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Research Article

Enzalutamide in Metastatic Castration-Resistant Prostate Cancer, Real-World Data

Aykut Bahceci,[1] Ali Murat Sedef,[2] Gokmen Aktas,[3] Polat Olgun,[4] Havva Yesil Cinkir,[5] Halil Taskaynatan,[6] Tulay Kus[7]

[1]Department of Medical Oncology, Hatay Trainig and Research Hospital, Hatay, Türkiye
[2]Department of Medical Oncology, Tarsus Medical Park Hospital, Mersin, Türkiye
[3]Department of Medical Oncology, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanras, Türkiye
[4]Department of Medical Oncology, Burhan Nalbantoğlu Public Hospital, Lefkosa, Cyprus
[5]Department of Medical Oncology, Gaziantep University, Faculty of Medicine, Gaziantep, Türkiye
[6]Department of Medical Oncology, Kahramanmaras Necip Fazıl City Hospital, Kahramanras, Türkiye
[7]Department of Medical Oncology, Gaziantep University, Faculty of Medicine, Gaziantep, Türkiye

Abstract

Objectives: Androgen deprivation therapy (ADT) is used alone or in combination with docetaxel or androgen inhibitors in the initial treatment of metastatic PC (mPC). Enzalutamide is an androgen receptor inhibitor that is used orally and plays a role in different steps of the androgen receptor (AR) signal pathway.

The aim of this study is to determine the real life data of patients using enzalutamide for metastatic PC.

Methods: 118 patients from totally 6 centers using enzalutamide treatment were included in this retrospective analysis. Clinical information of patients were recorded from patient files or automation records.

Results: Median OS was 71 months and median PFS was 5 months (4,1–5,9 months). There was no association of Gleason score with OS and PFS (p=0.5 and p=0.4, respectively). Although those who were metastatic at the time of diagnosis lived longer than those who developed metastases later, the difference was not statistically significant (p=0.9). Likewise, there was no relationship between the time of metastasis development and PFS (p=0.2). There was no difference in OS and PFS between patients with visceral metastasis and those without (p=0.3, p=0.5, respectively).

Conclusion: Enzalutamide is an effective and safe agent in accordance with the literature in the patient group included in this study, although some patients may have an unresponsiveness to enzalutamide or develop progression under the enzalutamide treatment. More studies are needed to understand which patient group can benefit more from enzalutamide.

Keywords: Enzalutamide, efficacy, Metastatic prostate cancer, real world experience, toxicity

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Prostate cancer (PC) is the second most common cancer in men.[1] Although initially an androgen-dependent disease, approximately 15% of patients diagnosed with PC can develop castration-resistant prostate cancer (CRPC) associated with an unresponsiveness to hormonal therapy or androgen deprivation therapy within 5 years.[2-4] CRPC is defined as an increase in serum prostate-specific antigen (PSA) level, the emergence of new metastases or the de-

Address for correspondence: Aykut Bahceci, MD. Hatay Egitim ve Arastirma Hastanesi Tibbi Onkoloji Anabilim Dali, Hatay, Türkiye
Phone: +90 326 229 44 40 **E-mail:** aykutbahceci@gmail.com

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velopment of progression in existing lesions in patients receiving androgen deprivation therapy (ADT) and whose serum tetosterone level is at a castrated level (<50 ng/dL).[5, 6]

The treatment of PC varies in various stages such as localized disease, hormone-sensitive non-metastatic PSA progression, hormone-sensitive metastatic disease and metastatic CRPC (mCRPC). The standard treatment in advanced stage PC is androgen blockade, surgically or medically.[7, 8] ADT is used alone or in combination with docetaxel or androgen inhibitors in the initial treatment of PC. In Turkey, the current standard treatment of mCRPC is docetaxel in combination with prednisone.

Enzalutamide is an androgen receptor inhibitor that is used orally and plays a role in different steps of the androgen receptor (AR) signal pathway.[9, 10] In mCRPC patients, the survival advantage of enzalutamide was demonstrated in the phase 3 PREVAIL study before chemotherapy [11] and in the phase 3 AFFIRM study after chemotherapy.[12] The aim of this study is to determine the real-life data of patients using enzalutamide for mCRPC.

Methods

In this study we retrospectively evaluated the 118 patients received enzalutamide treatment from Turkey and Cyprus (total of 6 centers) between 2016 and 2019 in advanced stage prostate cancer patients. Information such as pathological features at the time of diagnosis, European Cooperative Oncology Group (ECOG) performance score, presence and localization of metastases at the time of diagnosis, the number of metastatic sites, PSA level before and after enzalutamide, treatment history before enzalutamide, the best response obtained with enzalutamide and other demographic data were collected from patient files and automation records. Treatment response status of all patients included in the study were evaluated in their own centers according to standard imaging response criteria.

Overall survival was calculated in 2 different ways in all patients included in the study. Overall survival - 1 (OS-1) was calculated from developing metastasis until the death for any reason. Overall survival - 2 (OS-2) was calculated as the period from the date of initiation of enzalutamide to death for any reason. Progression-free survival (PFS) was calculated as the time from the date of initiation of enzalutamide to progressive disease radiologically or clinically.

The first draft version of the article was written by the first author and then reviewed and completed by all authors.

Ethical Approval

Ethical approval was taken from Hatay Mustafa Kemal University Ethical Comittee: 17.03.2022; Number 32.

Statistical Analysis

All statistical analyses were performed using the statistical package SPSS v22.0. Data expressed were means±SDs for continuous variables and as number (n) and percent (%) for categorical variables. T-test or ANOVA was used between independent groups. Categorical measurements were analysed by Chi square test. The Kaplan-Meier method was used to estimate the mean-median OS and PFS rates. Log-rank test was used to compare the survival distributions between groups. PFS was defined as the time from begining of the enzalutamide treatment to the time of any documented clinical progression, relapse, or death from any cause. Cox proportional regression model were used to estimate the hazard ratios (HRs). A value of $p<0.05$ was considered as significant in all of the tests.

Results

Study Patients

Patient demographic characteristics and disease features are shown in Table 1. The median age of the patients was 71 (range 41-91) years. 108 (91.5 %) patients' ECOG performance score was 0 or 1. The gleason score of 82 (69.5%) patients was ≥8. All of patients (n=118) were advanced stage. 72 patients (%61.1) have de-novo metastatic disease

Table 1. Patient and Tumor Characteristics

Characteristics	n (%)
Median age	71 (41-91) years old
Metastases Time	
DNM	72 (61.1)
LM	46 (38.9)
Gleason Score	
<8	36 (30.5)
≥8	82 (69.5)
ECOG Performance Status	
0	31 (26.3)
1	77 (65.3)
2	9 (7.6)
4	1 (0.8)
Metastases Sites	
Bone Metastases	68 (57.6)
Visceral Metastases	42 (35.6)
Bone + LN Metastases	2 (1.7)
LN Metastases	6 (5.1)
Number of Metastatic Sites	
Oligometastatic	25 (19.3)
Disseminated	93 (41)

DNM: De novo metastatic; LM: Later metastatic; ECOG: European Cooperative Oncology Group; LN: Lymph Node.

(DNM) and 46 (%38.9) patients have Later metastatic (LM) disease. 68 (57.6%) patients had bone metastases and 42 (35.6%) patients had visceral metastasis. While 25 (21.2%) patients were oligometastatic, 93 (78.8%) patients had extensive metastatic disease.

Before enzalutamide treatment, 45 (38.1%) patients received ADT only and 73 (61.9%) patients received chemotherapy after ADT. 65 (55.1%) of the patients received the enzalutamide treatment in the second line and 113 patients (95.8%) received ADT simultaneously with enzalutamide.

Treatments and Outcomes

The median follow-up time was 30 months and the median follow-up time after enzalutamide was 10 months. 34 (28.8%) of patients were died during follow-up and 46 (39 %) of patients had progressive disease after enzalutamide treatment. Progression-free survival (PFS) and overall survival-1 (OS-1) were estimated as 5 and 71 months, respectively (Figs. 1, 2). The median overall survival-2 (OS-2) was not reached. Partial response was obtained in 58 patients (49.2%) and stable disease response in 43 (36.4%) patients and response rates obtained with enzalutamid are shown in Table 2.

There was no statistically significant difference in PFS between low gleason score (<8) and high gleason score (≥8) group patients (p=0.36). There was no statistically significant difference in PFS between DNM and LM group patients (p=0.2). There was no statistically significant difference in PFS according to visceral metastasis status (p=0.5). There was no statistically significant difference in PFS between oligometastatic and extensive metastatic patients (p=0.1). There was no statistically significant difference in median OS-1 and OS-2 between groups receiving and not receiv-

Table 2. Treatment and Outcomes

Characteristics	n (%)
Pre-Enzalutamide Treatments	
ADT	45 (38.1)
Chemotherapy after ADT	73 (61.9)
Enzalutamide Timing	
1st Line	28 (23.7)
2nd Line	65 (55.1)
≥3rd Line	25 (21.2)
Best Response Rates	
Partial Response	58 (49.2)
Stable Disease	43 (36.4)
Progressive Disease	17 (14.4)
PSA Response	
No	23 (19.5)
<50% Reduction	30 (25.4)
>50 % Reduction	64 (54.2)
Normal (CR)	1 (0.8)
Progression After Enzalutamide	
Yes	46 (39)
No	72 (61)
Treatment Toxiciy	
Yes	10 (8.5)
No	108 (91.5)
Final Status	
Died	34 (28.8)
Alive	84 (71.2)
Survival Analysis	
Median PFS	5 (Months)
Median OS	71 (Months)

ADT: Androgene Deprivation Therapy; PSA: Prostate spesific antigene; PFS: Progression-free survival; OS: Overall survival.

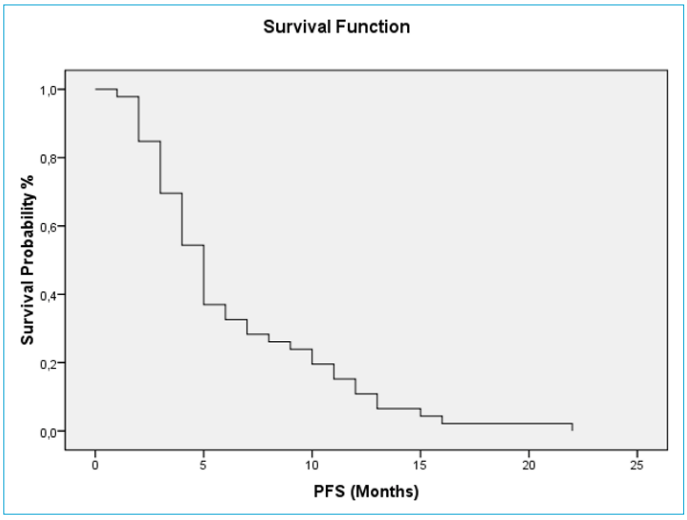

Figure 1. Kaplan–Meier survival curve for progression-free survival.

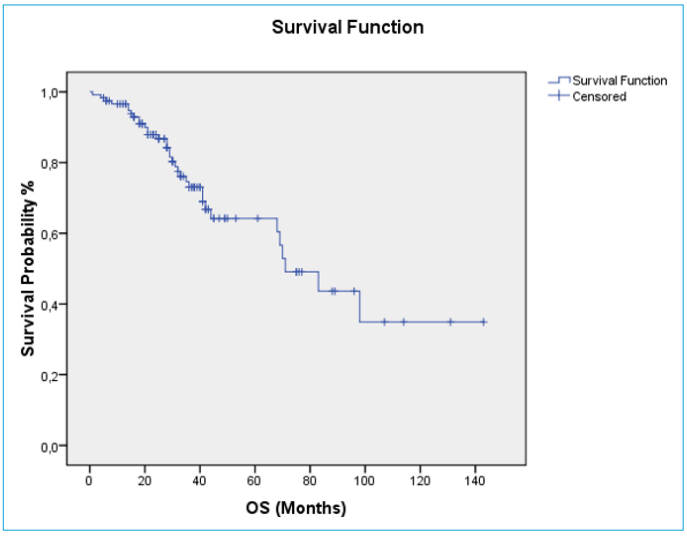

Figure 2. Kaplan–Meier survival curve for overall survival – 1 (OS-1).

ing chemotherapy (p=0.5). Relationship between clinical and treatment features with Progression Free Survival are shown in Table 3.

There was no statistically significant difference in median OS-1 and OS-2 between low gleason score and high gleason score group patients (p=0.5 and p=0.46, respectively). There was no statistically significant difference in median OS-1 and OS-2 between DNM and LM group patients (p=0.9 and p=0,36, respectively) (Fig. 3). There was no statistically significant difference in median OS-1 and OS-2 according to visceral metastasis status (p=0.3 and p=0.06, respectively) (Fig. 4). There was no statistically significant difference in median OS-1 and OS-2 between oligometastatic and extensive metastatic patients (p=0.8 and p=0.9, respectively). There was no statistically significant difference in median OS-1 and OS-2 between groups receiving and not receiving chemotherapy (p=0.9 and p=0.11, respectively) (Fig. 5). Relationship between clinical and treatment features with Overall Survival are shown in Table 4. There was no statistically significant relationship between groups receiving/not receiving chemotherapy and treatment response parameters (Table 5).

Table 3. Relationship between clinical and treatment features with Progression Free Survival

Variables	Median PFS	
	Months	p
Gleason Score		0.36
High (≥8)	5	
Low (<8)	4	
Metastases Time		0.2
DNM	4	
LM	5	
Visceral Metastasis		0.5
Yes	5	
No	5	
Number of Metastases		0.1
Oligometastatic	4	
Extensive metastatic	5	
Chemotherapy		0.5
Received	5	
Not Received	3	

PFS: Progression Free Survival; DNM: De novo metastatic; LM: Later metastatic.

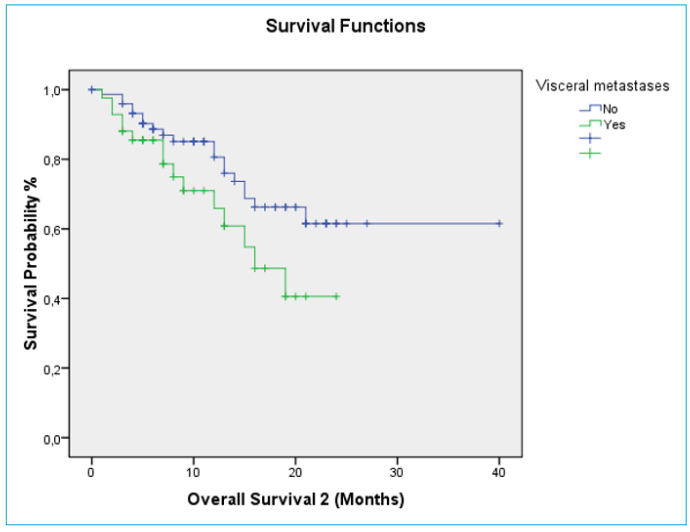

Figure 4. According to visceral metastases, Kaplan–Meier survival estimates for overall survival.

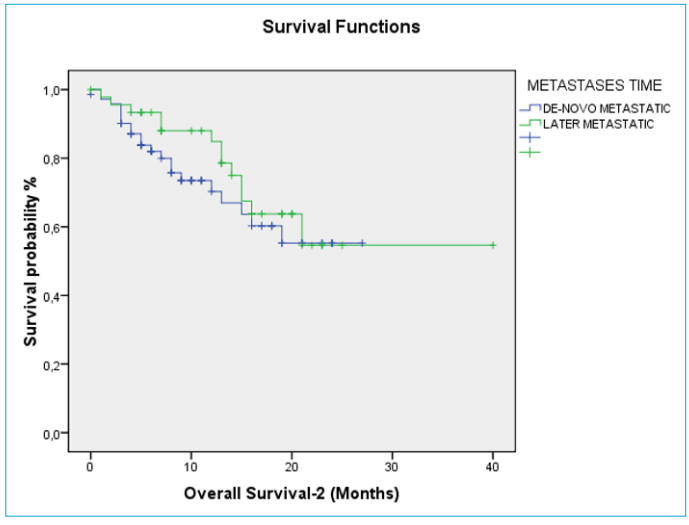

Figure 3. According to metastases time, Kaplan–Meier survival estimates for overall survival.

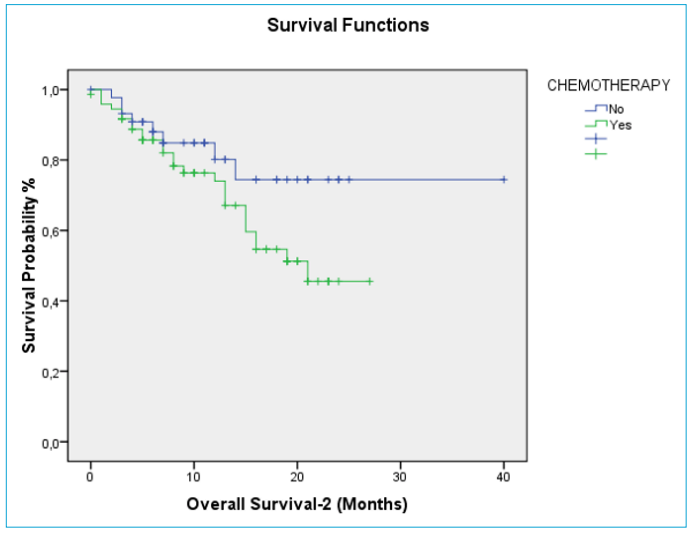

Figure 5. According to chemotherapy status before enzalutamide, Kaplan–Meier survival curve estimates for overall survival.

Table 4. Relationship between clinical and treatment features with Overall Survival

Variables	Median OS-1		Median OS-2	
	Months	p	Months	p
Gleason Score		0.5		0.46
High (≥8)	70		NR	
Low (<8)	98		21	
Metastases Time		0.9		0.36
DNM	83		NR	
LM	68		NR	
Visceral Metastasis		0.3		0.06
Yes	98		19	
No	71		NR	
Number of Metastases		0.8		0.9
Oligometastatic	71		21	
Extensive metastatic	98		NR	
Chemotherapy		0.9		0.11
Received	71		21	
Not Received	NR		NR	

OS-1: Overall Survival-1; OS-2: Overall Survival-2 (Post Enzalutamide Period); DNM: De novo metastatic; LM: Later metastatic; NR: Not reached.

Table 5. Treatment features according to chemotherapy status before enzalutamide

	CT (+) n (%)	CT (-) n (%)	p
Situaiton	73 (61.9)	45 (38.1)	
Progression With Enzalutamide			
No	39 (33.9)	30 (26.1)	0.058
Yes	34 (29.5)	12 (10.5)	
Best Response With Enzalutamide			
Partial Response	30 (26.3)	24 (21.0)	0.086
Stable Disease	33 (28.9)	10 (8.8)	
Progressive Disease	10 (8.8)	7 (6.2)	
PSA Response With Enzalutamide			
No	14 (12.5)	9 (7.9)	0.583
<50% Reduction	19 (16.9)	7 (6.2)	
>50 % Reduction	38 (33.6)	25 (22.1)	
Normal (CR)	1 (0.8)	0	
Toxicity			
No	67 (58.7)	37 (32.5)	0.781
Yes	6 (5.3)	4 (3.5)	

CT: Chemotherapy; PSA: Prostate spesific antigene; NR: Not reached.

Toxicity and Side Effects

Toxicity profiles were evaluated retrospectively according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Enzalutamide was well tolerated in the majority of the cases in our study. With enzalutamide treatment, 3 patients had grade 3 weakness and 1 patient had grade 3 nausea.

Discussion

Although ADT is the basis of advanced PC treatment, it causes relapse with the emergence of CRPC.[8, 13, 14] Previous studies show that AR signaling plays a critical role in triggering CRPC progression.[15, 16] In our study, results similar to previous studies were found with enzalutamide, an androgen receptor inhibitor that plays a role in different steps in the AR signaling pathway.

Median overall survival was 71 months (95% CI 54.0-87.9), and median progression-free survival was 5 months (95% CI 4.1-5.9) in all patients included in the study.

In the phase 3 AFFIRM study, median overall survival (time from randomization to death for any reason) was found to be 18.4 months, with an advantage of 4.8 months after chemotherapy in mCRPC with enzalutamide, and a 37% reduction in death due to any cause.[12] In our study, median OS-1 was 71 months and median OS-2 was 21 months in patients who received chemotherapy prior to enzalutamide. Median PFS was 5 months.

In the phase 3 PREVAIL study, the estimated median overall survival in mCRPC with pre-chemotherapy enzalutamide was found 32.4 months and a 29% reduction in death due to any cause was achieved.[11] In the same study, compared to the control group, a 81% reduction in the risk of radiological progression or death was detected in the enzalu-

tamide arm.[11] In our study, median OS-1 and OS-2 could not be reached in patients receiving enzalutamide prior to chemotherapy. Median PFS was found to be 3 months.

When the patients were examined according to the metastasis status at the time of diagnosis, the median overall survival of patients with metastatic disease at the time of diagnosis was 83 months, while it was 68 months in patients who developed metastases afterwards. Although those with metastatic disease at the time of diagnosis lived longer than those without, the difference was not statistically significant (p=0.9).

Median overall survival was 71 months in patients without visceral metastasis, while median overall survival was 98 months in patients with visceral metastasis. When patients with metastasis were grouped as oligometastatic and widespread metastatic, there was no statistically significant difference between them in terms of survival (median overall survival in oligometastatic patients was 71 months; 98 months in widespread metastatic patients, p=0.8).

When patients using enzalutamid were compared with those with a gleason score of ≥8 and those with <8, the median overall survival was calculated as 70 months in patients with a high-risk group with a gleason score of ≥8; medium and low-risk group was 98 months in patients with gleason score <8 and the difference was not statistically significant (p=0.3). In the PREVAIL study, while 50.6% of the patients had GS ≥8,[17] this rate was 69.5% in the current study, indicating that the tumor burden was higher in patients included in the current study than in the PREVAIL study.

In the literature, enzalutamide has been associated with seizures in approximately 1-2% of patients treated.[18] In our study, there was no seizures related to enzalutamide in any of the patients. Grade 3 and above toxicity, including weakness in three patients and nausea in 1 patient, was detected only in 4 patients and toxicities were easily managed.

Data from real-life is crucial for a comprehensive assessment of the effectiveness and side-effect profile of enzalutamide. However, factors such as retrospective design of this study and data collected from patient centers and hospital automation records from different centers, differences in clinical approaches of the centers, patient population being heterogeneous, timing differences in the evaluation of response to treatment according to prospective studies in retrospective studies and failure to fully apply the RECIST criteria constitute the limitations of this study. In addition, there is a possibility that some side effects that may be observed in patients may be under-recorded in patient records.

Conclusion

In conclusion; The selection of an appropriate anticancer agent for patients with mCRPC is important for the improvement of oncological outcomes. This multicenter retrospective study provides real-life data on the efficacy and safety of enzalutamide in mCRPC patients. Although the results obtained from this study show that enzalutamide is an effective and safe agent both before and after chemotherapy, some patients may become unresponsive to enzalutamide or develop progression under enzalutamide. More studies are needed to understand which patient group can benefit more from enzalutamide.

Disclosures

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was taken from Hatay Mustafa Kemal University Ethical Comittee: 17.03.2022; Number 32.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.B., A.M.S.; Design – A.B.; Supervision – A.B.; Materials – A.B.; Data collection &/or processing – A.B., A.M.S., G.A., P.O., H.Y.Ç., H.T., T.K.; Analysis and/or interpretation – A.B., A.M.S.; Literature search – A.B.; Writing – A.B.; Critical review – A.B., A.M.S.

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