meier estimate for the median Progression free survival (PFS) was 12.2 weeks (95% C.I.:11.7 – 14.3), the median overall survival (OS) was 43.5 weeks (95% CI 37.4 – 61.2) (Table 1) and median DER was 26.0 weeks (95% C.I.: >10.4) (Table 2). Two patients were excluded from the OS and PFS analysis due to lack of follow-up. Enz response, PFS and OS did not change when analysis was limited to patients treated with AA for a minimum of 12 weeks (86 patients), as advised by the PCWG2[14].

Clinical variables associated with PSA response

In Table 2 the characteristics of 26 Enz-responders and 76 non-responders are compared. Enz-responders had a significant longer median OS and PFS compared to non-responders (64.3 and 37.4 weeks; p=0.014 and 22.2 and 11.7 weeks; p=<0.0001, respectively). Eighty-six percent of the responders had a Gleason score ≥8 compared to 46% of the non-responders (p=0.006). Enz-responders had a significantly shorter PSA-DT (<3 months) compared to non-responders (44% and 16%, respectively; p=0.037).

The median IAE in the Enz responders and non-responders group were 24.6 weeks (IQR 4.0 - 48.1) and 8.9 weeks (IQR 3.7 – 25.9), respectively (p=0.08). Although the IAE did not differ significantly between responders and non-responders, the shape of the graph representing the relation between PSA response and IAE prompted more detailed investigation of this relation (Figure 1).

Table 1. Patient characteristics and treatment outcomes

Survival	*Median*	*95% C.I.*
Median PFS (weeks)	12.2	(11.7 – 14.3)
Median OS (weeks)	43.5	(37.4 – 61.2)
ECOG performance status	*n*	
0-1	61	(60%)
2	31	(30%)
3	4	(4%)
Not available	6	(6%)
Gleason score	*n*	%
≤6	15	(17%)
7	24	(27%)
≥8	49	(56%)
Not available	11	(18%)
Metastatic sites	*n*	
Bone metastases/ bone only	80 / 22	(78%) / (22%)
Lymph node involvement/ lymph node only	62 / 4	(61%) / (4%)
Bone and lymph nodes only	56	(55%)
Visceral	20	(20%)
PSA doubling time (n=66)	*n*	%
< 3 months	15	(23%)
≥ 3 months	51	(77%)
Disease progression	*n*	
PSA increase	97	(95%)
Progression on bone scan	60	(59%)
Progression: Clinical progression	90	(88%)
Progression: Measurable lesions	32	(31%)
Docetaxel treatment	*Median*	*IQR*
Number of cycles (all courses)	9	(6 – 10)
Cabazitaxel treatment	*n*	
Patients treated	36	(35%)
Number of cycles (all courses)	6	(4 – 8)
Abiraterone treatment	*Median*	*IQR*
Duration of treatment (weeks)	26	(14.3 – 38.1)
IDE (Weeks)	60.6	(40.9 – 87.9)
IAE (Weeks)	9.7	(3.7 – 31.4)
Enzdur (weeks)	14.3	(9.7 – 20.6)
Follow-up (weeks)	15.0	(11.7 – 15.7)

Time to maximum PSA decline (weeks)	6.5	(4.0 – 11.9)
Maximum PSA decline	*n*	
≥30%	44	(43%)
≥50%	26	(25%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PSA, prostate-specific antigen. C.I.: Confidence interval; IDE, time interval between discontinuation of Doc and start of Enz; IAE, time interval between discontinuation of AA and start of Enz; Enzdur, duration of Enzalutamide treatment; PFS, Progression free survival; OS, Overall survival

PSA response on Enz treatment as a function of time between AA and Enz treatment

Two distinct peaks in percentage of Enz-responders can be identified: a smaller group within an IAE<40 days (IAE<40) and a larger group with a linear relation between Enz response and IAE (IAE≥40) (Figure 1). In Figure 2 Swimmer plots are constructed of patients with an IAE≥40 (Upper panel) and IAE<40 (lower panel). Swimmer plots represent survival from first treatment of castration resistant disease and response on Enzalutamide in relation to response on other life-prolonging treatments on an individual basis.

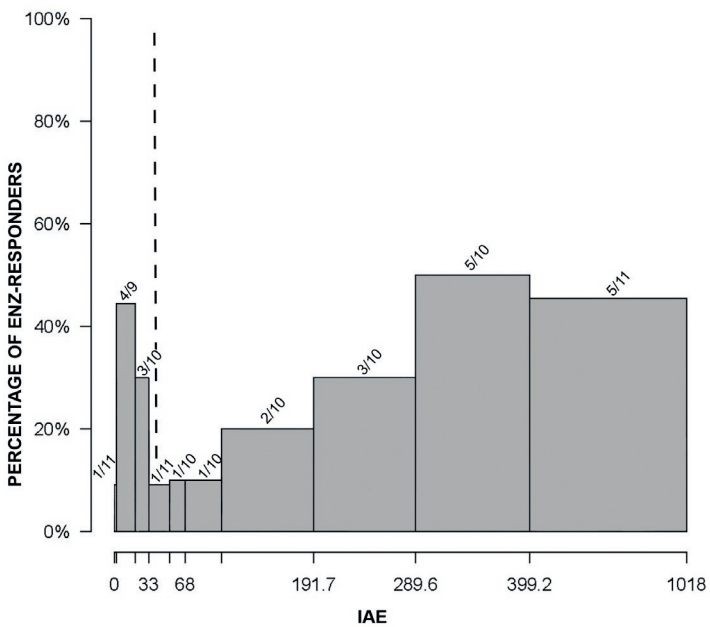

Figure 1. Percentage of Enz responders as a function of the interval between end of AA treatment and start of Enz treatment (IAE). The heights of the boxes represent the percentage of Enz-responders in that interval. Each box contains roughly 10% of all patients. The width of the box corresponds with the IAE. Two peaks of Enz-responders can be distinguished (separated by a vertical dotted line at 40 days).

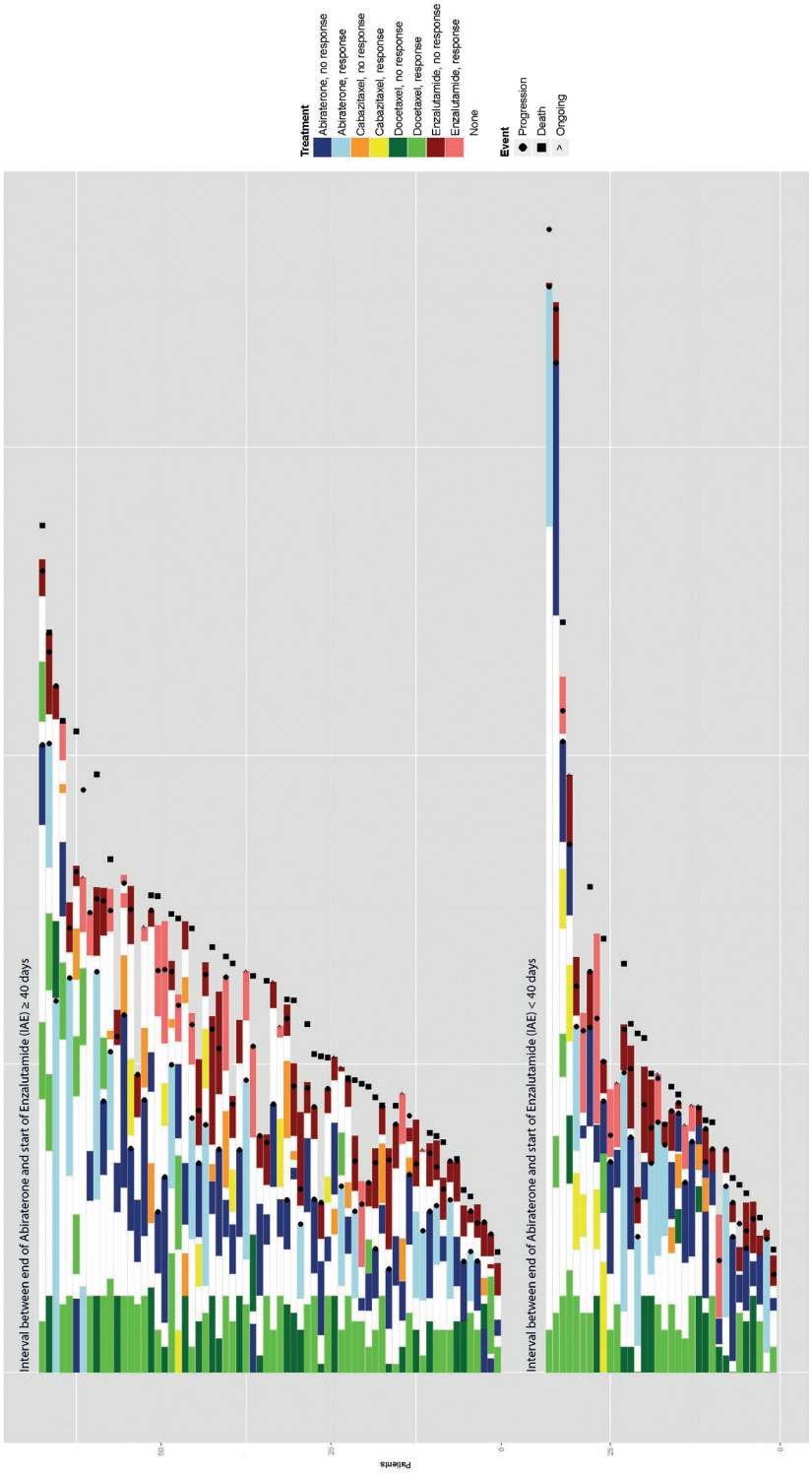

Figure 2. Swimmer plot of patients with an interval of at least 40 days between end of AA treatment and start of Enz treatment (IAE≥40)(Upper panel) and less than 40 days between end of AA treatment and start of Enz treatment (IAE<40)(Lower panel). Length of each bar represents survival of one patient. Bars are ordered by duration of follow-up, starting from first treatment of castration resistant cancer. The colors indicate duration of treatment and response on life-prolonging treatments. Progression was defined as either radiological, clinical of biochemical.

Baseline characteristics and univariate analysis of these two groups are listed in table 2 and supplementary table 2. Univariate analysis of all baseline characteristics of the IAE<40 days group of 34 patients revealed significant differences in neutrophil granulocytes levels and duration of Enz treatment between Enz responders and Enz non-responders. Baseline characteristics of the IAE≥40 group of 68 patients, showed significant differences in PSA levels, Gleason score, bone only metastases, PSA-DT <3 months, IDE, IAE and ILTE between Enz responders and Enz non-responders (table 2).

In the IAE≥40 group PSA responses on AA for Enz responders and non-responders were 29% and 28%, respectively, while, in the IAE<40 subgroup all but one (11%) of the Enz-responders were AA-non-responsive. However, the difference in AA response between the IAE<40 and IAE≥40 subgroups was not significantly different.

Logistic regression analysis

Logistic regression analysis of the probability of PSA response on Enz treatment was performed using IAE as the independent variable as well as using various disease and patient characteristics as the independent variable with IAE as a covariate. Analysis was performed for the entire cohort and for the IAE≥40 group, the adjusted p–values are displayed in table 3.

In the entire cohort (n=102), the logistic model of the influence of IAE on the rate of Enz-responders seemed to be more accurate than a model suggesting that IAE had no influence on the rate of Enz-responders, however was not statistically significant better (p=0.058 in a likelihood ratio test). In the bivariate logistic models, the predictors for Enz-response in the entire population compensating for IAE were PSA-DT <3 months (adj. p=0.037) and duration of Enz treatment (adj. p=0.003).

For the IAE≥40 subpopulation, IAE was a predictor of Enz-response in the univariate logistic model (p=0.007). The predictors for this subpopulation in the bivariate logistic models were PSA-DT <3 months (adj. p=0.019), involvement of lymph nodes (adj. p=0.017) and having only bone metastases (adj. p=0.005).

Table 2. Univariate analysis of baselines variables for sub-populations

	Entire Cohort			IAE<40			IAE ≥ 40		
	Number of patients (%), median values (IQR)			*Number of patients (%), median values (IQR)*			*Number of patients (%), median values (IQR)*		
	Responders n=26 (25%)	**Non-responders n=76 (75%)**	**p- value**	**Responders n=9 (26%)**	**Non-responders n=25 (74%)**	**p- value**	**Responders n=17 (25%)**	**Non-responders n=51 (75 %)**	**p-value**
Survival*									
Median OS (weeks)	64.3 (>47.8)	37.4 (28.7-54.3)	0.014						
Median PFS (weeks)	22.2 (14.8-36.9)	11.7 (10.0-12.2)	<0.0001						
Median DER (weeks)	26.0 (>10.4)	N/A	N/A						
Gleason score*			*0.006*			*0.17*			*0.024*
≤6	1 (5%)	14 (21%)		1 (14%)	4 (19%)		0 (0%)	10 (22%)	
7	2 (10%)	22 (33%)		0 (0%)	7 (33%)		2 (14%)	15 (33%)	
≥8	18 (86%)	31 (46%)		6 (86%)	10 (48%)		12 (86%)	21 (46%)	
Metastatic sites									
Bone only*	9 (35%)	13 (17%)	*0.09*	1 (11%)	6 (24%)	*0.64*	8 (47%)	7 (14%)	*0.007*
Baseline laboratory values*									
Neutrophil granulocytes (x10^9/L)*	4.9 (3.6-7.9)	5.5 (4.6-7.5)	*0.41*	4.1 (3.6-4.4)	6.0 (4.6-8.0)	*0.015*	6.6 (3.6-8.2)	5.2 (4.2-7.1)	*0.91*
PSA (μg/L)*	404 (138-1380)	311 (86-709)	0.09	112 (47-345)	311 (96-700)	0.5	656 (262-2554)	318 (84-727)	0.01

PSA doubling time *			*0.037*			*1*			*0.016*
< 3 months	7 (44%)	8 (16%)		1 (20%	3 (18%)		6 (55%)	5 (15%)	
≥ 3 months	9 (56%)	42 (84%)		4 (80%)	14 (82%)		5 (45%)	28 (85%)	
Previous systemic therapies*									
Duration of AA treatment (weeks)	26.1 (13.3-40.1)	26.0 (16.9-35.6)	0.81	28.3 (13.0-39.3)	34.9 (13.4-43.7)	*0.23*	26.1 (17.1-42.6)	25.1 (17.3-30.4)	*0.58*
AA-sensitivity	6 (23%)	21 (30%)	0.61	1 (11%)	8 (35%)	*0.38*	5 (29%)	13 (28%)	
Time between treatments									
IDE (weeks)*	71.4 (58.4-04.4)	53.1 (39.1-76.3)	0.26	60.7 (58.0-64.1)	52.6 (25.7-77.0)	*0.50*	91.1 (71.3-114.6)	56.9 (41.4-73.6)	*0.043*
IAE (weeks)*	24.6 (4.0-48.1)	8.9 (3.7-25.9)	0.08	1.9 (0.6-3.7)	0.9 (0-3.3)	0.55	45.7 (14.0-33.3)	15.0 (8.1-24.7)	0.023
ILTE (weeks)*	13.4 (4.0-28.6)	7.9 (3.1-12.6)	0.09	1.9 (0.6-3.7)	0.9 (0-3.3)	0.55	21.2 (14.0-33.3)	10.3 (7.9-21.4)	0.036
Enzdur (weeks)	17.9 (14.9-31.6)	12.1 (9.0-18.3)	0.017	22.6 (17.0-35.1)	11.7 (7.9-19.7)	0.048	17.3 (13.9-30.1)	12.3 (10.1-17.4)	0.18

Abbreviations: IQR, interquartile range; OS, Overall survival; PFS, Progression Free Survival; DER, Duration of Enz Response; N/A, Not Applicable; LN, lymph node; PSA, prostate-specific antigen; AA, Abiraterone acetate; AA-sensitivity was defined as ≥50% PSA decline from baseline; IDE, interval between discontinuation of Docetaxel and start Enzalutamide; IAE, Interval between discontinuation Abiraterone and start Enzalutamide; ILTE, Interval between discontinuation of last systemic treatment and start of Enzalutamide; Enzdur, Duration of Enz treatment; * Percentages are based on number of patients with available data.

Table 3. Multivariable analysis using IAE as independent variable

	Entire cohort (n=102)	**IAE ≥ 40 days sub-group**
Likelihood ratio test	26/102; *p= 0.058*	17/68; *p=0.0065*
Dependent variables	Adjusted *p*-value	Adjusted *p*-value
Metastatic sites		
Bone metastases	*0.7*	*0.39*
Lymph node involvement	*0.17*	*0.017*
Visceral	*0.56*	*0.75*
Bone only	*0.06*	*0.0049*
Lymph nodes only	*0.9*	*0.99*
Bone and lymph nodes only	*0.2*	*0.07*
Time between treatments		
IDE	*0.42*	*0.27*
ILTE	*0.29*	*0.65*
PSA-DT < 3 months	*0.037*	*0.019*
Enzdur	*0.0033*	*0.07*

Abbreviations: IAE, Interval between discontinuation Abiraterone and start Enzalutamide; IDE, interval between discontinuation of Docetaxel and start Enzalutamide; ILTE, Interval between discontinuation of last systemic treatment and start of Enzalutamide; Enzdur, Duration of Enz treatment

DISCUSSION

In this retrospective analysis of 102 mCRPC patients treated with Enz after Doc and AA, we describe the characteristics of patients with a ≥50% PSA response. The PSA response rates, median OS and PFS on Enz treatment of mCRPC patients pretreated with Doc and AA were comparable to our previous report and other retrospective studies[7–13]. Enz-responders had a significant longer OS and PFS compared to non-responders, which were in the same range as reported by Brasso et al [12]. The ≥50% PSA response rate on Enz in the current patient cohort is much lower than the 54% in AA-naïve patients as reported in the AFFIRM trial[3].

Several retrospective cohort studies suggest a significant clinical cross-resistance between Enz and AA[7–13, 17], which might be explained by the common molecular target of both drugs. However, preclinical evidence for cross-resistance is scarce. Higher Gleason scores (≥8) have been associated with higher recurrence rates and mortality. However, in the current cohort a relation was found between Gleason score ≥8 and a higher rate of PSA response. In the AFFIRM trial, Gleason ≥8 patients had a non-significant favorable hazard ratio over Gleason ≤7 patients with respect to OS (0.60 and 0.67, respectively)[18]. PSA-DT is a valuable tool in the pre-Docetaxel setting for predicting survival and risk for metastatic disease. However, it has not been evaluated for prediction of response to therapy[19–22]. Our observation, that patients with a PSA-DT <3

months were more likely to respond to Enz, was validated both univariately and related to IAE. The relation was stronger in the IAE≥40 group. The relation between PSA baseline level, Gleason ≥8 and PSA-DT <3 months and Enz response might be related to the rate of cell cycle passage and dependence on AR signaling.

Even though there was no statistical significant difference in IAE between PSA responders and non-responders for the whole population, analysis of Enz-responders as a function of IAE revealed two groups of patients responding to Enz, IAE<40 days and IAE≥40 days. An interesting difference between the groups was that only 1 (11%) Enz responder in the IAE<40 group was AA-sensitive, while 8 (35%) Enz responders in the IAE≥40 group were AA-sensitive. The low PSA response rates on AA and high response rates on Enz in the IAE<40 group, suggests a mechanism of AA resistance not shared with Enz resistance. This exclusive mechanism of AA resistance could be related to differences in the mode of action between the AR targeting drugs. However, the difference in AA response between the IAE<40 and IAE≥40 Enz response subgroups was not statistically significant, likely due to the low number of Enz responders.

In the IAE≥40 subgroup, IAE showed a linear relation with Enz response. The PSA response rates of 50% after an IAE of 390 days was comparable to AA-untreated patients as reported in the AFFIRM trial[3]. This time relation and reversibility of acquired cross-resistance suggests plasticity of the cells' behavioral repertoire to adapt to changes in their microenvironment[23]. Carver et al. reported that the androgen receptor pathway activates reciprocal negative feedback of the PI3K-pathway. Inhibition of the androgen receptor could promote activity of PI3K signaling, which results in androgen independent proliferation[24]. Possibly, these changes are energetically unfavorable and cells might reverse to testosterone dependence upon cessation of AR targeted therapy, which might explain the time relation between AA and Enz treatment.

Reversibility of sensitivity to AR targeted drugs might have consequences for sequencing of treatment options. Our data suggests that, when an interval between AA and Enz treatment is introduced, both treatment options can be deployed. Both AA and Enz have shown survival benefit in patients not treated with Doc[4, 5]. Therefore treatment with Doc and second line options Cabazitaxel and/or Radium-223 between AA and Enz treatment might be an optimal sequence. However, there is no data suggesting a relation between interval between AA and previous Enz treatment and response to AA.

In conclusion, in this retrospective study we identified 3 possible characteristics of Enz-responders after previous Doc and AA treatment: IAE, PSA-DT <3 months and Gleason ≥8. Our data suggests that PSA responses on both AA and Enz can be achieved, however with a long interval between the treatments. This is a retrospective study and as such more prone to bias and confounding. Therefore, recommendation on the timing and sequencing of Enz and

AA in the post-Docetaxel setting cannot be made. We also note that our analysis is largely data driven and exploratory: conclusions are only hypothesis generating and need to be validated prospectively.

FUNDING SUPPORT

No specific funding was requested for this project.

DISCLOSURES:

Conflict of Interest: Drs. van Oort, van den Berg, Hamberg, van Eertwegh and Bergman are on Advisory Boards of Janssen Pharma and Astellas. Dr. Hamberg, van Eertwegh and Bergman received speakers fee from Astellas, Jansen Pharma. Dr. Bergman has received a research grant from Astellas, not related to this study. All remaining authors have declared no conflicts of interest.

REFERENCES

1. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat. Rev. Cancer 2001; 1(1):34–45.
2. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N. Engl. J. Med. 2011; 364(21):1995–2005.
3. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J. Med. 2012; 367(13):1187–1197.
4. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N. Engl. J. Med. 2014; 371(5):424–33.
5. Ryan CJ, Smith MR, Fizazi K et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015; 16(2):152–160.
6. O'Donnell A, Judson I, Dowsett M et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br. J. Cancer 2004; 90(12):2317–25.
7. Badrising S, Van Der Noort V, Van Oort IM et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer 2014; 120(7):968–975.
8. Bianchini D, Lorente D, Rodriguez-Vida A et al. Antitumour activity of enzalutamide ({MDV}3100) in patients with metastatic castration-resistant prostate cancer ({CRPC}) pre-treated with docetaxel and abiraterone. Eur. J. Cancer 2014; 50(1):78–84.
9. Thomson D, Charnley N, Parikh O. Enzalutamide after failure of docetaxel and abiraterone in metastatic castrate-resistant prostate cancer. Eur. J. Cancer 2014; 50(5):1040–1041.
10. Schrader AJ, Boegemann M, Ohlmann C-H et al. Enzalutamide in Castration-resistant Prostate Cancer Patients Progressing After Docetaxel and Abiraterone. Eur. Urol. 2014; 65(1):30–36.
11. Thomsen FB, Røder MA, Rathenborg P et al. Enzalutamide treatment in patients with metastatic castration-resistant prostate cancer progressing after chemotherapy and abiraterone acetate. Scand. J. Urol. 2013; 48(3):268–275.
12. Brasso K, Thomsen FB, Schrader AJ et al. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. Eur. Urol. 2014. doi:10.1016/j.eururo.2014.07.028.
13. Caffo O, De Giorgi U, Fratino L et al. Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study. Eur. Urol. 2015; 68(1):147–53.
14. Scher HI, Halabi S, Tannock I et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. JCO 2008; 26(7):1148–1159.

15. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J. Natl. Cancer Inst. 2000; 92(3):205–216.

16. The R Core Team. R: A language and environment for statistical computing. R foundation for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2013.

17. Azad AA, Eigl BJ, Murray RN et al. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. Eur. Urol. 2015; 67(1):23–9.

18. EMA: Xtandi Summary of Product Characteristics. 2014.

19. Antonarakis ES, Feng Z, Trock BJ et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int. 2012; 109(1):32–9.

20. Nakano K, Komatsu K, Kubo T et al. External validation of risk classification in patients with docetaxel-treated castration-resistant prostate cancer. BMC Urol. 2014; 14:31.

21. Hamberg P, Verhagen PCMS, de Wit R. When to start cytotoxic therapy in asymptomatic patients with hormone refractory prostate cancer? Eur. J. Cancer 2008; 44(9):1193–7.

22. Simmons MN, Stephenson AJ, Klein EA. Natural history of biochemical recurrence after radical prostatectomy: risk assessment for secondary therapy. Eur. Urol. 2007; 51(5):1175–84.

23. Yates C. Prostate tumor cell plasticity: a consequence of the microenvironment. Adv. Exp. Med. Biol. 2011; 720:81–90.

24. Carver BSS, Chapinski C, Wongvipat J et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 2011; 19(5):575–86.

SUPPLEMENTARY MATERIALS

Supplementary table 1. Patient characteristics and treatment outcomes

Age	*Median*	*IQR*
	72	64-77
Number of metastatic sites	*N*	%
0	0	(0%)
1	1	(1%)
≥2	99	(97%)
Unknown	2	(2%)
Laboratory values at start of Enz treatment (entire cohort; n=102)	*Median*	*IQR*
PSA (μg/L)	335	(95 – 723)
Haemoglobin (mmol/L)	7.1	(5.7 – 7.9)
Leucocytes (x10^9/L)	7.5	(6.3 – 9.3)
Neutrophil granulocytes (x10^9/L)	5.2	(4.1 – 7.5)
Thrombocytes (x10^9/L)	272	(218 – 340)
ALP (U/L)	170	(94 – 285)
Albumin (U/L)	39	(35 – 42)
Bilirubin (μmol/L)	7	(5 – 8)
LDH (U/L)	244	(192 – 390)
EGFR (ml/min/1.73m^2/L)	62	(60 – 90)
Mitoxantrone treatment	*N*	%
Patients treated	3	(3%)
Antihormonal treatment while on Enzalutamide		
LHRH antagonist/agonist	98	(96%)
Orchidectomy	4	(4%)
Dexamethasone/prednisone mono therapy	12	(12%)
Previous antihormonal treatment (other than Abiraterone)	*N*	%
Ketoconazol	0	(0%)
Diethylstilbestrol	0	(0%)
Abiraterone treatment	*Median*	*IQR*
Reason for discontinuation:	*N*	%
Intolerance	6	(6%)
Relapse	57	(56%)
No response	38	(37%)
Unknown	1	(1%)

ALP, alkaline phosphatase; IQR, interquartile range; LDH, lactate dehydrogenase; EGFR, Estimated glomerular filtration rate; PSA, prostate-specific antigen.

Supplementary table 2. Univariate analysis of baselines variables for sub-populations

	Entire Cohort			IEA<40			IEA ≥ 40		
	Number of patients (%), median values (IQR)			*Number of patients (%) median values (IQR)*			*Number of patients (%), median values (IQR)*		
	Responders n=26 (25%)	**Non-responders n=76 (75%)**	**p- value**	**Responders n=9 (26%)**	**Non-responders n=25 (74%)**	**p- value**	**Responders n=17 (25%)**	**Non-responders n=51 (75 %)**	**p-value**
Age (years)	72 (64 – 76)	72 (64 – 77)	0.8	73 (69 - 78)	71 (63 - 77)	0.45	70 (63 – 75)	72 (64 – 76)	0.45
Metastatic sites									
Bone metastases	21 (81%)	59 (78%)	*1*	6 (67%)	19 (76%)	*0.67*	15 (88%)	40 (78%)	*0.49*
LN involvement	13 (50%)	49 (64%)	*0.25*	6 (67%)	14 (56%)	*0.7*	7 (41%)	35 (69%)	*0.08*
LN only	1 (4%)	3(4%)	*1*	1 (11%)	1 (4%)	*0.47*	0 (0%)	2 (4%)	*1*
Bone + LNs only	12 (46%)	46 (61%)	*0.25*	5 (56%)	13 (52%)	*1*	7 (41%)	33 (65%)	*0.1*
Visceral	4 (16%)	16 (22%)	*0.77*	2 (22%)	6 (24%)	*1*	2 (12%)	10 (20%)	*0.71*
Laboratory values at Enzalutamide initiation									
Haemoglobin (mmol/L)	7.0 (6.5-7.9)	7.1 (6.8-8.0)	0.64	7.7 (6.9-8.0)	7.40 (6.9-8.2)	0.57	6.8 (6.2-7.6)	6.9 (6.3-7.7)	0.4
ALP (U/L)	176 (137-292)	162 (88-282)	0.54	225 (135-240)	142 (103-308)	0.34	175 (143-341)	164 (83-280)	0.89
Albumin (U/L)	36 (30-40)	39 (36-43)	0.09	40 (38-42)	42 (38-44)	0.44	31 (30-37)	38 (36-41)	0.08
Bilirubin (μmol/L)	6.5 (5-8)	7 (5-8)	0.47	7 (6.0-8.0)	8 (4.9-10.0)	0.65	5.3 (4.8-7.0)	7.0 (5.0-8.0)	0.51
LDH (U/L)	233 (198- 433)	246 (191-381)	0.72	218 (192-259)	241 (207-531)	0.027	364 (205-552)	248 (190-340)	0.33
Previous systemic therapies*									
Number of Doc courses	9.5 (6 – 10)	8 (6 – 10)	0.88	9 (6 - 10)	8 (4 - 10)	0.66	10 (6 – 10)	9 (6 – 10)	0.92
Doc-sensitivity	21 (81%)	39 (57%)	0.05	7 (78%)	12 (52%)	0.25	14 (82%)	27 (60%)	0.14
Number of Cab courses	8 (6 – 8)	5.5 (4 – 8)	0.59	8 (7.0 - 8.0)	5 (4.5 - 10.0)	0.95	7 (5.0 – 8.2)	6 (3.0 – 8.0)	0.51

Abbreviations: IQR, interquartile range; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AA, Doc-sensitivity was defined as ≥50% PSA decline from baseline; Doc, Docetaxel; Cab, Cabazitaxel;

* Percentages are based on number of patients with available data.


ENZALUTAMIDE