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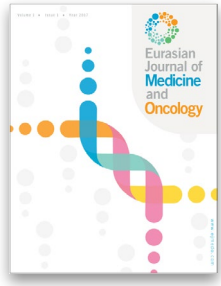

Research Article

Where Should Enzalutamide Be in The Metastatic Castration Resistant Prostate Cancer (mCRPC): A Multi-center Study

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Abstract

Objectives: Enzalutamide(ENZ) is an effective hormonal treatment modality in mCRPC. It can be used before or after docetaxel(DTX) in this setting. Herein, we aimed to show the efficacy of ENZ before or after DTX use and the factors predicting the efficacy.

Methods: We retrospectively collected the data of 320 patients from 12 centers who were treated with ENZ in mCRPC. The initial stage, age, line of treatment, serum prostate-specific antigen (PSA) levels before ENZ treatment and at nadir, site of metastasis, gleason score were evaluated.

Results: Median age of 320 patients were 69. At a median follow-up of 56 months, 271/320 (84.7%) disease progression and 230/320(71.9%) death had been observed. Median PFS was 11(8.9-13)) and median OS was 25(22.1-27.8) months in all patients group. Median PFS was 10(7.4-12.5) months, 11(8-13.9) months in pre-DTX and post-DTX groups respectively. Median OS was higher in the post-DTX group than the pre-DTX group (28(25.7-30.2) vs 19(15.0-22.9-46.6) (p:0.000). Gleason score≥8 (HR 0.59, 95%CI 0.46-0.77, p=0.00), presence of non-visceral metastasis (HR 0.72, 95%CI 0.53-0.97, p=0.031), initial PSA value<43(median) (HR 0.70, 95%CI 0.54-0.91, p=0.009), PSA at nadir <2 (HR 0.61, 95%CI 0.44-0.85, p=0.004), >50% decline in PSA (HR 0.27, 95%CI 0.19-0.36, p=0.000) significantly predicted ENZ response regarding rPFS.

Conclusion: ENZ has shown equal efficacy before and after DTX treatment in mCRPC regarding rPFS. But OS rate was significantly better in the pre-DTX group. Therefore, we recommend starting with DTX in patients who can tolerate chemotherapy in mCRPC setting.

Keywords: prostate cancer, enzalutamide, docetaxel, line of treatment

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Prostate cancer is the second most common cancer and the sixth leading cause of cancer-related death worldwide.[1] The natural course of prostate cancer is diverse regarding morphological and clinical behavior. The majority of patients represents in the local or loco-regional stage at the initial diagnosis.[2] Although tumors with low-grade tend to follow an indolent course, high-grade tumors develop disease progression more rapidly, ending up with advanced disease in 15-20% of patients. Blocking androgen-receptor signaling has been the backbone of treatment in the metastatic setting. LHRH agonists, antagonists, and orchiectomy are the treatment options for androgen deprivation therapy(ADT).[3]

Unfortunately, almost all castration-sensitive metastatic prostate cancer(mCSPC) patients eventually gain resistance to ADT, leading to progression termed castration-resistant prostate cancer (mCRPC). In the last two decades, new treatments options; chemotherapy(DTX,cabazitaxel), androgen synthesis inhibitors(abiraterone acetate(AA)), androgen receptor blocker(ENZ),an autologous dendritic cell vaccine (sipuleucel-T), alpha-particle emitting radionuclide (Radium-233), parp-inhibitor (olaparib) have been introduced in mCRPC.[4]

DTX was first shown to prolong survival in 2004. The TAX-327 trial showed improved overall survival (OS) with the use of DTX compared with mitoxantrone in men with mCRPC after disease progression on ADT (median 19.2 v 16.3 months; p<0.004).[5] AA and ENZ are novel hormonal therapies (NHT) targeting the androgen receptor axis. Abiraterone acetate, a prodrug of abiraterone, is a selective androgen biosynthesis inhibitor that potently blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis, thereby leading to persistent androgen biosynthesis inhibition. AA has shown efficacy both in pre-DTX and post-DTX settings. The COU-AA-301 trial showed improved OS using AA over placebo (14.8 months vs. 10.9 months; hazard ratio, 0.65; 95% confidence interval, 0.54 to 0.77; P<0.001) in the post-DTX setting.[6] The COU-AA-302 trial showed improved OS with the use of AA over placebo (34.7 months [95% CI 32.7-36.8] vs 30.3 months [28.7-33.3]; hazard ratio 0.81 [95% CI 0.70-0.93]; p=0.0033) in pre-DTX setting.[7]

ENZ is a targeted androgen-receptor inhibitor that competitively binds to the ligand-binding domain of the androgen receptor and inhibits androgen-receptor translocation to the cell nucleus, recruitment of androgen-receptor cofactors, and androgen-receptor binding to DNA. Similarly to AA, it showed efficacy over placebo in the post-DTX setting with AFFIRM trial median OS: 18.4 v 13.6 months; HR, 0.63; 95% CI, 0.53 to 0.75; P , .001) ; and in PREVAIL trial in pre-DTX setting (median OS: 32.4 v 30.2 months; HR, 0.71; 95% CI, 0.60 to 0.84; P , .001).[8, 9]

In terms of the increasing complexity of treatment selection in such patients, demonstrating the predictive biomarkers for efficacy and choosing the optimal treatment in the appropriate line of therapy and sequencing is crucial. Moreover, side effect profiles, comorbidities, and cost take part in the treatment decision. Our study retrospectively evaluated ENZ sequencing(before or after DTX) and predictive factors for ENZ efficacy by demonstrating the real-life experience.

Methods

Data collection: The data of 320 mCRPC patients treated with ENZ in the first or latter lines between 2014 and 2020 in 12 centers was recorded retrospectively. All patients had pathologically proven prostate adenocarcinoma and radiologically proven metastasis either by computerized tomography or bone scintigraphy or Gallium-68 prostate-specific membrane antigen positron tomography. Their age, initial PSA values, gleason score, site of metastasis, line of treatment, duration of response, PSA at nadir, baseline alkaline phosphatase(ALP) levels, and baseline lactate dehydrogenase levels have been recorded.

Institutional Review Board(IRB) approval for retrospective data collection and analysis of 320 patients was obtained from Istanbul Medeniyet University, covering all the participated centers (08.12.2021-2021/0619). Informed consent was waived by Istanbul Medeniyet University ethics committee due to the design of the study was retrospectively.

Clinical Assessment

The Prostate cancer Clinical Trials Working Group(PCWG2) was used to address the clinical, biochemical, and radiological progression. Overall survival(OS), radiological progression-free survival(rPFS), and biochemical progression-free survival (PSA PFS) were the study endpoints. The period from the initiation date of ENZ to radiological progression was defined as rPFS. OS was defined as the initiation date of ENZ to death or last follow-up visit. Radiological evaluation was done using thorax and abdomen CT and bone scintigraphy or Ga-68 prostate-specific membrane antigen positron emission tomography.

Statistical Analysis

IBM Statistical Package for the Social Science Statistics for Windows version 24 was used for the statistical analyses. We performed a Chi-square test to compare categorical variables, Mann-Whitney U test to compare continuous variables, and Students T-Test to compare mean age. PFS

and OS were calculated by the Kaplan-Meier method. We used the Log-rank test to demonstrate the univariate effects of predictive factors on PFS and OS. Independent factors associated with survival outcomes were selected for multivariate analysis.

Results

Demographic features and baseline characteristics of 320 patients are summarized in Table 1. 128 patients were in the pre-DTX group, and 192 were in the post-DTX group. The number of patients receiving ENZ in the pre-DTX group over 75 years old was significantly higher than in the post-DTX group. 198 of 320 patients were metastatic at the time of diagnosis. Gleason's score of 9-10 was significantly higher in the post-DTX group.

Median follow-up was 56(24-107) months. Median PFS was 11(8.9-13) months and median OS was 25(22.1-27.8) months in all patients groups. Median PFS was 10(7.4-12.5) months, 11(8-13.9) months in pre-DTX, post-DTX groups respectively(p:0.718). Median OS was higher in the post-DTX group than the pre-DTX group(28(25.7-30.2) vs. 19(15.0-22.9-46.6) p=0.000) Table 2 (Fig. 1).

The Kaplan-Meier plots of ENZ rPFS according to being metastatic at the presentation, Gleason score, bone only involvement, presence of visceral metastases, initial PSA values, PSA at nadir values, PSA decline rate, and initial

Table 1. Baseline patient characteristics and comparison between Pre-Post docetaxel groups., PSA prostate-specific antigen, SD standard deviation IQR interquartile range, rPFS radiological progression-free

	All patients (n=320)	Pre-docetaxel (128)	Post-docetaxel (192)	p
Mean age(± SD*), years	69.35±8.7	75.02±6.65	65.56±7.8	0.00
Median (IQR*) PSA, ng/mL	43±632	53.9±590	34.2±660	
Age				
<75	244(76.3)	65(50.8)	179(93.2)	0.00
≥75	76(23.8)	63(49.2)	13(6.8)	
Gleason, n (%)				
6-7-8	147(45.9)	68(53.1)	79(41.1)	0.04
9-10	173(54.1)	60(46.9)	113(58.9)	
Initial Stage n (%)				
Non-Metastatic	122(38.1)	58(45.3)	64(33.3)	0.035
Metastatic	198(61.9)	70(54.7)	128(66.7)	
50% PSA Decline n (%)				
No decline	67(20.9)	27(21.1)	40(20.8)	0.820
<50% decline	43(13.4)	19(14.8)	24(12.5)	
≥50% decline	210(65.6)	82(64.1)	128(66.7)	
Bone ONLY VS OTHER (%)				
Bone Only	108(33.8)	48(44.4)	60(55.6)	0.24
Other	212(66.3)	80(37.7)	132(62.3)	
Visceral metastasis status				
Visceral	79(24.7)	32(25.0)	47(24.5)	1.00
Non-visceral	241(75.3)	96(75.0)	145(75.5)	

Table 2. The subgroup analysis results of the pre-docetaxel and post-docetaxel settings. rPFS radiological progression-free survival, OS overall survival. CR complete remission, PR partial remission SD stable disease, PD progressive disease.

	All patients (n=320)	Pre-docetaxel (128)	Post-docetaxel (192)	p
Median Follow-up	56(24-107)	50.5(24-99)	57(26-107)	
rPFS	11±1(8.9-13)	10±1.3(7.4-12.5)	11±1.5(8-13.9)	0.718
OS	25±1.42(22.1-27.8)	19±2.0(15.0-22.9-46.6)	28±1.16(25.7-30.2)	0.000*
Enzalutamide Response(radiologic)				
CR+PR+SD	253(79.1)	101(78.9)	152(79.2)	1.00
PD	67(20.9)	27(21.1)	40(20.8)	

ALP are found to be independent predictors of efficacy (Figs. 2-9).

In the univariate analyses evaluating factors for ENZ efficacy in terms of rPFS and OS are shown in Table3. In univariate analysis having the non-metastatic disease at the time diagnosis, having Gleason score ≤8, having bone-only disease, initial PSA<43, PSA at nadir<2 with treatment,>%50 decrease in PSA with treatment, initial ALP<260 were predictors of ENZ efficacy regarding the rPFS. Being <75 years, non-metastatic disease at the time diagnosis, having gleason score ≤8, having bone-only disease, initial PSA<43, PSA at nadir<2 with treatment, >%50 decrease in PSA with treatment, initial ALP<260 were predictors of ENZ efficacy regarding the OS.

In the Multivariate analysis results revealed gleason score >8, presence of visceral metastasis, initial PSA>43, PSA at nadir<2 with treatment, >%50 decrease in PSA with treatment were independent factors associated with rPFS. Being <75 years, non-metastatic disease at the time diagnosis, having gleason score ≤8, having bone-only disease, initial PSA<43, PSA at nadir<2 with treatment, >%50 decrease in PSA with treatment, initial ALP<260 were independent factors associated with OS (Table 4).

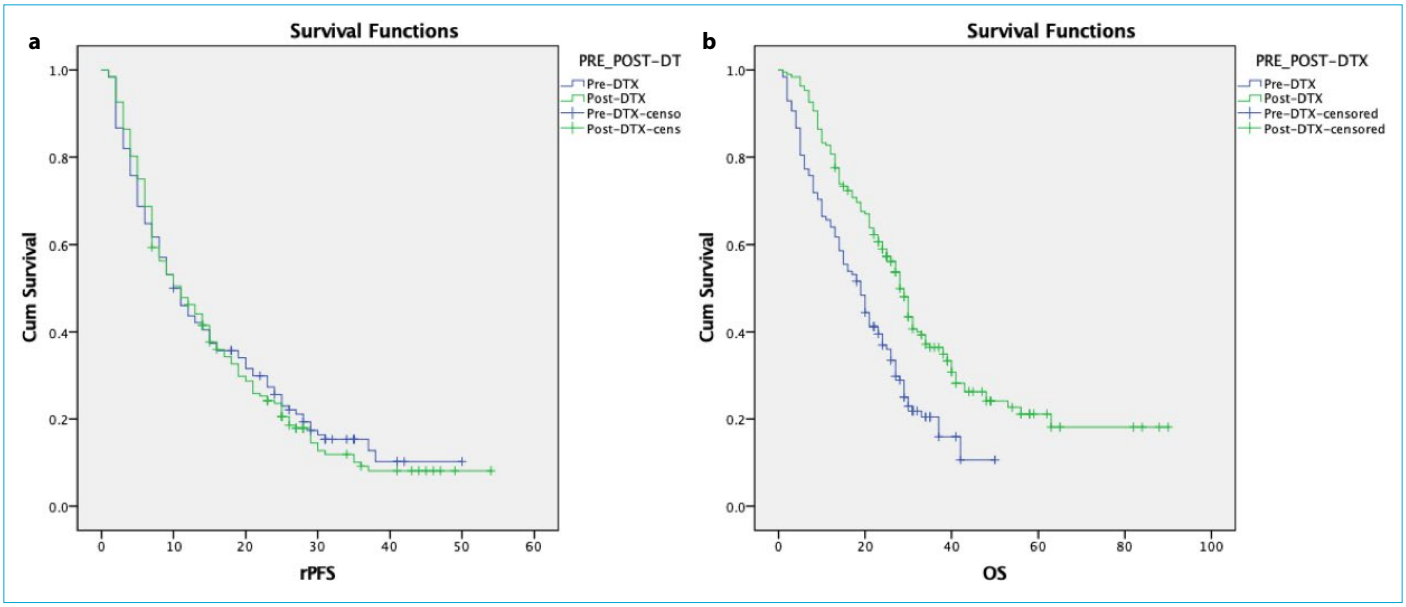

Figure 1. (a) Median rPFS in pre-DTX, post-DTX. **(b)** Median OS in pre-DTX, post-DTX.

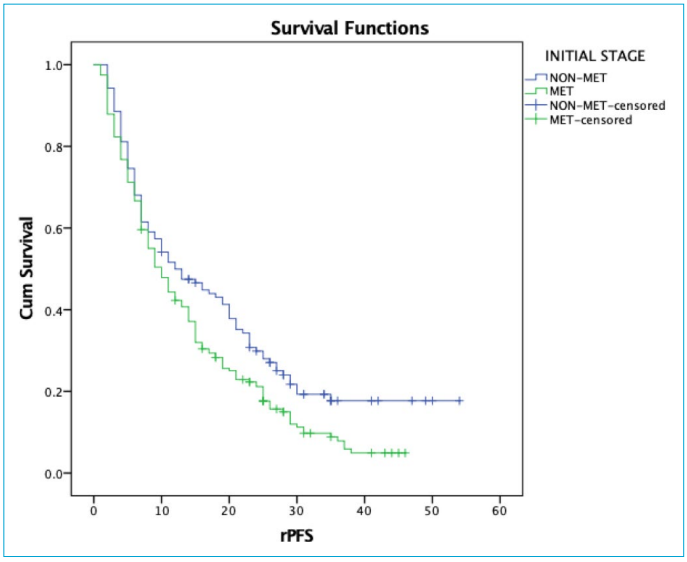

Figure 2. rPFS in initial stage.

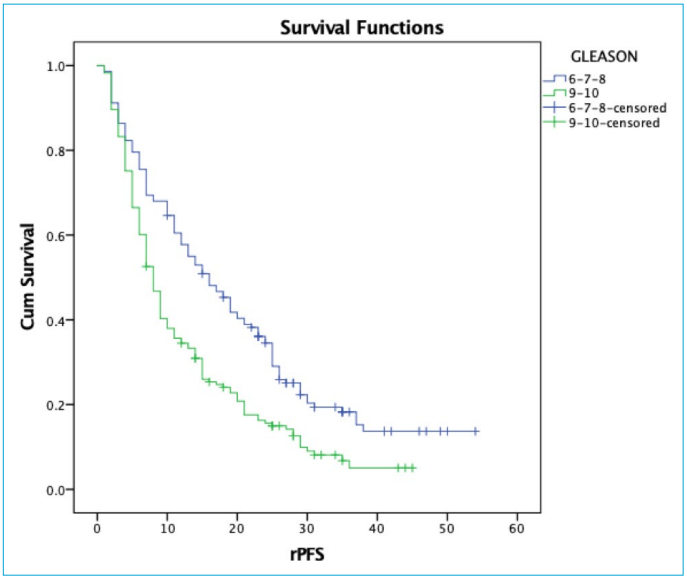

Figure 3. rPFS in Gleason score.

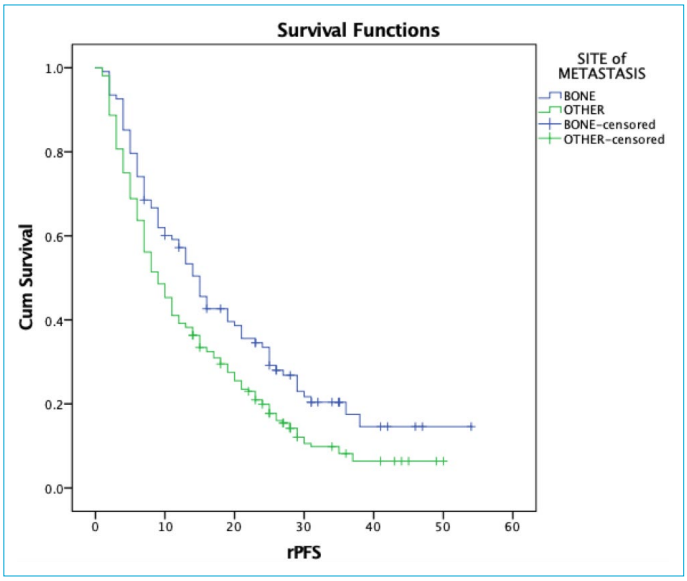

Figure 4. rPFS in site of metastasis.

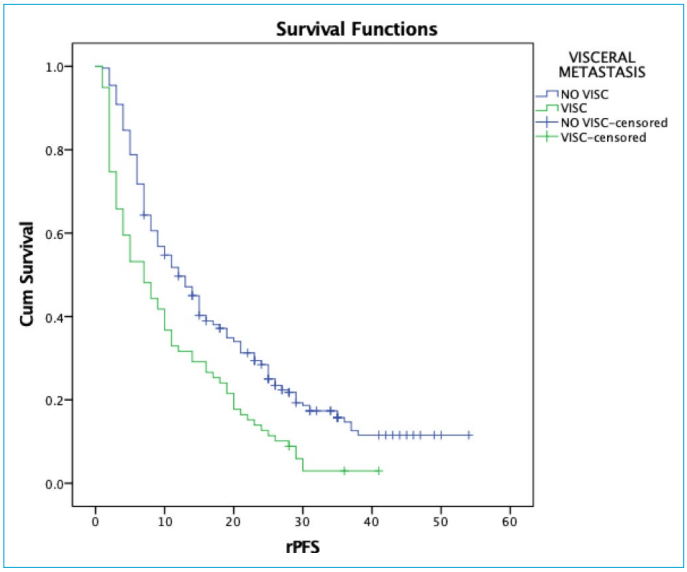

Figure 5. rPFS in presence of visceral metastases.

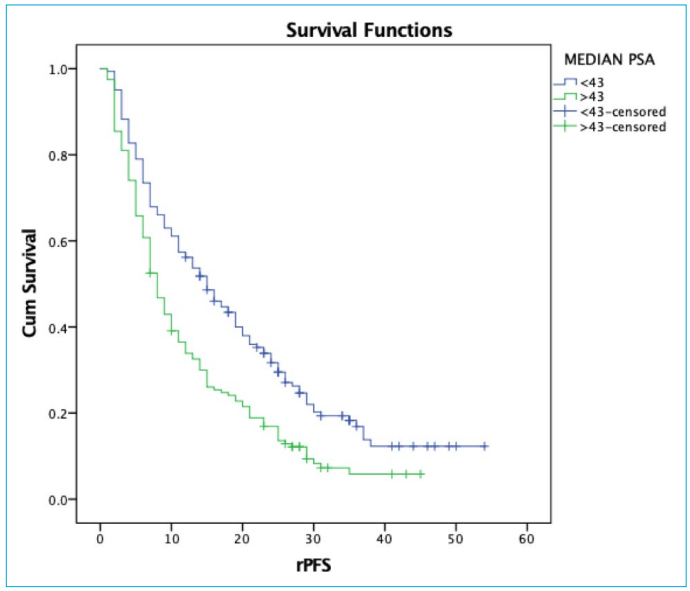

Figure 6. rPFS in initial median PSA values.

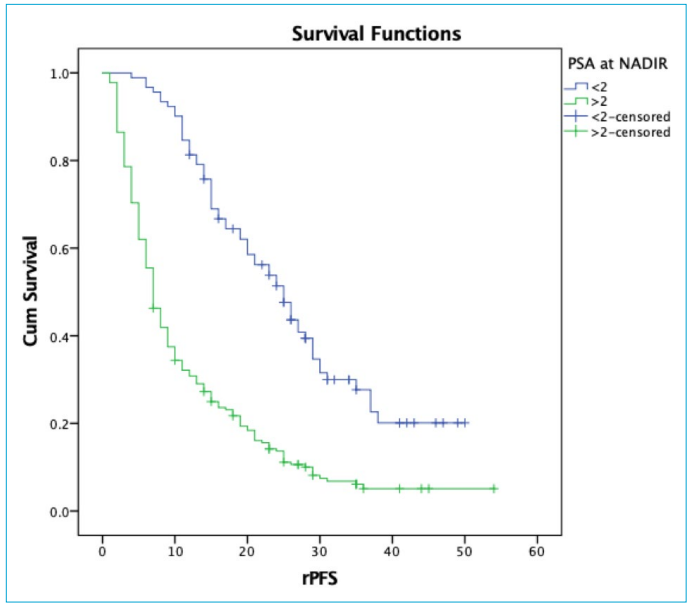

Figure 7. rPFS in PSA at nadir values.

Discussion

In this study, we mainly aimed to demonstrate the efficacy of ENZ before or after DTX in mCRPC and secondarily aimed to show the predictive factors of ENZ efficacy regarding rPFS.

In Affirm trial, the median OS was 18.4 months, and the median rPFS was 8.3 months. In our study, the median OS was 28 months, and PFS was 11 months in the post-DTX group. This result was consistent with better survival data as a consequence. We have enrolled patients who had used DTX in the castration-naive metastatic state to the post-DTX group. We sought if this discrepancy was originated from 69 patients who have received DTX in the castration naive state. We excluded those patients and calculated the survival rates with the rest of 251 patients, 123 in the post-DTX arm and 128 in the pre-DTX arm. The survival rates in this refined group were 19 months in the pre-DTX arm and 30 in the post-DTX arm, which was compatible with our general group.

But on the other hand, in PREVAIL trial, the OS was 35 months, and rPFS was 20 months, and in our study, OS was 19 months, and rPFS was 10 months in the pre-DTX group which was significantly lower. This situation can be explained with real-life conditions. In our country, ENZ reimbursement by the national insurance system in mCRPC

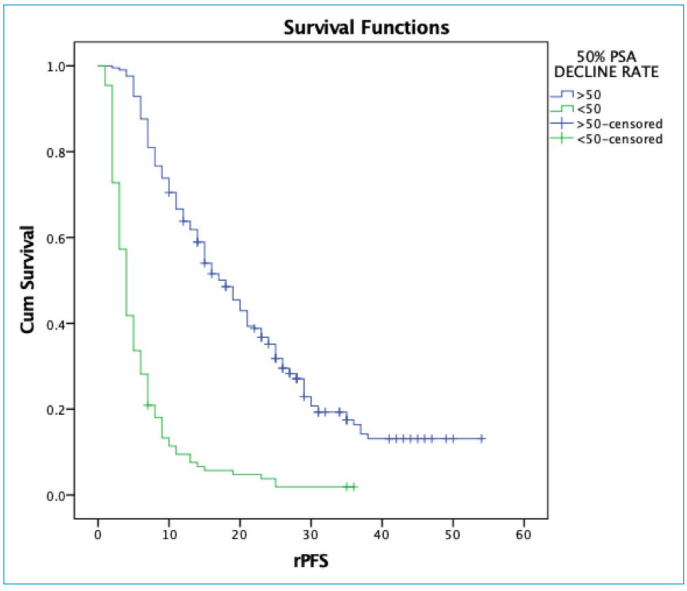

Figure 8. rPFS in %50 PSA decline rate.

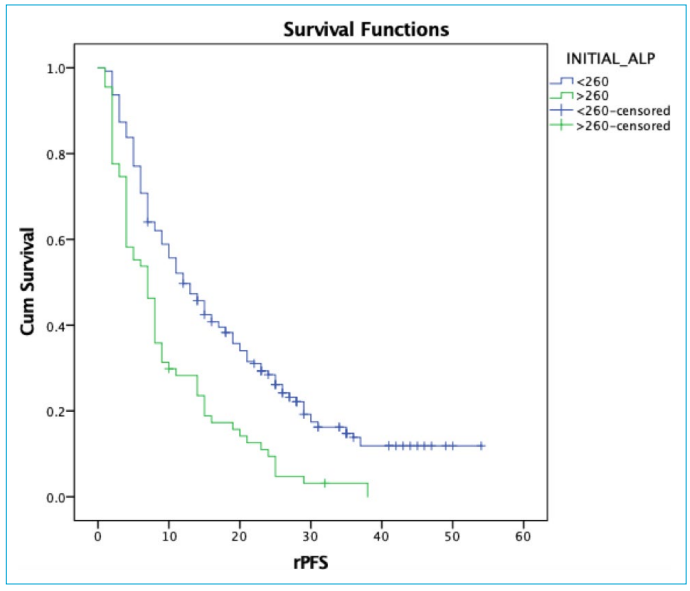

Figure 9. rPFS in initial ALP values.

Table 3. Univariate analysis of rPFS and OS in all patient populations.

	Univariate rPFS Median±SE(95%CI)	p	Univariate OS Median±SE(95%CI)	p
Age				
<75 years	10±1.6(6.85-13.14)	0.63	27±1.58(23.90-30.09)	0.000**
≥75	11±1.17(8.69-13.3)		16±2.37(11.34-20.66)	
Initial Stage				
(non-met)	12±2.52(7.04-16.95)	0.012*	25±2.23(20.62-29.37)	0.029**
met	10±0.99(8.04-11.95)		24±1.98(20.11-27.88)	
Gleason				
≤8	16±1.87(12.32-19.67)	0.000*	28±1.75(24.56-31.43)	0.007**
>8	8±0.57(6.87-9.12)		21±1.92(17.23-24.77)	
Bone ONLY vs. Other				
Bone ONLY	14±1.29(11.46-16.53)	0.01*	28±1.67(24.71-31.28)	0.031**
OTHER	8±0.85(6.32-9.67)		22±1.93(18.20-25.79)	
Visceral met				
Non-visceral	12±1.36(9.32-14.67)	0.000*	27±1.38(24.28-29.71)	0.000**
Visceral	7±1.48(4.09-9.90)		19±2.42(14.24-23.75)	
Initial PSA (median)				
≤43	15±1.71(11.63-18.36)	0.000*	30±1.40(27.25-32.74)	0.000**
>43	8±0.66(6.69-9.31)		18±1.92(14.22-21.77)	
PSA at Nadir				
≤2	25±2.14(20.80-29.19)	0.000*	40±3.42(33.28-46.71)	0.000**
>2	7±0.48(6.04-7.95)		19±1.60(15.86-22.13)	
PSA decrease %50				
>50%	18±1.30(15.44-20.55)	0.000*	31±1.41(28.22-33.77)	0.000**
≤50%	4±0.30(3.40-4.59)		11±1.10(8.83-13.16)	
Initial ALP				
≤260	12±1.18(9.67-14.33)	0.000*	28±1.39(25.27-30.73)	0.000**
>260	7±0.94(5.15-8.84)		13±2.04(8.99-17.00)	
Initial LDH				
≤220	12±1.56(8.94-15.06)	0.129	30±3.09(23.94-36.05)	0.006**
>220	9±1.34(6.35-11.64)		23±1.99(19.09-26.90)	

SE standard error, CI confidence interval, PSA prostate-specific antigen, rPFS radiological progression-free survival, OS overall survival, *Significant difference regarding rPFS ** Significant difference regarding OS.

Table 4. Multivariate Cox regression analysis of rPFS and OS in all patient populations.

	Factors predicting Enzalutamide efficacy in COX proportional hazard model				
	n/total	Multivariate(rPFS)		Multivariate(OS)	
		Hazard ratio (95 % CI)	p	Hazard ratio (95 % CI)	p
Age>75				0.67(0.48-0.95)	0.024
Initial Stage(non-met)	122/320	0.87(0.67-1.12)	0.290	0.70(0.52-0.94)	0.019
Gleason≤8	173/320	0.59(0.46-0.77)	0.000	0.71(0.54-0.94)	0.017
Bone ONLY vs Other	118/123	0.80(0.60-1.07)	0.140	0.73(0.53-1.00)	0.054
Non-Visceral met	79/320	0.72(0.53-0.97)	0.031	0.80(0.58-1.10)	0.170
Initial PSA<43(median)	158/162	0.70(0.54-0.91)	0.009	0.63(0.47-0.83)	0.002
PSA at Nadir<2	91/229	0.61(0.44-0.85)	0.004	0.53(0.36-0.80)	0.002
PSA decrease %50	210/320	0.27(0.19-0.36)	0.000	0.30(0.0.22-0.42)	0.000
Initial ALP<260	67/320	0.89(0.65-1.21)	0.460	0.68(0.49-0.94)	0.023
Initial LDH<220	216/329	1.239(0.957-1.603)	0.103	0.0.94(0.68-1.29)	0.710

HR hazard ratio, CI confidence interval, E enzalutamide, AA abiraterone acetate, PSA prostate-specific antigen, ECOG-PS Eastern Cooperative Oncology Group-Performance Status, rPFS radiological progression-free survival, OS overall survival.

before DTX administration is given only to patients with comorbidities and poor performance who are tought to be intolerant to receive chemotherapy. And most of the physicians tend to start with chemotherapy in patients with good PS score. Tagawa et al. evaluated the real-life efficacy of ENZ and abiraterone acetate in the chemo-naive mCRPC patients. The median treatment duration in ENZ was 9.93 months, consistent with our data.[10] It is a fact that patients acquire frailty and comorbidities with aging. And aging is associated with lower survival rates.[11] The median age was 75 in pre-DTX vs. 67 in the post-DTX group in our study. The lower OS rates in the pre-DTX group in our study can be attributed to these reasons.

Our secondary intention was to demonstrate factors predicting the efficacy of patients treated with ENZ in mCRPC. The impact of the Gleason score in predicting the efficacy in patients with ENZ was not evaluated in AFFIRM and PREVAIL trials. Our study showed marked reduced effectiveness in patients with a Gleason score over 8. It is a fact that patients with a Gleason score over 8 are associated with lower survival rates irrespective of treatment modality.[12,13] Terada et al. also evaluated 345 patients who were treated with ENZ in mCRPC. In his study, patients with GS>8 were found to have less efficacy like our results.[14] As aforementioned above, abiraterone acetate is another androgen pathway inhibitor used in pre-DTX and post-DTX settings. Although Fizazi et al. has documented that the Gleason score was not predictive of response regarding COU-301 and COU-302 trials, Verzoni et al. reported that GS≥8 was unexpectedly associated with long-term response in pts with AA administration in mCRPC.[15, 16]

Identifying pretreatment and interval markers predicting the duration of response would lead to the best management strategies. Our trial evaluated the treatment response by baseline PSA levels, PSA decline rate (50% cut-off), and PSA at nadir levels below and above 2 ng/ml. Our study showed that the median PSA level of 320 patients was 43 ng/ml (53 in pre-DTX vs. 34 in post-DTX). It was 107 in AFFIRM and 51 in PREVAIL, respectively. As in the Affirm trial, we conducted the median cut-off value for response evaluation and demonstrated that patients with baseline PSA levels below 43 ng/ml had better survival rates.

65% of all patients received >50% PSA response with ENZ. And the responsive group had significantly better rPFS and OS rates compared with the less and non-responsive group. It was 54% in AFFIRM and 78% in PREVAIL trials. To the best of our knowledge, this is the first study reporting the PSA at nadir levels as the best predictor of the extended response. 91 patients reached PSA values of less than 2 ngg/ml. 42 were in the pre-DTX group and 49 in the post-DTX. The rPFS was 25.2m vs. 7m, and OS was 40m vs. 19 m, reflecting the importance of PSA levels reaching below 2 ng/ml.

There are several limitations to our study that need to be considered when interpreting the results. First of all, this was a retrospectively multicenter-designed trial which led to a lack of appropriate ECOG-PS evaluation and the registry of comorbidities. And also, adverse events and dose adjustments were not included in our database. The biopsies were not reported in a single center.

Conclusion

In real-life, patients with mCRPC represent with comorbidities and diminished performance scores. And during the treatment, patients seek parameters indicating the duration of response. Our study demonstrated that PSA decreases more than 50%, and reaching the PSA values below 2ng/ml are strongly associated with extended efficacy. And it is scientifically proven that administrating ENZ before or after DTX both has efficacy. But it should be kept in mind that DTX is an effective treatment regimen in this group of patients. Our study demonstrated the same rPFS in ENZ before or after DTX. But ENZ administration is significantly correlated with better OS in post DTX usage. Therefore, we recommend starting with DTX in patients who can tolerate chemotherapy mCRPC setting.

Disclosures

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