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Immediate Prostate-specific Antigen Decline After Enzalutamide Following Abiraterone Predicts Survival in Castration-resistant Disease

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Abstract. *Background/Aim: Although the sequential use of abiraterone and enzalutamide is not recommended because of possible cross-resistance, many patients with metastatic castration-resistant prostate cancer (mCRPC) are receiving sequential abiraterone and enzalutamide in the real world, and a subset of patients can benefit from sequential therapy with these drugs. This study aimed to identify patients who could benefit from the sequential use of enzalutamide after abiraterone use. Patients and Methods: We included 70 patients with mCRPC who received enzalutamide sequentially following abiraterone treatment. Decline in the prostate-specific antigen (PSA) levels at 4 weeks after enzalutamide initiation and the association between decline in PSA levels and survival were analyzed. Results: Sixteen men (22.9%) achieved a decline of >50% in PSA levels after 4 weeks of enzalutamide administration. Overall survival (OS) after enzalutamide among men with >50% decline at 4 weeks was significantly better than that among men with a PSA decline <50% (not reached vs. 34 months, p=0.008). OS after first-line abiraterone treatment for men with PSA decline >50% and <50% was not reached and 46 months, respectively (p=0.007). A PSA decline of >50% at 4 weeks of enzalutamide administration was an independent predictor of longer OS. Conclusion: A PSA decline of >50% at 4 weeks after the start of sequential enzalutamide treatment following abiraterone treatment predicted long-term survival in patients with mCRPC. Early PSA decline can identify patients who benefit from second-line enzalutamide after abiraterone treatment and can be useful as a decision-making tool regarding treatment.*

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Advanced prostate cancer can progress to metastatic castration-resistant prostate cancer (mCRPC), a fatal disease, despite a favorable initial response to androgen deprivation therapy (ADT) (1). Androgen receptor axis-targeted (ARAT) therapies, chemotherapeutic agents, alpha-emitter radium-223, and poly (ADP-ribose) polymerase (PARP) inhibitors are used in patients with mCRPC. Although large-scale phase III clinical trials have demonstrated the efficacy of these therapeutics, the survival of patients with mCRPC is less than 3 years (2, 3). Knowledge of the optimal sequence of these agents could maximize therapeutic efficacy; however, this remains to be determined. ARAT agents and docetaxel are frequently used as first- and second-line therapies for mCRPC. Abiraterone and enzalutamide account for 65% of first-line and 51-54% of second-line therapies (4, 5), and both abiraterone and enzalutamide are usually preferred for early-phase mCRPC.

Clinical studies have demonstrated the reduced efficacy of second-line ARAT agent following another ARAT agent (6-11), and sequential use of these ARAT agents is not recommended (3) because of possible cross-resistance (12-14). A randomized controlled trial, the CARD study (15), compared the efficacy of cabazitaxel and alternative ARAT agent in patients with mCRPC who received docetaxel and abiraterone or enzalutamide and showed that cabazitaxel

achieved significantly better outcomes in terms of radiographic progression-free survival (PFS) and overall survival (OS). However, in the real world, a substantial number of patients with mCRPC receive sequential abiraterone and enzalutamide (4, 5, 16), and sequential ARAT agent use is beneficial in a subset of patients (6-11, 16). It is valuable to identify this subset of patients who will benefit from sequential ARAT therapy; however, this remains a major challenge. Regarding the sequence order, enzalutamide after abiraterone achieved better outcomes in terms of PFS and PSA response than therapy in the reverse order (6-11, 17-19). Prostate-specific antigen (PSA) change at 4 weeks (PSA4w) of an ARAT agent, either abiraterone or enzalutamide, predicts clinical outcome, and early PSA reduction by >30% is strongly associated with longer OS (20, 21).

We conducted this study to identify subgroups that can benefit from the sequential use of enzalutamide after abiraterone.

Patients and Methods

Patient population. A retrospective study was conducted to determine the clinical activity of enzalutamide following abiraterone among patients with mCRPC. Consecutive patients who received sequential abiraterone-to-enzalutamide therapy at six hospitals in Japan were included. All patients had histologically proven adenocarcinoma, and the diagnosis of mCRPC was made according to European Association of Urology (EAU) guidelines (3). Eligible patients were started on enzalutamide after abiraterone treatment for mCRPC between October 2014 and July 2021. These patients received abiraterone 1,000 mg and prednisolone 10 mg/day until progression, then shifted to enzalutamide 160 mg/day. Ongoing ADT with luteinizing releasing hormone analogs was continued for the study duration if patients did not undergo surgical castration. PSA levels were measured every 1-3 months after the initiation of abiraterone administration. Imaging studies were performed at the discretion of the physician.

Outcome measure. PFS was defined as the time between enzalutamide initiation and the date of progression, which was defined by PSA, radiographic, or clinical progression according to the criteria of the Prostate Cancer Working Group 3 (22). OS was defined as the time from first-line abiraterone or second-line enzalutamide initiation to the date of death or the last follow-up for survivors.

Statistical analysis. Survival curves were generated using the Kaplan–Meier method, and a log-rank test was used to compare survival between groups. Hazard ratios and associated 95% confidence intervals (CIs) were estimated using a stratified Cox proportional hazard model. Uni- and multivariate analyses were performed using EZR (Easy R, Vienna, Austria), a graphical user interface for R (The R Foundation for Statistical Computing). Differences were considered to be statistically significant at $p \leq 0.05$.

Ethics approval. This study was approved by the local institutional review board of each hospital.

Table I. *Baseline characteristics at the start of ADT and enzalutamide (n=70).*

At the start of ADT	
PSA (ng/ml), median (IQR)	112 (22.6-625.5)
Gleason grade group, n (%)	
1	2 (2.9)
2	2 (2.9)
3	10 (14.3)
4	19 (27.1)
5	37 (52.9)
M status, n (%)	
M0	16 (22.9)
M1	54 (77.1)
Local treatment, n (%)	
Prostatectomy	3 (4.3)
Radiation therapy	9 (12.9)
At the start of Enz	
Age (yr), median (IQR)	75 (71.3-80.8)
PSA (ng/ml), median (IQR)	11.3 (2.8-26.4)
Time to CRPC (months), median (IQR)	18 (11.25-36)
Visceral metastasis, n (%)	9 (12.9)
Lung only	7 (10.0)
Lung and liver	2 (2.9)
PSA response to Abi (%)	
(>50% decline)	31 (44.3)
Interposed drugs, n (%)	
Docetaxel	5 (7.1)
Others	2 (2.9)
None	63 (90.0)
Treatment period, median (IQR)	4 (2.5-6)

Abi: Abiraterone; ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; Enz: enzalutamide; IQR: interquartile range; PSA: prostate-specific antigen.

Results

Patient characteristics. A total of 89 patients with mCRPC received sequential treatment with abiraterone and enzalutamide during the study period. Of these, 19 were excluded because of discontinuation of abiraterone before progression, a history of enzalutamide use before abiraterone administration, or a lack of detailed clinical and follow-up data. The remaining 70 patients were eligible for the analysis, and baseline characteristics at the start of ADT and enzalutamide administration are listed in Table I. At the start of enzalutamide administration, the median age and PSA value were 75 [interquartile range (IQR)=71.3-80.8] years and 11.3 (IQR=2.8-26.4) ng/ml, respectively. The median time to CRPC was 18 (IQR=11.3-36.0) months; 9 (12.9%) patients had visceral metastases. A PSA response (>50% decline of PSA) to previous abiraterone was noted in 31 (44.3%) patients. Interposed drugs between abiraterone and enzalutamide were used in only 7 (10%) patients, and the median treatment period was 4 (IQR=2.5-6.0) months.

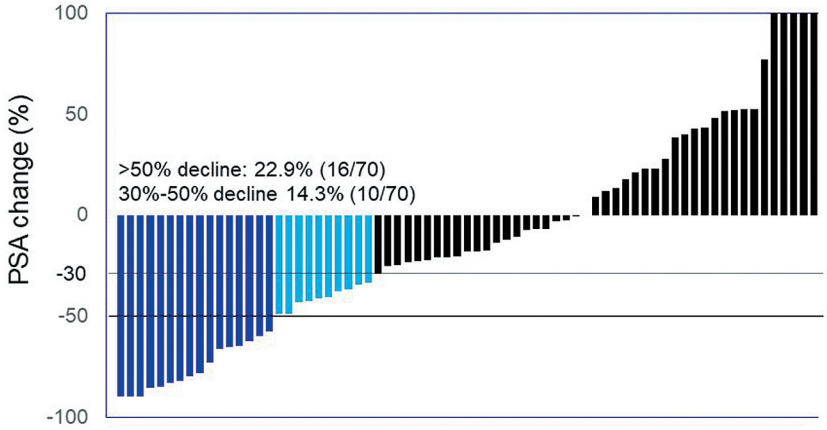

Figure 1. *Waterfall plot of prostate-specific antigen change at 4 weeks after the start of enzalutamide.*

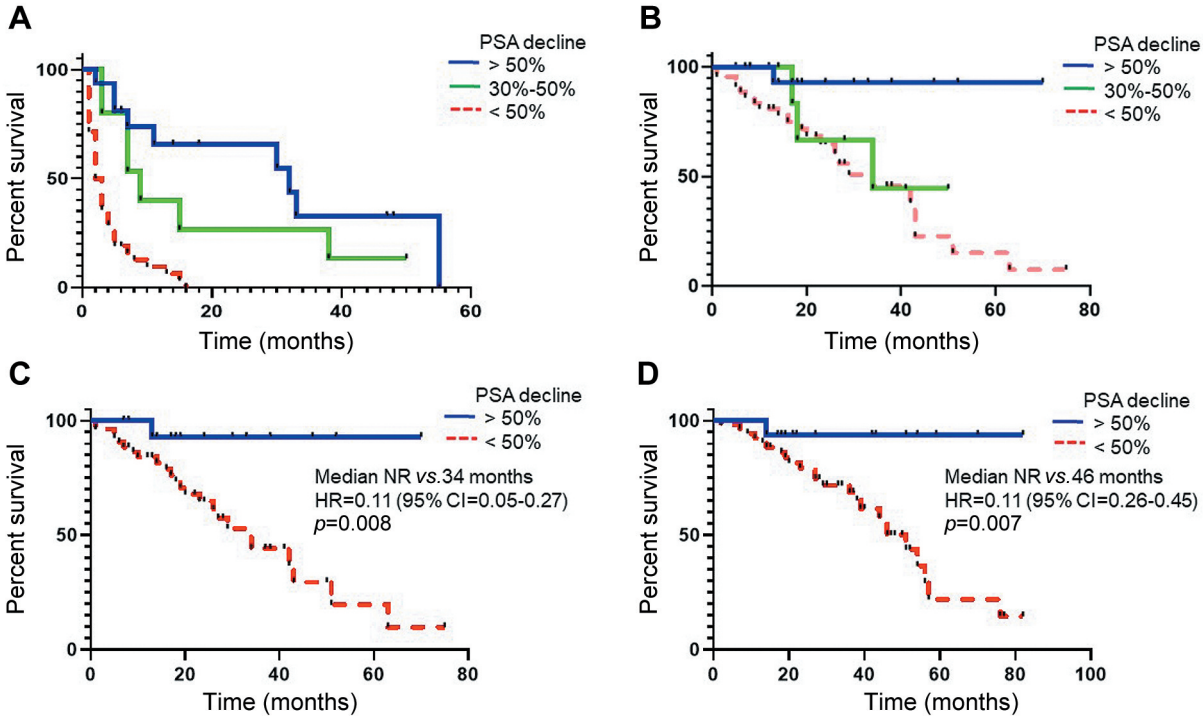

Figure 2. *Kaplan–Meier estimate of progression-free (PFS) and overall survival (OS) according to different prostate-specific antigen (PSA) decline cut-off values of 50% and 30% at 4 weeks of enzalutamide. A: PFS after enzalutamide administration (PSA decline >50% vs. 30%-50% vs. <30%). B: OS after enzalutamide administration (PSA decline >50% vs. 30%-50% vs. <30%). C: OS after enzalutamide administration (PSA decline >50% vs. <50%). D: OS after abiraterone administration (PSA decline >50% vs. <50%).*

PSA4w and oncologic outcomes.

PSA response. Median PSA4w was 7.4 (IQR=1.2-22.1) ng/ml, and the rate of reduction ranged from 92.2% to -484%. PSA decline of >50% (PSA4w>50D) and that of 30% to 50% at PSA4w (PSA4w30-50D) were observed in 16 (22.9%) and 10 (14.3%) patients, respectively (Figure 1).

Survival. The median follow-up times from abiraterone and enzalutamide initiation were 30 (IQR=18-47) months and 19 (IQR=12-32) months, respectively. The median PFS from enzalutamide initiation for men with PSA4w>50D, PSA4w30-50D, and PSA reduction <30% or increase (PSA4w<30D) was 32.0 months, 9.0 months, and 2.5 months, respectively, and

Table II. *Univariate and multivariate Cox regression hazard model for overall survival after enzalutamide initiation.*

	Univariate		Multivariate	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age >75 y (median)	0.78 (0.35-1.73)	0.541		
Gleason group ≥4	1.34 (0.50-3.61)	0.561		
M1 at diagnosis	1.20 (0.45-3.20)	0.723		
Time to CRPC <18 months (median)	2.69 (1.14-6.35)	0.023	2.01 (0.88-4.57)	0.096
>50% PSA decline on Abi	0.60 (0.27-1.33)	0.211		
PSA at Enz initiation >11.3 ng/ml (median)	2.47 (1.08-5.65)	0.03	2.08 (0.93-4.62)	0.074
>50% PSA decline at 4 w of Enz initiation	0.11 (0.01-0.80)	0.03	0.12 (0.02-0.89)	0.039

Abi: Abiraterone; CI: confidence interval; CRPC: castration-resistant prostate cancer; Enz: enzalutamide; HR: hazard ratio; PSA: prostate-specific antigen; w: weeks.

PFS rates for men with PSA4w>50D and PSA4w30-50D were significantly longer than those for men with PSA4w<30D ($p<0.0001$, $p=0.001$, Figure 2A and B). During the follow-up period, 19 deaths occurred in patients without PSA4w>50D, while one death, due to renal cancer, occurred among those with PSA4w>50D. Thus, no prostate cancer death was noted if PSA declined by >50% 4 weeks after enzalutamide initiation. The median OS from enzalutamide initiation for men with PSA4w>50D, PSA4w30-50D, and PSA4w<30D was not reached (NR), 34 months, and 34 months, respectively. OS for men with PSA4w>50D was significantly better ($p=0.032$); however, OS for men with PSA4w30-50D was comparable to that of those with PSA4w<30D ($p=0.456$). Thus, we compared OS between men with and without PSA4w>50D (Figure 2C and D). The median OSs from the start of enzalutamide for men with and without PSA4w>50D was NR and 34 months, respectively, and men with PSA4w>50D had significantly longer OS [HR=0.11 (95%CI=0.05-0.27), $p=0.008$]. Similarly, OS from the start of first-line abiraterone for men with PSA4w>50D was significantly better than that for men who did not achieve a reduction in PSA4w by >50% (NR *vs.* 46 months, HR=0.11, 95%CI=0.26-0.45, $p=0.007$).

Univariate and multivariate analyses using the Cox proportional hazards model were performed to identify clinicopathological factors associated with OS. Univariate analysis revealed that the time to CRPC, PSA value at enzalutamide initiation, and PSA decline at 4 weeks of enzalutamide administration were associated with OS. Multivariate analysis identified that only PSA4w>50D was an independent prognostic factor for longer OS (Table II, HR=0.10, 95%CI=0.01-0.90, $p=0.029$).

Discussion

Four ARAT agents, abiraterone, enzalutamide, apalutamide, and darolutamide, are available and effective in CRPC. Sequential use of these ARAT agents is of great interest, and it is important to use these ARAT agents as effectively as possible. Although sequential use of ARAT agents is not recommended (3), consecutive ARAT regimens are frequently used in the real world (4, 5), and a subset of patients demonstrates a favorable response to second-line ARAT agent and achieves long-term survival (16). In addition, sequential therapy with ARAT agents is considered for patients who are unsuitable for chemotherapy. A recent clinical study revealed that the OS between those who received ARAT-ARAT agent and ARAT agent-docetaxel sequences was comparable, suggesting that the ARAT-ARAT agent sequence might be a preferred treatment (23). Retrospective and prospective studies have reported treatment results with abiraterone to enzalutamide therapy, as well as the reverse. The PSA response (>50% decline) to abiraterone after enzalutamide was only 4-13%, whereas the PSA response to enzalutamide after abiraterone treatment was 18-40% (7, 10, 11, 17, 18). PFS was also better in the abiraterone to enzalutamide sequence than in the opposite direction (7, 10, 11, 17, 24). These different clinical outcomes noted with different sequences may be explained by the distinct mechanisms of action of abiraterone and enzalutamide. Abiraterone is a potent inhibitor of androgen biosynthesis, whereas enzalutamide strongly inhibits androgen receptor activity. The biology of CRPC is heterogeneous. A subset of CRPC cells is activated at very low concentrations or even in the absence of androgen by over-expression of the androgen receptor or by cross-activation through other signaling pathways. This state is called "ligand-independent, androgen receptor-dependent" (25). In this case, abiraterone is no longer effective; however, enzalutamide retains clinical activity in this state, suggesting that enzalutamide could exert clinical activity in some patients with progression despite previous abiraterone use.

Previous studies investigating the efficacy of enzalutamide following abiraterone treatment have shown modest efficacy and limited survival (6-11, 18). These studies assessed OS

for all patients together without considering individual differences in the biology of prostate cancers among different patients. The efficacy of sequential therapy should be assessed by stratifying patients based on biomarkers.

Our study assessed survival by stratifying patients according to PSA decline 4 weeks after the start of second-line enzalutamide administration. A PSA reduction of >50% was associated with long-term survival. Survival was quite poor in patients who did not achieve PSA4w>50D, and these patients should be immediately switched to alternative treatment options such as docetaxel, cabazitaxel, or PARP inhibitors if there are mutations in homologous recombination repair genes (26). This demonstrates the importance of early treatment decision-making so as to improve patient outcomes. Thus, PSA4w>50D could be used as a marker to facilitate earlier treatment switching decisions. Previous studies have reported that PSA reduction by >30% at 4 weeks after first-line abiraterone or enzalutamide initiation was associated with longer OS (20, 21). PSA4w30-50D was associated with a better PFS but not with a better OS compared to a PSA decline of <30% or more. In contrast, PSA4w>50D was associated with longer PFS and OS, and no patient died due to prostate cancer during the follow-up period. Greater than 50%, but not 30%, decline in PSA at 4 weeks was strongly associated with favorable outcomes in men receiving second-line enzalutamide following abiraterone. Therefore, patients with PSA4w>50D can be continued on enzalutamide, but other treatments should be offered immediately to others.

The baseline clinical and pathological characteristics make it difficult to predict the efficacy of second-line ARAT agent (27). Liquid biopsy samples such as plasma circulating tumor DNA fraction and mutations in the androgen receptor may be able to predict treatment outcomes in patients treated with sequential ARTA agents (12). These predictive molecular biomarkers will help identify subgroups that can benefit from sequential ARAT treatment in the future. At present, we propose that PSA4w is useful for determining the efficacy of sequential treatment with abiraterone and enzalutamide.

Recently, upfront combination therapy with ADT and ARAT agent, including abiraterone, has become the standard of care for metastatic castration-sensitive prostate cancer (3, 28). For those who develop CRPC later, after upfront combination therapy with an ARAT agent, a standard of care is yet to be determined, but another ARAT agent and docetaxel can be a treatment option. However, care should be taken as there could be cross-resistance between the ARAT agents (6-11, 18). For these patients, early PSA response to a second-line ARTA agent may help determine further appropriate treatment, as shown in this study.

Our study has several limitations such as the limited cohort size, retrospective study design, restriction to only Japanese patients, and relatively short follow-up period. Therefore, larger prospective studies are needed to validate our results.

In conclusion, a PSA decline of >50% at 4 weeks after the start of sequential abiraterone and enzalutamide treatment was associated with long-term survival in patients with mCRPC. Early PSA decline can identify patients who benefit from this second-line therapy and can be used as a marker for treatment-related decision-making.

Conflicts of Interest

The Authors report no conflicts of interest regarding this work.

Authors' Contributions

Naohiro Fujimoto conceived the presented idea, selected eligible patients, analyzed data, and wrote the manuscript. Akinori Minato analyzed data. Wataru Obara, Tasuku Hiroshige, Tsukasa Igawa, Atsushi Fukuda, Yujiro Nagata, Yui Mizushima, collected the clinical data. Kenichi Harada, Ikko Tomisaki critically reviewed the manuscript. All Authors discussed, verified and approved the final version of the manuscript.

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