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Research Article

Assessment of androgen receptor signaling inhibitors therapy in metastatic hormone-sensitive prostate cancer

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ABSTRACT

Androgen receptor signaling inhibitor (ARSI) therapy plays an important role in treating advanced prostate cancer. However, in Thailand, the efficacy and safety data of ARSI therapy remain limited. This study aimed to assess the efficacy and safety of ARSI therapy to treat patients with metastatic castration naïve prostate cancer. We collected data from electronic medical records based on disease progression and any reported adverse events. The primary outcome was progression-free survival (PFS) after initiating ARSI therapy. Secondary outcome was PFS according to abiraterone and enzalutamide, risk factors associated with PFS of ARSI therapy and adverse events. A total of 49 eligible patients were enrolled having received ARSI therapy (abiraterone or enzalutamide) to treat metastatic prostate cancer. The median time to follow-up was 17 months (interquartile range, 12-31). PFS among patients treated with ARSI therapy was 22 months (95% confidence interval [CI], 17-33), PFS among patients with abiraterone and enzalutamide was 21 and 23 months, respectively (hazard ratio [HR], 0.48; 95% CI, 0.17-1.41, *P*=0.185). Patients with Eastern Cooperative Group status 1-2 exhibited significantly decreased risk of disease progression (HR, 0.44; 95% CI, 0.20-0.96, *P*=0.038). The common adverse events included hypertension and fluid retention and edema. In conclusion, abiraterone and enzalutamide showed a trend to improve PFS among patients with metastatic castration naïve prostate cancer. Adverse events were rarely reported, and patients were able to tolerate treatment.

Keywords:
Androgen receptor signaling inhibitor, Castration naïve, Prostate cancer, Abiraterone, Enzalutamide

1. INTRODUCTION

Prostate cancer is a common health problem and considered one of most significant cancer-related deaths among men worldwide[1]. Several studies have shown that patients with metastatic stage including the bone, lung and liver exhibit higher complications and mortality rates[2]. Although androgen deprivation therapy (ADT) with a luteinizing hormone-releasing agonist/antagonist or bilateral orchidectomy to castration status has been recommended as the standard of treatment for metastatic prostate cancer, most patients with metastatic hormone sensitive prostate cancer (mHSPC) are defined as patients with metastatic prostate cancer not previously treated with ADT or sensitive to ADT to achieve castration state (testosterone level <50 ng/mL). Those treated with ADT alone exhibiting rapidly progress despite a castrate testosterone level to castration-resistance prostate cancer (mCRPC) within one to three years due to the effect of androgen receptors overexpression and upregulation of androgen biosynthesis from the progression of prostate cancer[3].

Based on clinical data demonstrating significantly improved overall survival (OS), progression-free survival (PFS), quality of life and delayed complications, patients with mHSPC receive a combination of ADT and chemotherapy (docetaxel) or androgen receptor signaling inhibitor (ARSI) therapy[4-7]. Currently, these combinations are recommendation to the standard of care for mHSPC by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network, and the European Society of Medical Oncology (ESMO)[8-10].

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Interestingly, the evidence of ARSI is increasingly regarding as effective and safe for mHSPC[4,11]. Abiraterone acetate, the first generation of ARSIs, is a potently selective inhibitor cytochrome P-450 c17 (CYP17), constituting the most important key enzyme for testicular and extragonadal androgen biosynthesis[12-13]. Likewise, the second generation ARSI (enzalutamide, apalutamide and darolutamide) is a potent androgen receptor (AR) inhibitor[13]. The mechanism of actions includes competitive binding to AR, inhibiting androgen receptor nuclear translocation and androgen-receptors-mediated DNA binding[14].

Although no head-to-head trials have been conducted, a network meta-analysis study was conducted to compare the effectiveness of active treatment in prostate cancer[15]. Based on a large randomize controlled trial, larger OS benefits were shown in abiraterone acetate and apalutamide treatment whereas enzalutamide was associated with a greater improvement in PFS. Moreover, large population retrospective studies have found several factors related to ARSI efficacy, including tumor volume, level of prostate specific antigen (PSA) at diagnostic, age and visceral metastasis[16].

Besides efficacy, the side effects of chemotherapy should be concerned. Concomitant abiraterone acetate with prednisolone should be carefully administered among patients with cardiovascular disease such as congestive heart disease, uncontrolled hypertension and diabetes. Moreover, transaminitis should be monitored as well. On the other hand, patients with underlying seizure and uncontrolled hypertension must be evaluated before and during enzalutamide treatment. As one reason for cognitive and physical function impairment, enzalutamide should be mediated with caution for patients older than 75 years[17-18].

In Thailand, ARSI is becoming more widely used in clinical practice. Abiraterone and enzalutamide were widely used to treat mHSPC and mCRPC[9]. Nevertheless, information is limited to support clinical benefits of abiraterone and enzalutamide for mHSPC in Thai populations. Hence, this study aimed to determine the efficacy and safety of ARSI (abiraterone and enzalutamide) based on a real-world setting among patients with mHSPC.

2. MATERIALS AND METHODS

This single-center, retrospective cohort study was conducted by reviewing electronic medical records (EMR) of patients with prostate cancer and receiving abiraterone acetate or enzalutamide between January 2017 and June 2021 at Maharaj-Nakorn Chiang Mai Hospital, Chiang Mai, Thailand, the largest university-affiliated cancer center in northern Thailand. The study design was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (EC approval number: No. 199/2022).

2.1. Patients

This study included patients with castration naïve metastatic prostate cancer or hormone-sensitive metastatic disease ether newly diagnosed or recurrent after prior local treatment of prostate cancer. All eligible patients had maintained ADT and were receiving abiraterone acetate or enzalutamide at least six months during the study. Patients receiving abiraterone acetate to treat prostate cancer during the nonmetastatic stage or prior treatment metastatic stage with ADT and docetaxel or documented confirmed CRPC were excluded (Figure 1).

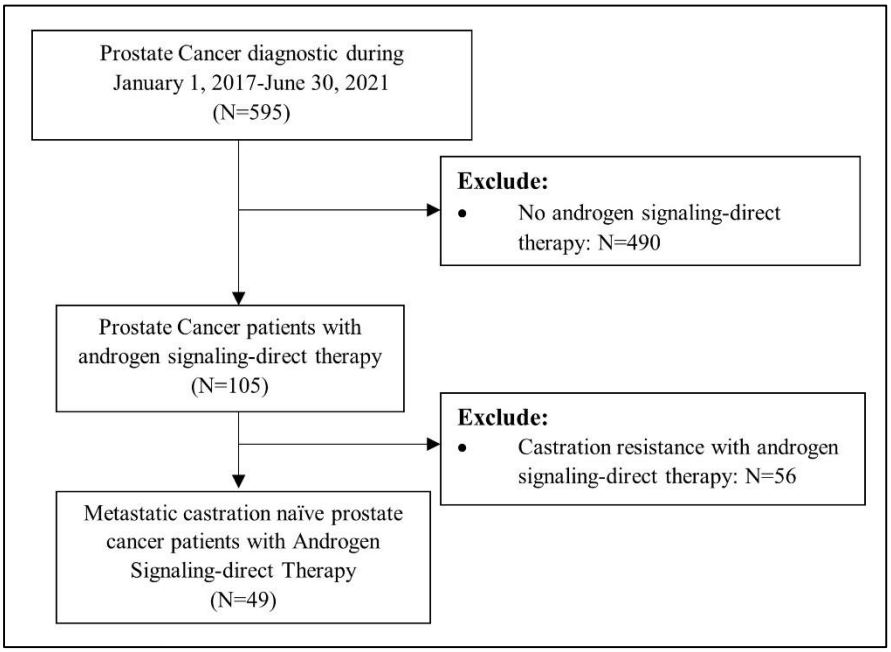

Figure 1. consort diagram.

2.2. Data collection and outcomes

The patients' characteristics including date of prostate cancer diagnosis, site of metastasis, Eastern Cooperative Oncology Group (ECOG) score, type of castration therapy, comorbidity, date of initiating and discontinuing androgen signaling-direct therapy, adverse events, PSA at diagnosis or before initiating androgen signaling-direct therapy and every hospital visit until disease progression were retrieved from the EMR.

The primary outcome was PFS after initiating ARSI. All patients were followed up from initiating ARSI to disease progression. Disease progression was confirmed by medical progress notes according to Response Evaluation Criteria in Solid Tumors and Prostate Cancer Clinical Trials Working Group-2 criteria for radiologic progression and PSA progression, respectively[19-20]. The patients were censored when lost to follow-up or showed no disease progression at the study end date (December 31, 2021), whichever came first. The secondary outcomes were PFS according to abiraterone acetate and enzalutamide, risk factors associated with PFS of ARSI and adverse events. All adverse events were confirmed and recorded by individual oncologist records in medical progress notes based on the Common Terminology Criteria for Adverse Events, Version 5.0[21].

2.3. Statistical analysis

Patient demographics were examined using descriptive analysis, and continuous variables were compared using 'Student's t-tests or Mann-Whitney U-tests, as appropriate. Fisher's exact test was used to compare categorical variables between groups, and Kaplan-Meier estimates were calculated for PFS. Risk factors related to PFS were assessed using Cox proportional hazards models. The potential risk factors including ECOG, age, type of metastasis and baseline PSA level above median were adjusted in the multivariable analysis. Schoenfeld's global test method was performed to test proportional hazards assumption,[22] and a two-sided *p*-value less than 0.05 was considered statistically significant. STATA, Version 15 (StataCorp LP, College Station, TX, USA), was used for statistical analysis and data management.

3. RESULTS

3.1. Baseline characteristics

This study included 49 patients with castration naïve metastatic prostate cancer meeting the inclusion criteria, of which, 41 received abiraterone and 8 were treated with enzalutamide. The median (standard deviation [SD]) age was 67.6 (8.50) years at diagnosis. Bone metastasis was found in the majority of patients (87.7%). The most common castration therapy was orchidectomy (55.1%), and median time to follow-up was 17 months (interquartile range [IQR], 12 to 31 months). All baseline characteristics were shown in Table 1.

3.2. Progression-free survival after initiating androgen signaling-direct therapy

The median PFS among patients treated with androgen signaling-direct therapy was 22 months (95% CI, 17 to 33) (Figure 2A). Median PFS among patients receiving abiraterone and enzalutamide was 21 and 23 months, respectively (hazard ratio [HR], 0.48; 95% CI,

Table 1. Baseline characteristics of 49 eligible patients receiving Androgen receptor signaling inhibitor (ARSI) therapy.

Characteristic	Total (%) N=49	Abiraterone (%) N=41	Enzalutamide (%) N=8	*P*-value
Age (Mean ± SD)	67.6±8.50	67.3±8.45	69.4±9.12	0.536
Metastasis				
Bone	43 (87.7)	37 (90.2)	6 (75.0)	0.250
Lung	7 (14.3)	5 (12.2)	2 (25.0)	0.320
Liver	2 (4.1)	2 (4.9)	0	1.000
ECOG				
0	23 (46.9)	22 (53.7)	1 (12.5)	0.052
1-2	26 (53.1)	19 (46.3)	7 (87.5)	0.052
Type of castration therapy				
Orchidectomy	27 (55.1)	23 (56.1)	4 (50.0)	1.000
GnRH agonist/antagonist	22 (44.9)	18 (43.9)	4 (50.0)	1.000
Co-morbidity				
Cardiovascular disease	26 (53.1)	22 (53.7)	4 (50.0)	1.000
Diabetes mellitus type 2	12 (24.5)	11 (26.8)	1 (12.5)	0.660
Other disease	13 (26.5)	12 (29.3)	1 (12.5)	0.663
Baseline PSA, Median (IQR)	56.2 (287.4)	56.2 (415.9)	67.2 (146.9)	0.829
Time to follow-up, Median (IQR)	17 (12,31)(19)	17 (12,30)(18)	21 (13.5,49.5)(36)	0.205

Hypertension, Dyslipidemia, Heart failure, Venous thrombosis
Chronic kidney disease, Anemia, Chronic Obstructive Pulmonary disease, and Gout.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GnRH, Gonadotrophin Releasing Hormone; PSA, Prostate Specific Antigen; SD, Standard deviation; IQR, Inter Quartile Range

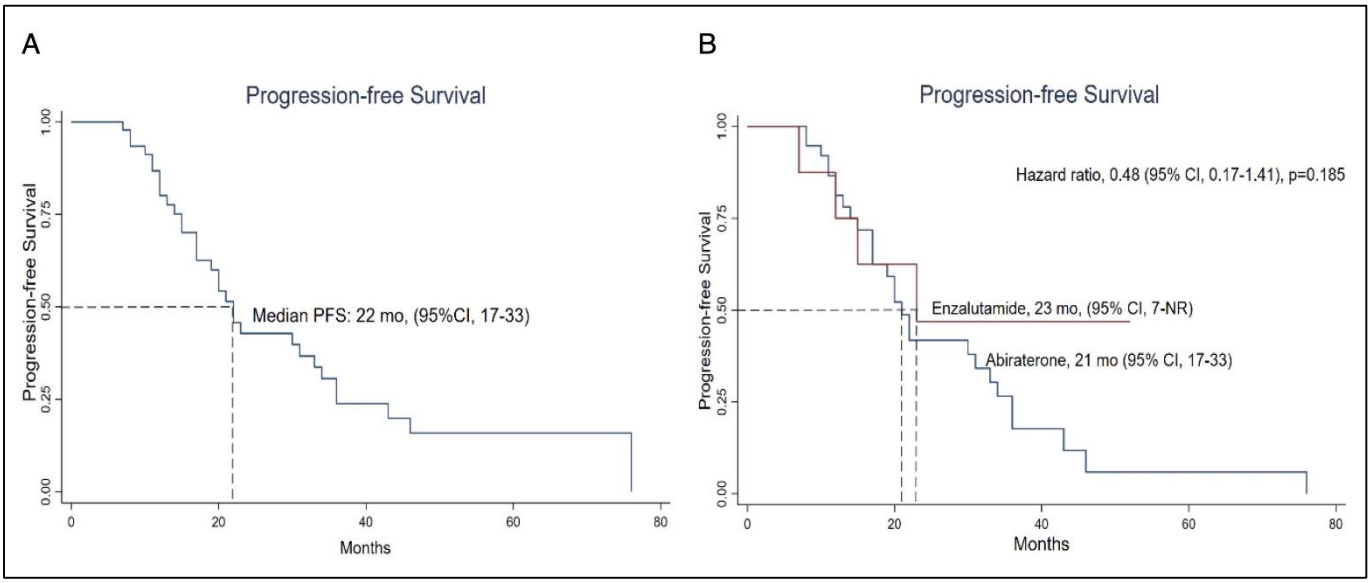

Figure 2. Progression-free survival for all patients (A) and comparison of progression-free survival on patients with abiraterone versus enzalutamide (B).

Table 2. PSA and radiologic progression-free survival (PFS).

End Point	Total (95% CI)	HR (95% CI)	Abiraterone (95% CI)	Enzalutamide (95% CI)	*P*-value
PFS, median (95%CI)	22 (17-33)	0.48 (0.17-1.41)	21 (17-33)	23 (7-NR)	0.185
PSA PFS, median (95%CI)	23 (19-34)	0.56 (0.20-1.67)	22 (19-34)	23 (7-NR)	0.300
Radiological PFS, median (95%CI)	43 (22-NR)	1.00 (0.27-3.69)	43 (22-NR)	NR	0.999

Abbreviations: PFS, Progression-Free Survival; PSA, Prostate Specific Antigen; NR, Not Reached; HR, Hazard ratio; CI, Confidence interval.

Table 3. Subgroup analysis by risk factors related to PFS.

End Point	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ECOG				
0	1		1	
1-2	0.41 (0.20-0.87)	0.020	0.42 (0.19-0.92)	0.030
Age				
<65 year	1		1	
≥65 year	0.72 (0.35-1.46)	0.361	0.87 (0.40-1.89)	0.721
Type of metastasis				
Non-visceral metastasis	1		1	
Visceral metastasis	0.91 (0.34-2.37)	0.843	1.15 (0.41-3.22)	0.789
Baseline PSA above median				
No	1		1	
Yes	1.34 (0.67-2.79)	0.394	1.38 (0.67-2.86)	0.386

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, Prostate Specific Antigen; HR, Hazard ratio; CI, Confidence interval

Table 4. Adverse events[†].

Event	Abiraterone N=48 (%)	Enzalutamide N=10(%)
Hypertension	13 (27.10)	2 (20.00)
Fluid retention and edema	0 (0.00)	1 (10.00)

[†] All patients were clinically documented at grades 1-2 adverse events

0.17 to 1.41, *P*=0.185) (Figure 2B). Median PFS due to PSA progression only was 23 months (95% CI, 19 to 34) and radiologic progression was 43 months (95% CI, 19 to not reached[23]). No difference was found among abiraterone and enzalutamide in both PSA progression only and radiologic progression (HR, 0.56; 95% CI, 0.20 to 1.67, *P*=0.3; and HR, 1.00; 95% CI, 0.27 to 3.69, *P*=0.999, respectively; Table 2).

3.3. Association between prespecified risk factors and PFS

Univariable and multivariable subgroup analysis (Table 3) revealed no significance among all potential risk factors, except ECOG status 1 to 2 significantly decreased the risk in both univariable and multivariable analysis (HR, 0.41, 95% CI, 0.20 to 0.87, *P*=0.02; and HR, 0.44; 95% CI, 0.20 to 0.96, *P*=0.038, respectively). The proportional hazard assumption test showed no evidence of violating all the tested models (*P*=0.564).

3.4. Adverse events

Sixteen patients reported clinically documented grade 1 to 2 adverse events (Table 4). Of a total of 58 adverse events, the common episodes included hypertension (27.1% in the abiraterone group and 20% in the enzalutamide group). Additionally, fluid retention and edema were recorded in the enzalutamide group (10%).

4. DISCUSSION

This retrospective study was conducted to demonstrate the recent real-life efficacy of ARSIs in a single tertiary university-affiliated cancer center in northern Thailand. The median PFS of all patients was 22 months. A longer median PFS was found in the enzalutamide group compared with the abiraterone group (23 versus 21 months). However, statistical significance was undetected. Using multivariable analysis, ECOG status was presented as a predictive factor associated with PFS (*P*=0.038). Fifty-eight adverse events were reported by 16 patients. Nevertheless, these events did not lead to treatment discontinuation.

Additional abiraterone and enzalutamide improved the PFS. This result was consistent with several related studies demonstrating the efficacy of ARSI in mHSPC[4,6,24]. The results from two randomized controlled trials showed improvement using enzalutamide and abiraterone for mHSPC[4,25]. The ARCHES study showed a greater OS and PFS for enzalutamide over placebo[4]. In addition, the COU-AA 302 study demonstrated significantly improved OS and PFS from abiraterone over chemotherapy[23]. Our study also showed clinical benefit from ARSI for PFS using real-world data confirming that ARSI affected extragonadal androgen synthesis improving clinical benefit over conventional therapy regardless of tumor volume or disease burden. Moreover, durable antitumor effect and safety profile from ARSI were confirmed to be associated with long term treatment without serious adverse events.

According to the PFS compared with other treatments, enzalutamide demonstrated clinically meaningful benefits from potent AR inhibition with a second-generation nonsteroidal antiandrogen[15]. In the PREVAIL study, enzalutamide revealed better outcome in terms of OS and PFS, although other studies did not find this difference in OS outcome[26]. Similar to related studies, longer PFS was found in the enzalutamide group over that of the abiraterone group. However, this trend did not reach statistical significance.

Several factors were reported as predictive factors of PFS including age and PSA, according to LATITUDE and CHAARTED studies[6,25]. Older age at diagnosis of mHSPC, PSA at three months, PSA nadir ≤0.2 at six months and LATITUDE low risk showed better PFS, whereas CHAARTED low volume disease at baseline did not result in prolonged PFS using multivariable analysis[6,15,25]. However, the association between those factors and PFS were not found in this study.

ECOG performance status is a known significant prognostic factor of mortality regarding prostate cancer. The related study demonstrated the potential predictive value of ECOG (ECOG ≥2 vs <2) for OS among patients with metastatic prostate cancer[27]. A significant difference between ECOG score of 0 and 1 to 2 on OS and PFS was not found[28]. However, in this study, ECOG 1 to 2 showed significantly better PFS. This result might have been affected from a higher proportion of ECOG 1 to 2 group compared with ECOG score of 0 (87.5% vs. 12.5%, respectively; *P*=0.052).

According to related studies, hypertension was a common complication in both abiraterone and enzalutamide groups[6,24]. Because of the concomitant use with prednisolone, the mineralocorticoid effect might have caused adverse events in the abiraterone group[24]. Even though serious adverse events, e.g., seizure and febrile neutropenia from enzalutamide or tachycardia and transaminitis form abiraterone were reported, none of those were presented in this study[6,24,27]. All adverse events were grades 1 to 2 and did not lead to treatment withdrawal.

To our knowledge, this study highlighted the clinical benefit of ARSI in a Thai population. This constituted single-center retrospective research and was the first cohort study to reflect the real-world effectiveness of abiraterone and enzalutamide on PFS among patients with mHSPC in Thailand. This study encountered some limitations. First, because of the retrospective design, all data were collected from databases of healthcare records. As a result, missing data on clinical outcome could have occurred. Moreover, incomplete and inadequate records were found as well. However, cases were confirmed

individually by a physician. Secondly, several confounding factors may have affected PFS outcome; some residual risk factors could have remained in this study such as disease volume (high vs. low) and Gleason score. Although multivariable analysis was used to adjust the potential risk factors, we could not adjust for disease volume and Gleason score because this record was unavailable in the EMR. Finally, the small sample size might not have exhibited insufficient power to evaluate the effects of some factors concerning PFS. Because patients with mHSPC are considered as self-pay for treatment with ADT+ARSI and unavailable for reimbursement from the Oncology Prior Authorization (OCPA) Program or Universal Health Care Coverage in Thailand, a small number of patients were included in this study. A large sample size will be required to confirm the difference in PFS between abiraterone and enzalutamide as well as any association between factors and PFS. Moreover, comparing clinical benefits between ADT+ARSI and ADT+chemotherapy in mHSPC should be performed in a further study.

5. CONCLUSION

This study revealed that additional abiraterone and enzalutamide to ADT improved clinically meaningful outcome across PFS among patients with metastatic castration naïve prostate cancer. Furthermore, an advantageous safety profile was shown. Adverse events were rarely reported, and patients were able to tolerate treatment. This finding supported the use of abiraterone and enzalutamide as effective therapy for mHSPC.

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Conflicts of Interest
The authors declare they have no conflicts of interest.

Ethics approval
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee at the Faculty of Medicine, Chiang Mai University (Study code: NONE-2565-09027; approval number: No. 199/2022).

Author Contributions
Conceptualization, J.Y., W.P., C.D. and O.L.; method, J.Y. C.D. and O.L.; formal analysis, J.Y., C.D, O.L. and W.P.; data curation, J.Y., W.P., C.D. and O.L.; writing-original draft preparation, J.Y., C.D, O.L. and W.P.; writing-review and editing, J.Y. and W.P. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement
Patient consent was waived due to the retrospective design by the Research Ethics Committee at the Faculty of Medicine, Chiang Mai University.

Data Availability Statement
No additional data was generated in the study.

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