















# Enzalutamide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: A retrospective Korean multicenter study in a real-world setting

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**Purpose:** This study aimed to evaluate the clinical efficacy of enzalutamide in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients using real-world data from Korean patients.

**Materials and Methods:** We retrospectively reviewed the medical records of 199 chemotherapy-naïve patients with mCRPC at 13 tertiary centers in Korea between 2014 and 2017. All patients received enzalutamide daily and 89 patients received concurrent androgen deprivation therapy (ADT).

**Results:** The median age of the patients was 74 years. Initial results showed that 81.5% of the patients had Gleason score  $\geq 8$  and 33.3% of the patients had European Cooperative Oncology Group Performance Status 0. The overall mortality rate was 12%. The median OS was not achieved and 76.7% of patients were alive at 30 months. Median time until PSA progression was 6 months. The overall survival rate at 2 years was significantly higher (84.6% vs. 71.7%,  $p=0.015$ ) and the duration of PSA progression-free survival was significantly longer (8.0 vs. 4.6 months,  $p=0.008$ ) in patients receiving concurrent ADT than in those receiving enzalutamide alone. The incidence of adverse events of grade 3 or higher was 1.7%. Multivariate Cox proportional hazard analysis indicated that ADT administered concurrently with enzalutamide significantly improved the overall survival (hazard ratio, 0.346; 95% confidence interval, 0.125–0.958).

**Conclusions:** Enzalutamide is effective and safe for chemotherapy-naïve patients with mCRPC. Furthermore, the overall survival was significantly higher in patients receiving enzalutamide and concurrent ADT than in patients receiving enzalutamide alone.

**Keywords:** Androgen antagonists; Neoplasm metastasis; Prostate neoplasms; Treatment outcome

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## INTRODUCTION

In 2012, prostate cancer was the fifth most commonly diagnosed malignancy in Korean men [1]. The incidence of prostate cancer is lower in Korea than in western countries [2]. However, a steady increase has been observed in the prevalence of prostate cancer in Korea during the last decade [3]. Progression of prostate cancer leads to metastasis, and most patients respond to androgen deprivation therapy (ADT). However, patients develop resistance to ADT, and this condition is known as metastatic castration-resistant prostate cancer (mCRPC). Metastatic CRPC is defined by progression of cancer despite the effective lowering of serum testosterone levels to castrate levels [4]. Docetaxel plus prednisone is the current standard of care for mCRPC in Korea, but this therapy has toxic effects and leads to the development of drug resistance [5]. Recent findings have shown that androgen receptor signaling plays an important role in CRPC, which suggests that inhibition of this pathway using non-cytotoxic therapies may confer a survival benefit. The results of the international, randomized, double-blind, phase 3, PREVAIL trial in chemotherapy-naïve men showed that enzalutamide improves overall survival (OS) [6].

Results of the PREVAIL showed that treatment with enzalutamide showed positive outcomes on all secondary endpoints, including the time until the first skeletal-related event (SRE), soft-tissue response rate, time until prostate-specific antigen (PSA) progression, and PSA response rate ( $\geq 50\%$  decline), as well as patient-reported outcomes [6-9]. Enzalutamide was approved in Korea in June 2013 for use in men with CRPC post-chemotherapy based on the results of the AFFIRM trial. In May 2015, the indication was expanded to include men with CRPC regardless of previous exposure to chemotherapy based on results of the PREVAIL trial [10]. This study aimed to evaluate the clinical results of enzalutamide in chemotherapy-naïve mCRPC patients using Korean, multicenter, real-world data and to compare them with the results of the PREVAIL study. In Korea, continuous ADT for mCRPC patients was prohibited until January 2017; subsequently, concurrent ADT was allowed. Thus, we were able to analyze the efficacy of enzalutamide and concurrent ADT in the treatment of patients with chemotherapy-naïve mCRPC. This study will support evidence to the current recommendations for continuing luteinizing hormone-releasing hormone (LHRH) therapy, which can improve the benefits of enzalutamide treatment in patients with chemotherapy-naïve mCRPC.

## MATERIALS AND METHODS

### 1. Study design and patients

We retrospectively reviewed the medical records of 199 chemotherapy-naïve patients with mCRPC at 13 tertiary centers in Korea between 2014 and 2017. The exclusion criteria were previous docetaxel chemotherapy, brain metastasis, or epidural disease. Patients who had already received enzalutamide treatment included in a clinical trial were excluded. Enzalutamide was administered daily at an initial dose of 160 mg, and ADT was administered in a conventional manner. Unlike the PREVAIL trial, our trial did not have stringent eligibility criteria to reflect a real clinical environment. The endpoint of this trial was OS, which was defined as the time from the start of treatment to any cause of death. We followed the protocol mentioned in the PREVAIL trial for the definition of response criteria and endpoints in Prostate Cancer Clinical Trial Working Group 2, Solid Tumor Version 1.1 (RECIST 1.1). For patients with a decreased PSA levels at week 13, the time to PSA progression was defined as the day on which PSA levels increased by more than 25% and the day on which PSA levels increased by at least 2 ng/mL over a minimum of two consecutive days. For patients without a decreased PSA levels at week 13, the day on which PSA levels increased by more than 25% and the day on which a 2 ng/mL increase over baseline levels was recorded was identified as the second consecutive value. Radiographic progression-free survival (rPFS) was defined as the time of initial objective evidence of radiological progression or death. Radiographic progression is defined as the appearance of two or more new lesions according to RECIST 1.1 or on the bone scan for soft tissue disease. SREs are defined as the events that necessitate changes in chemotherapy, such as radiation therapy or bone surgery for the treatment of pathological fractures, spinal cord compression, or bone pain. Adverse events (AEs) were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3.

### 2. Data collection and statistical analysis

The research data were collected using the Research Electronic Data Capture (REDCap) program designed to support data capture. We performed the chi-square or Mann-Whitney U tests to compare the categorical and continuous variables, respectively, between the two groups. PFS and OS were analyzed using Kaplan-Meier methods and log-rank tests. Univariate and multivariate Cox proportional hazards regression analyses were performed to assess the association between baseline parameters and OS. All p-values correspond

to two-sided tests, with p-values <0.05 considered statistically significant. PSA response summaries were presented as percentages of patients who showed a decrease in PSA levels by more than 50% or 90%, respectively, from baseline to lowest point, and were visualized using waterfall plots. AEs were described as the rate of all grade or grade ≥3 events.

**3. Ethical statement**

This study was approved by the Institutional Review Boards at each participating center (representative IRB: Seoul National University Hospital IRB no. H-1604-099-755). Subjects provided written informed consent, and the study was performed according to the Declaration of Helsinki.

**RESULTS**

Demographic features and disease characteristics of patients are shown in Table 1 [6,10]. Initial results showed that 81.5% of the patients had Gleason score (GS) ≥8 and 33.3% of the patients had European Cooperative Oncology Group Performance Status (ECOG PS) 0. Eighty-nine patients (44.9%) received concurrent ADT. Median follow-up is 9.4 months (interquartile range, 3.9–13.5 months). The overall mortality rate was 12%. The Kaplan–Meier curves for OS and rPFS

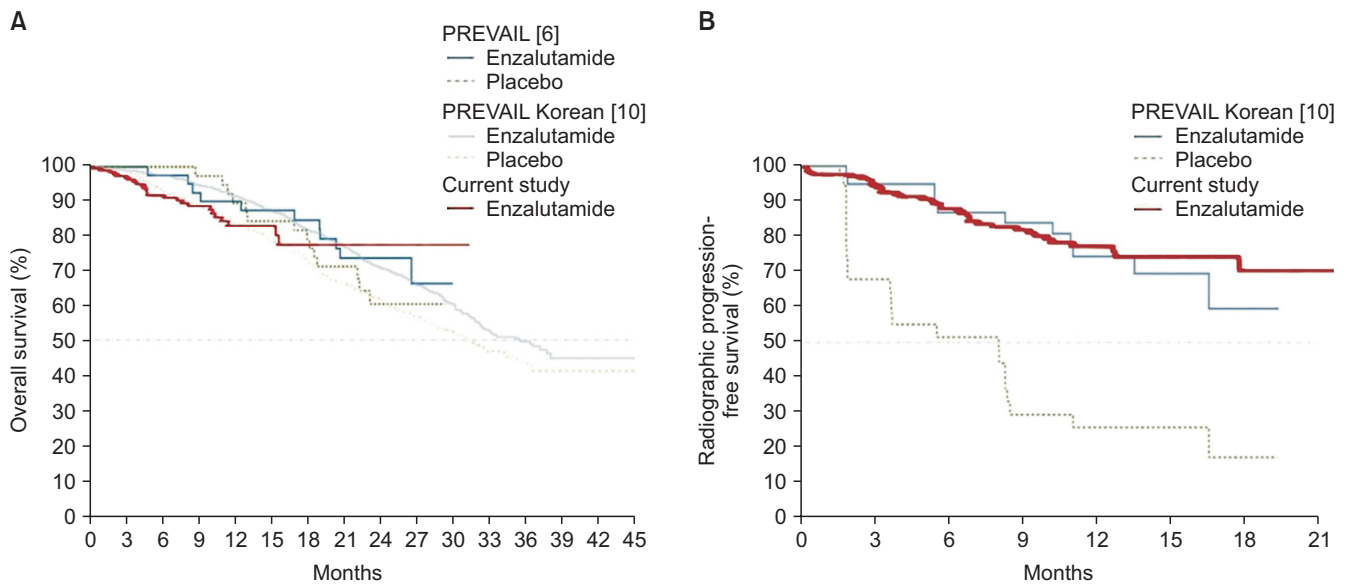
are shown in Fig. 1 [6,10]. Median OS, median rPFS, median time until chemotherapy, median time until first SRE was not reached until our analysis (Fig. 1, Table 2) [6,10]. Median time until PSA progression was 6 months (Table 2) [6,10]. After enzalutamide treatment, 35.2% of patients received more than one systemic chemotherapy (Table 3) [6,10]. The median OS was not achieved and 76.7% of patients were alive at 30 months. In a Kaplan–Meier curve with 95% confidence interval (CI), OS was 0.84 (95% CI, 0.76–0.91) at 12 months and 0.77 (95% CI, 0.67–0.87) at 24 months (Supplementary Fig. 1). The results of the univariate Cox proportional hazard analysis for OS showed that concurrent ADT, ECOG PS, and baseline PSA levels were significant predictors of OS (Table 4). Results of multivariate analysis showed that enzalutamide and concurrent ADT significantly improved the OS (hazard ratio, 0.346; 95% CI, 0.125–0.958). The median duration of enzalutamide treatment was 5 months, and the incidence of AEs of grade 3 or higher was 17% (Table 5) [6,10]. The Kaplan–Meier curves for OS, PSA PFS, and rPFS after concurrent ADT are shown in Fig. 2. The OS by 2 years was significantly improved with concurrent ADT (84.6% vs. 71.7%, p=0.015). In addition, patients receiving concurrent ADT showed a significant improvement in PSA PFS (8.0 vs. 4.6 months, p=0.008). However, rPFS at 2 years was not dif-

**Table 1.** Baseline patient and disease characteristics

Characteristic	PREVAIL (n=1,717) [6]		PREVAIL Korean (n=78) [10]		Current study (n=199)
	ENZA (n=872)	Placebo (n=845)	ENZA (n=40)	Placebo (n=38)	
Median age (y)	72 (43–93)	71 (42–93)	71 (56–83)	67 (42–85)	74 (51–94)
Median body weight (kg)	83.1	82.8	67.0	70.5	66.0
Body mass index (kg/m <sup>2</sup> )	27.5	27.5	24.4	25.5	24.2
Gleason score ≥8 at initial diagnosis	424 (50.6)	423 (52.4)	30 (81.1)	31 (81.6)	145 (81.5)
Missing	34	37	3		21
ECOG PS grade=0	584 (67.0)	585 (69.2)	22 (55.0)	29 (76.3)	62 (33.3)
Missing					13
Median PSA (ng/mL)	54.1	44.2	25.4	26.2	51.6
Median LDH (IU/L)	185.0	185.0	191.0	184.5	333.0
Prior radical prostatectomy (%)	226 (25.9)	225 (26.6)	11 (27.5)	4 (10.5)	36 (18.2)
Missing					1
Bone disease (%)	741 (85.0)	690 (81.7)	36 (90.0)	30 (78.9)	160 (82.5)
Missing					5
≥20 bone metastases	145 (16.6)	150 (17.8)	Unknown	Unknown	15 (9.9)
Missing					47
Soft-tissue disease (lymph node, visceral, or other)	517 (59.3)	504 (59.6)	22 (55.0)	22 (57.9)	110 (58.5)
Missing					11
Concurrent ADT	872 (100.0)	845 (100.0)	40 (100.0)	38 (100.0)	89 (44.9)
Missing					1

Values are presented as median (range), number only, or number (%).

ENZA, enzalutamide; ECOG PS, European Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; LDH, lactate dehydrogenase; ADT, androgen deprivation therapy.



**Fig. 1.** Kaplan–Meier survival curves for (A) overall survival and (B) radiographic progression-free survival in PREVAIL study [6], in PREVAIL Korean *post hoc* analysis [10], and in this study.

**Table 2.** Summary of oncologic outcomes

Variable	PREVAIL (n=1,717) [6]		PREVAIL Korean (n=78) [10]		Current study (n=199)
	ENZA (n=872)	Placebo (n=845)	ENZA (n=40)	Placebo (n=38)	
Median time until chemotherapy (mo)	28.0	10.8	NYR	11.2	NYR
HR (95% CI)	0.35 (0.30–0.40)		0.21 (0.08–0.51)		
Median time until PSA progression (mo)	11.2	2.8	11.1	2.9	6.0
HR (95% CI)	0.17 (0.15–0.20)		0.31 (0.17–0.56)		
Median time until first SRE (mo)	31.1	31.3	NYR	20.1	NYR
HR (95% CI)	0.72 (0.61–0.84)		1.40 (0.46–4.33)		
PSA decline of					
≥50% from baseline (n/total n; %)	666/854 (78.0)	27/777 (3.5)	28/40 (70.0)	4/38 (10.5)	139/187 (74.3)
≥90% from baseline (n/total n; %)	400/854 (46.8)	9/777 (1.2)	Unknown	Unknown	88/187 (47.1)

ENZA, enzalutamide; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; SRE, skeletal-related event; NYR, not yet reached.

**Table 3.** Subsequent anti-neoplastic and endocrine therapies

Type of treatment	PREVAIL (n=1,717) [6]		PREVAIL Korean (n=78) [10]		Current study (n=199)
	ENZA (n=872)	Placebo (n=845)	ENZA (n=40)	Placebo (n=38)	
Any systemic treatment	382 (43.8)	642 (76.0)	7 (17.5)	25 (65.8)	70 (35.2)
Missing					23
Antineoplastic agent	308 (35.3)	515 (60.9)	6 (15.0)	22 (57.9)	40 (22.7)
Docetaxel	286 (32.8)	479 (56.7)	5 (12.5)	22 (57.9)	34 (19.3)
Abiraterone acetate	179 (20.5)	385 (45.6)	1 (2.5)	4 (10.5)	9 (5.1)
Cabazitaxel	51 (5.8)	110 (13.0)	0 (0.0)	3 (7.9)	2 (1.1)
Mitoxantrone	5 (0.6)	9 (1.1)	0 (0.0)	1 (2.6)	0 (0.0)

Duplicated count was allowed.

ENZA, enzalutamide.

ferent in patients receiving concurrent ADT (71.8% vs. 68.4%,  $p=0.154$ ). The waterfall plot of the change in PSA levels in patients receiving concurrent ADT is shown in Fig. 3. To compare Korean real-world data with the result of the PRE-

VAIL study, we described data of PREVAIL study in Table 1, Table 2, Table 3, Table 5 and Fig. 1 [6,10].

Table 4. Cox regression analysis for overall survival

Variable	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (y)						
<65	Reference					
≥65	0.808	0.302–2.162	0.672			
ECOG PS						
0–1	Reference					
≥2	2.993	1.160–7.723	0.023			
No. of HT						
≤2	Reference					
>2	1.048	0.247–4.453	0.949			
Type of progression at study entry						
PSA only	Reference					
Radiographic progression +/- PSA progression	0.699	0.350–2.020	0.699			
No. of bone lesions						
<20	Reference					
≥20	1.090	0.141–8.435	0.934			
Lymph node involvement						
No	Reference					
Yes	0.943	0.415–2.139	0.888			
Visceral metastasis						
No	Reference					
Yes	1.170	0.342–4.006	0.802			
Gleason score						
≤7	Reference					
≥8	6.059	0.818–44.86	0.078			
Baseline PSA						
≤Median	Reference			Reference		
>Median	2.517	1.084–5.840	0.032	2.507	0.958–6.563	0.061
Concurrent ADT						
No	Reference			Reference		
Yes	0.335	0.133–0.845	0.020	0.346	0.125–0.958	0.041

HR, hazard ratio; CI, confidence interval; ECOG PS, European Cooperative Oncology Group Performance Status; HT, hormonal treatment; PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

## DISCUSSION

The effects of enzalutamide observed in our study with asymptomatic or mildly symptomatic Korean chemotherapy-naïve patients with mCRPC were consistent with those observed in the study population of the PREVAIL trial [6,10].

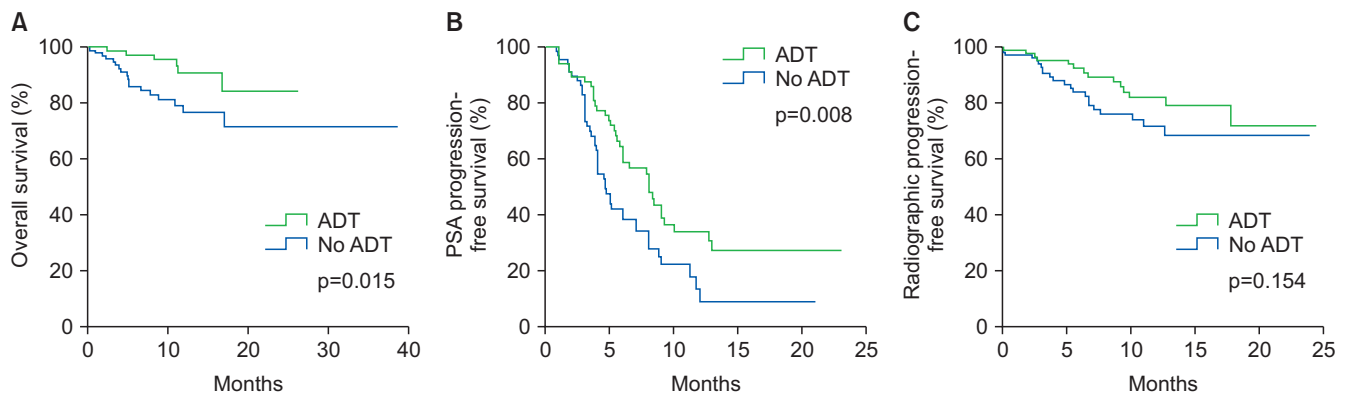
However, the baseline disease characteristics of the subjects in our study were different from those of the subjects in the PREVAIL trial, which may be because of the differences in real clinical practice. A high percentage of Korean patients had a GS of at least 8, which indicates a high disease burden. Our finding was consistent with that observed in the PREVAIL trial in that 50.6% and 81.1% patients receiving enzalutamide among the overall population and in Korean subgroup, respectively, has a GS ≥8 [10]. Some dif-

ferences were observed in the characteristics of the disease between the real-world Korean patients and the subjects in the PREVAIL trial; these differences may be related to differences in ethnicity. Compared to the overall study population of the PREVAIL trial, a larger proportion of Korean patients had poor PS. A lower proportion of patients in our study had ECOG PS=0 (33.3% vs. 67.0% in the PREVAIL study). In clinical practice, the physicians, patients, and relatives of chemotherapy-naïve patients with mCRPC with poor PS are reluctant to undergo chemotherapy. Therefore, they prefer treatment with enzalutamide despite its high cost before commencing chemotherapy. Thus, this finding may explain why our data showed that a high proportion of Korean patients had poor performance status. Korean patients receiving enzalutamide had a short median time

**Table 5.** Summary of adverse events

Parameter	PREVAIL (n=1,715) [6]		PREVAIL Korean (n=78) [10]		Current study (n=199)
	ENZA (n=871)	Placebo (n=844)	ENZA (n=40)	Placebo (n=38)	
Median duration of treatment (mo)	16.6	4.6	13.0	5.1	5.0
Any AEs	844 (96.9)	787 (93.2)	37 (92.5)	30 (78.9)	59 (34.9)
Missing					30
Serious AEs	279 (32.0)	226 (26.8)	14 (35.0)	3 (7.9)	3 (1.7)
Missing					22
Grade ≥3 AEs	374 (42.9)	313 (37.1)	13 (32.5)	4 (10.5)	3 (1.8)
Missing					30
Drug-related grade ≥3 AEs	67 (7.7)	54 (6.4)	0 (0.0)	0 (0.0)	3 (1.7)
Missing					23
Most common AEs					
Musculoskeletal pain	87 (10.0)	73 (8.6)	4 (10.0)	2 (5.3)	8 (4.7)
Fatigue	310 (35.6)	218 (25.8)	8 (20.0)	4 (10.5)	6 (3.6)
Decreased appetite	158 (18.1)	136 (16.1)	Unknown	Unknown	5 (3.0)
Constipation	193 (22.2)	145 (17.2)	6 (15.0)	2 (5.3)	2 (1.2)
Diarrhea	142 (16.3)	119 (14.1)	Unknown	Unknown	2 (1.2)
Hypertension	117 (13.4)	35 (4.1)	Unknown	Unknown	2 (1.2)
Hot flush	157 (18.0)	65 (7.7)	5 (12.5)	2 (5.3)	2 (1.2)
Headache	91 (10.4)	59 (7.0)	Unknown	Unknown	2 (1.2)
Back pain	235 (27.0)	187 (22.2)	7 (17.5)	3 (7.9)	1 (0.6)
Nausea	201 (23.1)	190 (22.5)	6 (15.0)	4 (10.5)	1 (0.6)
Asthenia	113 (13.0)	67 (7.9)	Unknown	Unknown	1 (0.6)
Upper respiratory infection	53 (6.1)	30 (3.6)	8 (20.0)	3 (7.9)	0 (0.0)

Values are presented as number only or number (%). ENZA, enzalutamide; AE, adverse event.

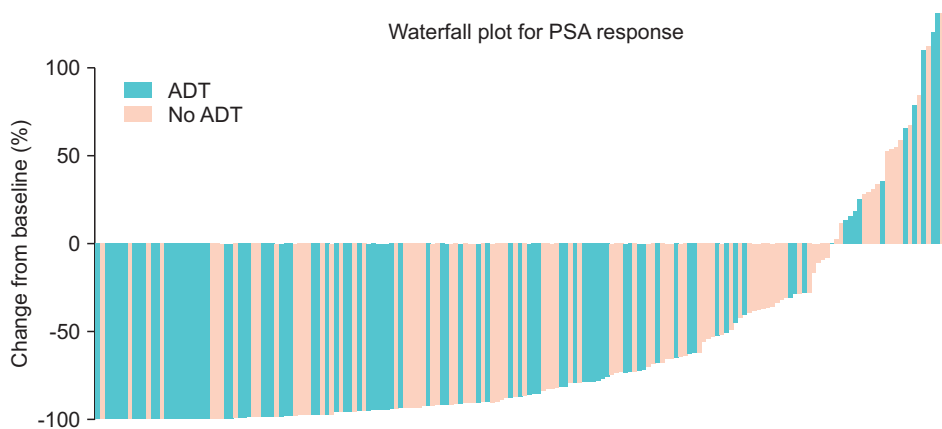


**Fig. 2.** According to concurrent androgen deprivation therapy (ADT), Kaplan–Meier survival estimates for (A) overall survival and (B) time to prostate-specific antigen (PSA) progression-free survival, and (C) radiographic progression-free survival.

until PSA progression, and poor baseline characteristics and PS may be attributed to this result. In addition to baseline characteristics, concurrent ADT affects the OS. Unlike the patients in the PREVAIL trial, a larger proportion of Korean patients (55%) had did not receive concurrent ADT with enzalutamide in the clinical setting because the Korean medical insurance system prohibited continuous ADT for mCRPC until January 2017. Our results showed that ADT administered concurrently with enzalutamide improved the

oncologic outcomes of chemotherapy-naïve patients with mCRPC.

To date, no study has established evidence supporting continuation of LHRH therapy for CRPC [11]. Few studies have investigated the effects of termination of LHRH therapy in patients with CRPC and, therefore, the current European guidelines recommend medical castration [12]. The Korean medical insurance system prohibited continuous ADT for mCRPC because of lack of evidence until January 2017.



**Fig. 3.** Waterfall plot for prostate-specific antigen (PSA) response according to concurrent androgen deprivation therapy (ADT).

Continuation of LHRH therapy may cause considerable side effects and unnecessary expenses [13]. Results from previous clinical trials indicate that castration offers only a marginal survival benefit [14,15]. Taylor et al. [14] reported the results of a retrospective study, which showed a significant marginal survival benefit for patients continuing an LHRH agonist along with anthracycline, platinum, or ketoconazole treatment for mCRPC. However, a consensus remains to be achieved about the continuation of LHRH treatment. Analysis of 5 Southwest Oncology Group phase II chemotherapy trials conducted in the 1990s failed to show an obvious advantage of continuous ADT in terms of response to cytotoxic chemotherapy or OS in patients with CRPC [15]. The results of another retrospective study of 78 patients failed to show a survival benefit of docetaxel and concurrent ADT in patients with CRPC [16]. However, it could be an underpowered study because of the small number of patients. Lee et al. [16] found that serum testosterone levels did not recover to those observed in noncastrated individuals in most patients after withdrawal of ADT for the entire duration of chemotherapy. A similar phenomenon was observed in men with hormone-sensitive prostate cancer, in which approximately half of the patients who received ADT for a long-term remained castrated at 2.5 years after ADT cessation [17]. Results of previous studies indicate that serum testosterone levels remain low after long-term treatment with LHRH agonists [18-20]. Therefore, cessation of LHRH therapy may have only little clinical relevance since serum testosterone levels remain low and may not affect proliferation of cancer cells. However, unlike serum testosterone levels, serum LH levels recover after several weeks to months after cessation of LHRH therapy [18-20]. Cessation of LHRH therapy leads to rapid recovery of LH levels after a median of 58 days to 4.5 months, even after long-term medical castration [18,19]. Apart from its action on the testes and adrenal glands, LH acts directly on prostate cancer cells via LH-specific receptors

and increases the expression of several key steroidogenic enzymes [21]. Administration of abiraterone alone increases the LH [22]. To date, the SPARE trial (NCT02077634) is the only trial that provides further insights into the complex hormonal changes that occur after treatment with abiraterone with or without concurrent LHRH therapy [23]. The SPARE trial is investigating the role of continuation of LHRH therapy when starting treatment with abiraterone in patients with asymptomatic or mild symptomatic chemotherapy-naïve CRPC. To date, no study has investigated the efficacy of enzalutamide and concurrent ADT in the treatment of chemotherapy-naïve mCRPC. Therefore, the results of our trial provide important evidence based on unique data.

This study is subject to the usual limitations inherent with retrospective design and data collection. The follow-up period of this study was relatively short. Further, some missing values are another weakness of the data. The rate of AEs in our study was lower than those in the PREVAIL trial, which may be because of the retrospective study design. The advantages of our study are that we analyzed real-world data from multiple institutions. Furthermore, the primary endpoint was OS, which is relatively objective and less confounded even in a retrospective study. Thus, our results provide novel data about the efficacy of enzalutamide and concurrent ADT for the treatment of men with chemotherapy-naïve mCRPC due to the previous medical environment in Korea, in which continuous ADT therapy for mCRPC patients was prohibited.

## CONCLUSIONS

A higher proportion of patients in our cohort study showed a GS  $\geq 8$  and poor ECOG performance status than those in the PREVAIL study, but the efficacy results in our study were similar to those in the PREVAIL study. Despite the limitations of retrospective studies, the safety

was also acceptable. Enzalutamide is effective and safe for chemotherapy-naïve patients with mCRPC in the real-world setting. Further, compared to enzalutamide alone, concurrent administration of ADT with enzalutamide significantly prolonged the survival. Thus, we recommend concurrent administration of ADT with enzalutamide for the treatment of chemotherapy-naïve patients with mCRPC.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## AUTHORS' CONTRIBUTIONS

Research conception and design: Chang Wook Jeong, Seung Il Jung, Cheol Kwak, and Dong Deuk Kwon. Data acquisition: all authors. Data analysis and interpretation: Myung Soo Kim, Chang Wook Jeong, and Seung Il Jung. Drafting of the manuscript: Myung Soo Kim and Seung Il Jung. Approval of final manuscript: all authors.

## SUPPLEMENTARY MATERIAL

Scan this QR code to see the supplementary material, or visit <https://www.icurology.org/src/sm/icurology-61-19-s001.pdf>.



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