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Original Article

Enhancing outcomes in mCRPC: the impact of androgen receptor inhibitor sequencing before ^{177}Lu-PSMA-617 therapy

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Abstract

Background: Prostate-specific membrane antigen (PSMA) is a key target in metastatic castration resistance prostate cancer (mCRPC). Enzalutamide, an androgen receptor pathway inhibitor (ARPi), increases PSMA expression, potentially enhancing ^{177}Lu-PSMA-617 radioligand therapy. This study evaluates the impact of prior ARPi (enzalutamide vs abiraterone acetate [AA]) on PSMA expression, PFS, and OS.

Materials and Methods: A retrospective analysis of 214 mCRPC patients treated with ^{177}Lu-PSMA-617 across six Turkish centers (2015-2025) was conducted. Patients were grouped by prior ARPi therapy. PFS and OS were analyzed using Kaplan-Meier and Cox regression methods.

Results: Among 103 patients receiving ARPi before ^{177}Lu-PSMA-617, 59 (57%) had enzalutamide and 44 (43%) AA. Median PFS was 7.6 months for enzalutamide versus 5.3 months for AA ($P = .068$). Median OS was significantly longer with enzalutamide (12.8 vs 6.9 months, $P = .021$). Patients with Eastern Cooperative Oncology Group Performance Scores (ECOG PS) 0-1 had significantly longer OS (27.6 vs 6.9 months for PS 2-3, $P < .0001$). Higher PSMA SUVmax (>20) correlated with longer OS (15.1 vs 7.8 months, $P = .016$). Among 86 patients with detectable PSMA SUVmax, 53 had SUVmax > 20; 66% had prior enzalutamide and 34% AA. Median OS was four months longer with enzalutamide (18.1 vs 13.9 months $P = .120$). Multivariate analysis identified ARPi type (HR: 2.24, $P = .033$) and ECOG PS (HR: 5.22, $P < .0001$) as independent OS predictors.

Conclusion: Enzalutamide prior to ^{177}Lu-PSMA-617 significantly improves OS and enhances PSMA expression compared to AA. These findings highlight the importance of treatment sequencing in mCRPC and warrant further prospective studies.

Key words: Abiraterone acetate; ARPi; Enzalutamide; ^{177}Lu-PSMA-617; PSMA.

Key Points

Prior enzalutamide use significantly affects overall survival and PSMA expression in patients with mCRPC treated with 177Lu-PSMA-617.
Enzalutamide is linked to longer overall survival compared to abiraterone acetate.
The type of androgen receptor pathway inhibitor and ECOG Performance Status independently predict overall survival.
Treatment sequencing is crucial for optimizing outcomes in mCRPC.

Introduction

Prostate-specific membrane antigen (PSMA) is a glycoprotein expressed on the surface of prostate carcinoma cells and serves as a key therapeutic target in metastatic castration-resistant prostate cancer (mCRPC).[1,2] Among current treatment approaches, Lutetium-177- PSMA-617 (^{177}Lu-PSMA-617) radioligand therapy is distinguished by its specific targeting of PSMA, with high PSMA expression serving as a reliable

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predictor of treatment response.[3] PSMA expression in prostate cancer is regulated by a multifaceted interplay of genetic, epigenetic, and microenvironmental factors, resulting in marked heterogeneity across different tumor sites and stages of disease progression. Elements such as hypoxia and cellular stress, as well as epigenetic modifications—including DNA methylation and histone acetylation—along with influences from the tumor microenvironment, including cytokines and stromal interactions, collectively modulate PSMA levels. This underscores the dynamic and context-dependent regulation of this antigen.[4] Androgen receptor (AR) signaling serves as a primary regulator of PSMA expression, with androgen deprivation or AR pathway inhibition leading to the upregulation of PSMA, particularly in castration-resistant prostate cancer. Both PSMA and AR function as key receptors involved in cell proliferation and exhibit a strong interrelationship in the context of metastatic prostate cancer.[5,6] AR blockade leads to increased PSMA expression within specific clonal subpopulations of prostate cancer cells.[7] Enzalutamide has been shown to upregulate PSMA expression in both preclinical and clinical settings.[8–10] In mCRPC, elevated PSMA expression is associated with reduced overall survival in patients receiving androgen receptor pathway inhibitor (ARPi) therapy.[11] However, high PSMA expression is crucial for the effective delivery of radiation with ^{177}Lu-PSMA-617 therapy and is correlated with improved treatment outcomes.[12] Upregulation of PSMA through enzalutamide administration before ^{177}Lu-PSMA-617 therapy may enhance treatment efficacy and extend survival in androgen-resistant prostate cancer clones. This study aimed to evaluate the impact of ARPi selection before ^{177}Lu-PSMA-617 radioligand therapy on PSMA expression and, in this context, progression-free survival (PFS) and overall survival (OS).

Methods

Patients and data

We conducted a retrospective cohort study involving patients with mCRPC who received sequential treatment with ^{177}Lu-PSMA-617 (second or third line) and ARPi between January 2015 and January 2025 across six cancer centers in Turkey. Patients were categorized into two groups based on the type of ARPi received before ^{177}Lu-PSMA-617: enzalutamide and abiraterone acetate (AA). Exclusion criteria included the absence of consecutive ARPi-^{177}Lu-PSMA-617 treatment, use of ARPi combined with PARP inhibitors (PARPi) before ^{177}Lu-PSMA-617, or missing data that prevented survival analysis. Demographic details, prostate cancer diagnosis dates, Eastern Cooperative Oncology Group Performance Status (ECOG PS), laboratory and pathological results, treatment initiation and completion dates, as well as progression and death dates, were collected retrospectively.

Statistical analysis

The primary objective of the study was to assess the impact of ARPi selection before ^{177}Lu-PSMA-617 on PFS and OS. PFS was defined as the time from the initiation of ^{177}Lu-PSMA-617 to the first documented disease progression or death, while OS was defined as the time from the start of ^{177}Lu-PSMA-617 to death.

Statistical analyses were performed using IBM SPSS Statistics 21.0. Continuous variables were summarized as medians with interquartile ranges (IQR), and categorical variables were presented as percentages. The Chi-square test was used to compare categorical variables, while continuous variables were analyzed using either the Mann-Whitney *U* test or Student's t-test, as appropriate. Survival rates and curves were estimated using the Kaplan-Meier method, and Cox regression analyses were conducted to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). All *P*-values were two-sided, with values <.05 considered statistically significant.

Ethics statement

The study was approved by the Ankara University Non-Interventional Clinical Research Ethics Committee (Registration No: 2024000389-2, dated 28.06.2024) and conducted in full compliance with the principles outlined in the Declaration of Helsinki. Given the retrospective design of the study, the Institutional Review Board waived the requirement for obtaining individual informed consent.

Results

The study included 214 patients who underwent ^{177}Lu-PSMA-617 treatment between January 2015 and January 2025. Among those meeting the study criteria, 103 patients had received ARPi before ^{177}Lu-PSMA-617, with 59 (57%) treated with enzalutamide and 44 (43%) treated with AA. The baseline characteristics were comparable between the two groups (Table 1).

Progression-free survival

At a median follow-up of 12 months (IQR: 3.5-17.0 months), PFS was 7.6 months (95% CI: 5.2-10.1) in the enzalutamide group and 5.3 months (95% CI: 0-10.9) in the AA group (*P* = .068). PFS was significantly longer in patients with a PSMA maximum standardized uptake value (SUVmax) >20 compared to those with ≤20 (9.2 months vs 3.4 months, *P* = .003). Median PFS was significantly longer in the enzalutamide group for both patients with a SUVmax of 10-20 (4.8 months vs 2.5 months) and those with a SUVmax >20 (12.6 months vs 8.1 months) (*P* = .026; Table 2).

Overall survival

The median OS was 12.8 months (95% CI: 6.4-19.2) in the enzalutamide group and 6.9 months (95% CI: 0.8-13.0) in the AA group (*P* = .021) (Figure 1). When analyzed by ECOG PS, patients with ECOG PS 0-1 had a median OS of 27.6 months (95% CI: 15.2-40.1), compared to 6.9 months (95% CI: 4.8-9.0) for those with ECOG PS 2-3 (*P* < .001). OS was significantly longer in patients with a PSMA SUVmax >20 compared to those with ≤ 20 (15.1 months vs 7.8 months, *P* = .016). Among the 86 patients with assessable pretreatment PSMA SUVmax, 53 had an SUVmax > 20. Of these, 35 (66%) had received enzalutamide in their prior line of therapy, while 18 (34%) had been treated with AA. Median OS was significantly longer in the enzalutamide group for both patients with an SUVmax of 10-20 (8.4 months vs 5.0 months) and those with

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Table 1. Patients' characteristics according to ARPi groups.

Variable	Pre-lutetium enzalutamide (*N*=59) (%)	Pre-lutetium abiraterone acetate (*N*=44) (%)	*P*
Age			.085
<65	28 (47)	27 (61)	
≥65	31 (53)	17 (39)	
Pretreatment PSA median (IQR)	42 (14-282)	103 (31-234)	.376
T-stage (clinical/pathological)			.353
T1	1 (2)	1 (2)	
T2	13 (22)	16 (36)	
T3	26 (44)	12 (27)	
T4	7 (12)	3 (7)	
N-stage (clinical/pathological)			.286
N0	19 (32)	18 (41)	
N1	29 (49)	18 (41)	
Grade group			.179
GG1	2 (3)	2 (5)	
GG2	6 (10)	1 (2)	
GG3	9 (15)	4 (9)	
GG4	13 (22)	5 (11)	
GG5	27 (46)	28 (64)	
ECOG PS			.781
0-1	18 (31)	10 (23)	
2-3	23 (39)	11 (25)	
De-novo metastatic disease status			.206
No	18 (31)	19 (43)	
Yes	40 (68)	25 (57)	
Metastasis site			
Bone	55 (93)	43 (98)	.865
Lymph node	33 (56)	30 (68)	.313
Lung	4 (7)	7 (16)	.158
Liver	6 (10)	5 (11)	.941
PSMA SUVmax			.820
≤20	21 (36)	12 (27)	
>20	35 (60)	18 (41)	
Lutetium cycle number			.281
<4	28 (47)	26 (59)	
≥4	24 (41)	14 (32)	
Number of pre-lutetium treatments			.526
1	50 (85)	35 (80)	
2	9 (15)	9 (20)	

Abbreviations: GG: grade group, ECOG PS: Eastern Cooperative Oncology Group Performance Status, PSMA SUVmax: Prostate-Specific Membrane Antigen Maximum Standardized Uptake Value, IQR: interquartile ranges, PSA: prostate-specific antigen.

an SUVmax >20 (18.1 months vs 13.9 months) ($P = .040$). Baseline factors, including age at diagnosis, T- and N-stage at diagnosis, grade group, presentation with de-novo metastatic disease, bone metastases, lymph node involvement, and liver or lung metastases, were not associated with OS (Table 2). Multivariate analysis identified ARPi type (HR: 2.24, $P = .033$) and ECOG PS (HR: 5.22, $P < .001$) as independent OS predictors (Table 3).

Discussion

This study investigated the impact of ARPi selection on PSMA expression and survival outcomes in patients receiving second or third-line ^{177}Lu-PSMA-617 following prior ARPi treatment. The results demonstrated that prior use of enzalutamide was associated with a numerical advantage in PFS, a trend toward increased PSMA expression, and a significantly prolonged OS. These findings suggest that enzalutamide may enhance PSMA expression and improve survival in specific patient subgroups.

PSMA expression is inversely correlated with androgen receptor signaling. Enzalutamide inhibits androgen binding to the androgen receptor, resulting in the upregulation of the folate hydrolase gene responsible for PSMA expression.[13] Enzalutamide has been demonstrated to enhance PSMA expression in both clinical and preclinical settings. Staniszewska et al. reported that enzalutamide treatment induced PSMA expression in a human xenograft model characterized by low baseline PSMA levels.[8] In a retrospective study by Rosar et al., involving 30 patients with mCRPC, a significant increase in PSMA expression was observed through Ga-68 PSMA PET-CT (Positron Emission Tomography/Computed Tomography) imaging conducted, on average, 13 days after initiating enzalutamide treatment, compared to baseline measurements.[10] Aggarwal et al. reported the case of a patient with mCRPC who received ^{177}Lu-PSMA-617 therapy following disease progression after androgen deprivation therapy and docetaxel. After experiencing prostate-specific antigen (PSA) progression following the third cycle of ^{177}Lu-PSMA-617, the patient was treated with enzalutamide for two weeks. Subsequently, after the fourth cycle of ^{177}Lu-PSMA-617, an increase in the avidity of metastatic lesions was observed, followed by a notable decrease in PSA levels.[14] Additionally, in phase 3 randomized, controlled PSMAfore trial, the efficacy of ^{177}Lu-PSMA-617 was evaluated in patients with PSMA-positive mCRPC who were taxane-naïve and considered for an ARPI switch following progression on a prior ARPI. The study demonstrated that ^{177}Lu-PSMA-617 significantly prolonged radiographic PFS compared to an ARPI switch, with a favorable safety profile. Subgroup analysis revealed that among patients previously treated with AA before receiving ^{177}Lu-PSMA-617, the HR was 0.57 (0.42-0.77). Notably, in patients previously treated with enzalutamide, the risk reduction was even more pronounced, with an HR of 0.37 (0.26-0.54).[15]

Recent studies have identified DNA damage repair (DDR) as one of the determinants of PSMA expression. In a study by Paschalis et al., the relationship between immunohistochemistry, next-generation sequencing data, and clinical outcomes was evaluated. The study demonstrated an association between DDR aberrations and higher PSMA expression.[16] Similarly, a retrospective analysis by Raychaudhuri et al. demonstrated enhanced OS in the DNA damage group among mCRPC patients treated with ^{177}Lu-PSMA-617.[17] However, due to incomplete data regarding the DDR status of our patient population, it was not possible to specifically assess this relationship within the context of our study. This limitation restricts the generalizability of our current findings. In addition, given the limited size of our study population, the disproportionate representation of patients with potential DDR alterations in the enzalutamide group may have contributed to increased PSMA expression, thereby allowing this subgroup to derive greater benefit from ^{177}Lu-PSMA-617 treatment.

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Table 2. Univariate analysis of progression-free survival and overall survival.

	Progression-free survival		Overall survival	
Variable	Month (median, %95 CI)	*P*	Month (median, %95 CI)	*P*
Age		.216		.382
<65	5.2 (2.9-7.5)		9.2 (3.1-15.4)	
≥65	8.6 (6.5-10.6)		14.3 (7.1-21.4)	
T-stage (clinical/pathological)		.772		.296
T3	7.3 (3.1-11.6)		10.7 (7.6-13.8)	
T4	5.3 (1.8-8.8)		8.4 (4.5-12.3)	
N-stage (clinical/pathological)		.608		.195
N0	8.1 (5.2-11.1)		13.9 (6.8-20.9)	
N1	5.2 (1.6-8.9)		8.8 (5.1-12.5)	
Grade Group		.535		.443
GG3	9.1 (0-18.5)		14.7 (0-32.2)	
GG4	6.5 (1.7-11.3)		9.7 (0.5-18.9)	
GG5	6.9 (4.5-9.3)		8.8 (5.1-12.4)	
ECOG PS		.195		**<.001**
0-1	11.4 (6.5-16.2)		27.6 (15.2-40.1)	
2-3	5.2 (0.9-9.5)		6.9 (4.8-9.0)	
De-novo metastatic disease status		.058		.261
No	9.1 (5.8-12.5)		13.9 (4.1-23.6)	
Yes	5.3 (2.1-8.5)		9.2 (4.9-13.6)	
Metastasis site				
Bone	7.3 (4.6-10.1)	.985	10.7 (6.1-15.3)	.315
Lymph node	8.7 (6.5-10.8)	.674	11.1 (5.0-17.2)	.686
Lung	7.1 (6.2-8.1)	.983	9.7 (2.8-16.6)	.687
Liver	3.9 (0-8.7)	.327	6.3 (0-12.9)	.104
PSMA SUVmax		**.003**		**.016**
≤20	3.4 (1.6-5.2)		7.8 (3.5-12.0)	
>20	9.2 (5.2-13.1)		15.1 (7.5-22.6)	
Pre-lutetium ARPI variant		.068		**.021**
Enzalutamide	7.6 (5.2-10.1)		12.8 (6.4-19.2)	
Abiraterone acetate	5.3 (0-10.9)		6.9 (0.8-13.0)	
SUVmax values and previous ARPI type		**.026**		**.040**
SUVmax 10-20		.126		.140
Enzalutamide	4.8 (2.0-7.7)		8.4 (2.9-10.9)	
Abiraterone acetate	2.5 (0.6-4.3)		5.0 (3.2-6.7)	
SUVmax > 20		.109		.120
Enzalutamide	12.6 (3.5-21.8)		18.1 (7.9-28.2)	
Abiraterone acetate	8.1 (5.2-11.0)		13.9 (4.0-23.7)	

Abbreviations: GG: grade group, ECOG PS: Eastern Cooperative Oncology Group Performance Status, PSMA SUVmax: Prostate-Specific Membrane Antigen Maximum Standardized Uptake Value, ARPI: androgen receptor pathway inhibitor. The bold values indicate variables with statistically significant p values.

In our study, consistent with findings in the literature, we observed a trend toward an increase in PSMA SUVmax in patients treated with enzalutamide before ^{177}Lu-PSMA-617 therapy compared to those receiving AA. However, interpreting this effect remains challenging due to the absence of follow-up Ga-68 PSMA PET-CT results, leaving changes in SUVmax over time unknown. Notably, OS outcomes were significantly improved in patients treated with enzalutamide before ^{177}Lu-PSMA-617 compared to those treated with AA. Moreover, subgroup analysis based on PSMA SUVmax revealed that enzalutamide retained its OS advantage over AA in both the PSMA SUVmax 10-20 and >20 groups. Follow-up imaging studies are required to comprehensively evaluate the clinical significance of the observed increasing trend in PSMA SUVmax values. The findings indicate that enzalutamide offers superior overall survival before ^{177}Lu-PSMA-617 treatment, with this benefit remaining consistent irrespective of PSMA SUVmax levels.

Our study has several limitations, including its retrospective design, the absence of Ga-68 PSMA PET-CT follow-up imaging, a relatively small patient cohort, a limited follow-up duration, incomplete data regarding the DDR status of the patient population, potential inter-center heterogeneity, and the lack of focus on post-treatment side effects and quality of life. Despite these limitations, we successfully evaluated the impact of ARPi selection before ^{177}Lu-PSMA-617 treatment on survival outcomes.

Conclusion

In conclusion, this study underscores the significant influence of ARPi selection on clinical outcomes in patients with mCRPC undergoing ^{177}Lu-PSMA-617 radioligand therapy. Specifically, prior treatment with enzalutamide was associated with superior OS compared to AA and was correlated with higher PSMA expression. These findings suggest that enzalutamide may

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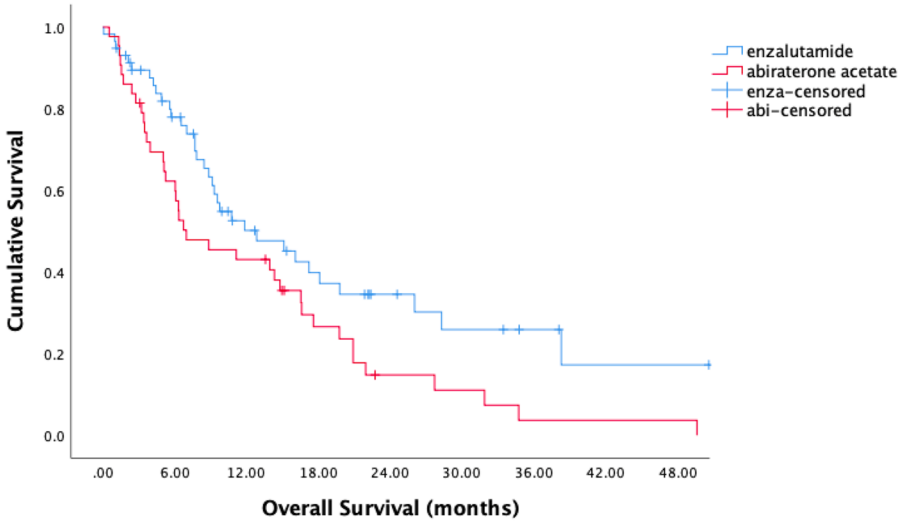


Figure 1. Kaplan-Meier survival analysis according to ARPi groups.

Table 3. Multivariate analysis of overall survival.

Variable	HR (%95 CI)	*P*
Pre-lutetium ARPI variant	2.24 (1.06-4.69)	**.033**
ECOG PS	5.22 (2.20-12.34)	**<.001**
PSMA SUVmax	0.71 (0.35-1.44)	.350

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status, PSMA SUVmax: Prostate-specific membrane antigen maximum standardized uptake value, ARPI: androgen receptor pathway inhibitor. The bold values indicate variables with statistically significant p values.

enhance PSMA expression and improve survival in select patient subgroups. Further prospective studies are warranted to confirm these observations and to refine treatment sequencing strategies in mCRPC.

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Author contributions

Sati Coskun Yazgan (Data curation, Formal analysis, Writing—original draft); Kamıl Kayas (Data curation); Caner Kapar (Data curation); Sura Oztekın (Data curation); Furkan Ceylan (Data curation); Hatıce Bolek (Data curation); Cagatay Arslan (Data curation, Formal analysis, Visualization). Umut Elboga (Formal analysis); Ozturk Ates (Data curation, Formal analysis, Visualization); Denız Tural (Data curation, Formal analysis, Visualization); Tulay Kus (Data curation, Formal analysis, Visualization); Mehmet Alı Nahıt Sendur (Data curation, Formal analysis, Visualization); Emre Yekeduz (Methodology, Supervision, Visualization, Formal analysis); Nurıye Ozlem Kucuk (Visualization, Formal analysis); Elıf Cıngı Ozdemır (Visualization, Formal analysis). Yuksel Urun (Supervision, Methodology, Writing—review and editing, Conceptualization, Visualization)

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Conflicts of interest

Yüksel Ürün declared research funding (Institutional and personal) from Turkish Oncology Group. Yüksel Ürün has served on the advisory board for Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Eczacıbası, Gilead, Janssen, Merck, Novartis, Pfizer, Roche. Yüksel Ürün received honoraria or has served as a consultant for Abdi-İbrahim, Astellas, Bristol Myers-Squibb, Eczacıbasi, Janssen, Merck, Novartis, Pfizer, Roche. All remaining authors have declared no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

AI and AI-assisted technologies were not used in the preparation of this study.

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