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Treatment of Metastatic Castration-resistant Prostate Cancer With Abiraterone and Enzalutamide Despite PSA Progression

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Abstract. *Background/Aim: National guidelines offer little guidance on the use of PSA progression (PSA increase as defined below) as a clinical endpoint in metastatic castration-resistant prostate cancer (mCRPC). The aim of the study was to examine treatment patterns/outcomes with abiraterone (abi)/enzalutamide (enza) throughout PSA progression and near the end of life (EOL). Patients and Methods: Cases of mCRPC treated with abi or enza from the New York Veterans Affairs (VA) from 6/2011-8/2017 were reviewed. Regression analyses were conducted to identify factors associated with continuation of abi/enza treatment up to the EOL, and survival. Results: Of 184 patients, 72 received abi alone, 28 received enza alone, and 84 received both. Treatment was changed for PSA progression alone in 39.1% (abi) and 25.7% (enza) of patients. A total of 37 patients (20%) received abi/enza within 1 month before death, 30% of whom were receiving hospice services. Older patients and black patients were less likely to receive abi/enza up to the EOL. Conclusion: Abi/enza are frequently discontinued for PSA progression alone and continued at EOL. The clinical benefit of these practices warrants additional study.*

Disease progression in advanced prostate cancer is generally identified by an increase in prostate specific antigen (PSA), worsening symptoms, enlarged metastatic lesions, and/or development of new metastatic lesions (1). Once patients have progression of disease, there is no universal consensus guiding appropriate treatment. The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) has defined PSA progression as an increase in PSA greater than 25% and >2 ng/ml above nadir, confirmed by progression at 2 timepoints at least 3 weeks apart (2). The PCWG3 has further specified, however, that PSA progression does not mandate therapy change in clinical trials. PSA progression frequently occurs during treatment, but without a clear impact on overall survival (OS); thus, continuation of therapy despite PSA increases is frequently employed (3). No data supports a clinical benefit from changing hormonal therapy based on PSA progression alone. Abiraterone (abi), an oral androgen synthesis inhibitor initially approved by the FDA in 2011, and enzalutamide (enza), an androgen receptor blocker initially approved in 2012, both improve overall survival in metastatic castration-resistant prostate cancer (CRPC) (4-9).

There are limited data describing practice patterns with abi and/or enza despite PSA increase. Continuation of androgen-deprivation therapy (ADT) with gonadotropin-releasing hormone (GNRH) agonists despite PSA progression is standard prostate cancer care based on the premise that increased androgen levels would promote tumor growth at any stage of prostate cancer treatment (10, 11). Finally, it is unknown how many men with CRPC are continuing to receive expensive hormonal therapy up to the end of life, the benefit of such therapy immediately prior to death is also unproven.

This retrospective cohort study sought to characterize practice patterns of abiraterone and enzalutamide treatment, as well as patient outcomes in the multi-hospital Veterans Affairs (VA) healthcare system with a focus on their use despite PSA progression, and up to the end of life (EOL).

Materials and Methods

Study design. A multi-center, retrospective cohort study of patients with advanced prostate cancer at 2 participating VA medical centers (Manhattan, Brooklyn) was conducted to characterize abiraterone and enzalutamide treatment and patient outcomes. The study was approved by the institutional review board.

Population and variables. A total of 184 patients with metastatic prostate cancer who received prescriptions for abiraterone acetate or

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enzalutamide from the New York VA (VA-NYHHS) from June 2011 – August 2017 were identified. Both, inpatient and outpatient medication prescribing data were reviewed. The baseline sociodemographic variables were recorded using the nationwide VA Computerized Patient Record System (CPRS). Age at time of first diagnosis was classified as follows: 41-50, 51-60; 61-70; 71-80; 81-90. Race was classified as White, Black, or Other, and Ethnicity as Hispanic or non-Hispanic. PSA values were recorde at the time of enzalutamide or abiraterone initiation, at the nadir on a given therapy, and at the time of therapy change or discontinuation. Additional clinical characteristics were collected including documented bone or visceral metastases, hospice enrollment, surgical treatment, radiation and/or chemotherapy. Based on in depth chart review, the reason for each change in therapy was further characterized. The reasons for change in therapy or discontinuation were categorized using the following code set: 1a – PSA increase less than 50 ng/ml; 1b – PSA increase greater than 50 ng/ml; 2 – radiographic progression (any increase in tumor burden as determined by our radiology staff) +/– PSA change; 3 – clinical progression (as determined by treating physician) +/- PSA change; 4 – miscellaneous reasons (*i.e.* poor tolerance due to side effect profile, or other) +/- PSA change; 5 – death; 6 – denotes patients who remained on the medication at the end of the study period;

Outcome measures. The primary study outcome was duration of abi/enza treatment after PSA has reached the nadir. For calculations of time from nadir to peak, 11 patients who had no interval values between nadir and peak were excluded, ensuring that treating physicians intentionally treated while the PSA was rising. Secondary outcomes of interest included abi/enza continuation despite radiographic and clinical progression, use of abi/enza within the last month of life, and reasons for medication change. Additional secondary outcomes included PSA nadir and peak on abi/enza therapy, and survival from initiation of abi/enza therapy.

Statistics. Descriptive statistics were applied and univariate and multivariable logistic regression was used to explore associations between clinical/demographic variables (age, race, presence of bone metastases, ethnicity) and continuation of abi/enza despite PSA progression Cox PH models were used to examine associations between clinical/demographic factors and overall survival. All statistical analyses were conducted using SAS 9.2 software, with $p<0.05$ used as the level of statistical significance.

Results

Baseline clinical characteristics of study participants are listed in Table I. This study identified 184 patients diagnosed with metastatic CRPC who had received abi/enza from June 2011 – August 2017. Eleven (6%) patients were excluded from calculations of time of treatment despite PSA progression because they had no rising value above the nadir. Of the study population, 46% were white, 44% were black, and 10% were another race; along ethnic lines, 6.5% were Hispanic and 93.5% were non-Hispanic. The median age of cases was 68 (with ages ranging from 43-90), with 49.5% of patients alive and 50.5% of patients deceased by the time of study analysis. 24% of patients had received surgery, 25.5% chemotherapy, and 57% radiation. Seventy-eight percent had bone metastases.

Of 184 patients, 72 patients received abi alone, 28 received enza alone, and 84 received both (*i.e.*, 156 patients received abi and 112 received enza overall). Median starting PSA on abi was 26.7 ng/ml, median PSA decrease on abi was 22.47 ng/ml and median increase from nadir was 23.78 ng/ml. Median continuation of therapy beyond PSA nadir was 7 months. The median time to nadir was 5 months. These data are illustrated in Figure 1. Of patients who were treated with abiraterone, 78% were continued through PSA increase. Comparatively, median starting PSA for enzalutamide was 33.5 ng/ml, median PSA decrease on enza was 21.58 ng/ml and median increase from nadir was 37.8 ng/ml. Median continuation of therapy beyond PSA nadir was 4.5 months and median treatment time prior to nadir was 2 months. Overall, 64% of patients continued enza through PSA increase.

Biochemical progression alone was the rationale for treatment cessation in 39.1% and 25.7% of patients receiving abi and enza, respectively, while the remaining of treatment changes involved combined biochemical, radiographic and clinical changes, as shown in Figure 2. Among the 61 patients whose abi was stopped because of PSA progression only, the median duration of abi treatment was 364 days vs 216 days among those whose abi was stopped for other reasons ($p=0.03$; Wilcoxon-Mann-Whitney test). No clinical or demographic characteristics predicted PSA related stoppage of abiraterone. In multivariable logistic regression (Table II), when adjusted for age, race, and presence of bone metastases, older patients (OR=0.57, 95%CI=0.36-0.91) and black patients (OR=0.41, 95%CI=0.18-0.93) were less likely to receive a prescription within 1 month prior to death. In a Cox PH model, black race (HR=2.21, 95%CI=1.28-3.82) and receipt of medication within 1 month prior to death (HR=9.39, 95%CI=5.29-16.66) were associated with worse overall survival from abi/enza initiation. Continuation of abi despite PSA change by >50 ng/ml was not associated with improved overall survival. Of 37 (20.1%) patients who received abi/enza within 1-month prior death, 30% received continued treatment while receiving hospice services.

Discussion

PSA increase provides initial evidence that neoplastic resistance to the medication is increasing, and frequently precedes clinical progression. PSA increase has not, however, been shown to be a clinically meaningful endpoint for changes in therapy. Based on the observation that prostate cancer maintains testosterone responsiveness after PSA progression, continuation of hormonal therapy despite increase in PSA is common. Real-world practice outside of clinical trials after PSA increase is unknown.

Our study revealed that in our VA population, more patients were treated with abiraterone than enzalutamide, likely in part because abiraterone was approved first (April 2011 vs. August 2012). Both drugs were available at the VA

Table I. *Demographics table (Raw Data). Characteristics of subjects with castrate resistant prostate cancer treated with abiraterone, enzalutamide, or both.*

	All Patients N=184	Abiraterone 72	Enzalutamide 28	Abiraterone and Enzalutamide 84
Age Dx, mean (yrs)	68.7458	66.157	63.7	66.976
41-50	1 (0.5)	0	0	1 (1.2)
51-60 (%)	30 (16.3)	11 (15.7)	4 (13.33)	15 (17.85)
61-70	78 (42.4)	27 (38.6)	14 (46.67)	37 (44.0)
71-80	48 (26.1)	18 (25.7)	7 (23.33)	23 (27.4)
81-90	20 (10.9)	10 (14.28)	3 (10.0)	7 (8.04)
Unknown	7 (4.35)	4 (5.71)	2 (6.67)	1 (1.2)
Treatment Received:				
Surgical intervention (%)	24.46 (45/184)	18.57 (13/70)	13.33 (4/30)	33.33 (28/84)
Radiation therapy (%)	58.15 (107/184)	51.42 (36/70)	46.67 (14/30)	67.86 (57/84)
Chemotherapy (%)	25.54 (47/184)	15.71 (11/70)	20.0 (6/30)	35.71 (30/84)
Percentage with bone metastases (%)	77.77 (143/184)	81.43 (57/70)	53.33 (16/30)	83.33 (70/84)
Race, No. (%)				
Black	81 (44.0)	32 (55.7)	11 (36.67)	38 (45.2)
White	84 (45.65)	31 (44.3)	15 (50)	38 (45.2)
Other	19 (10.33)	7 (10)	4 (13.33)	8 (9.52)
Ethnicity				
Hispanic	12 (6.52)	3 (4.3)	2 (6.67)	7 (8.33)
Non-Hispanic	172 (93.47)	67 (95.7)	28 (93.33)	77 (91.67)
Median survival lived past initial diagnosis (mo.)	120	107	120	144
Median survival lived past abi/enza initiation (mo.)	21	13	14	28
Date of first treatment with abi/enza				
Unknown		1	0	0
2011		5	0	Abi 4; Enza 0
2012		18	0	Abi 10; Enza 3
2013		18	2	Abi 29; Enza 13
2014		10	3	Abi 15; Enza 20
2015		9	5	Abi 13; Enza 17
2016		6	10	Abi 9; Enza 15
2017		5	8	Abi 4; Enza 16
Living/Deceased, No. (%)				
Living	91 (49.46)	27 (38.57)	21 (70.0)	43 (51.19)
Deceased	93 (50.54)	43 (61.43)	9 (30.0)	41 (48.81)

For some patients the age at first diagnosis is missing.

within 6 months of approval. Additionally, patients were treated with abiraterone, on average, for more than twice the period patients were treated with enzalutamide, also likely related to the fact that it was more often used first. Remarkably, PSA levels at time of abi initiation and time of abi discontinuation were similar and PSA nadir was located approximately in the middle of these time points. The median PSA values illustrated in Figure 1, suggest that treatment despite PSA increase yields a clinically significant period without clinical or radiographic progression. Enzalutamide was started at higher PSA levels in general, continued through nadir and then frequently to PSA levels higher than those at enzalutamide initiation. Again, enzalutamide continuation despite PSA nadir was associated with a clinically meaningful interval without radiographic or clinical progression. Our study is consistent with a recently published study, which suggested an OS benefit for patients treated with abiraterone and prednisone despite PSA and radiographic progression, relative to patients whose therapy was stopped pending for radiographic and/or PSA progression (12).

As illustrated in Figure 3, patients who received both (sequentially, not concurrently) abiraterone and enzalutamide lived longer than those who received only abiraterone (median values 36 months compared to 20 months, median for patients treated with enzalutamide was not yet reached). These differences are likely due to selection of stable patients with limited comorbidities for second- and third-line therapies. Nonetheless, the survival in our VA population is comparable to that seen in clinical trials (4, 7) supporting the real-world efficacy of these medications.

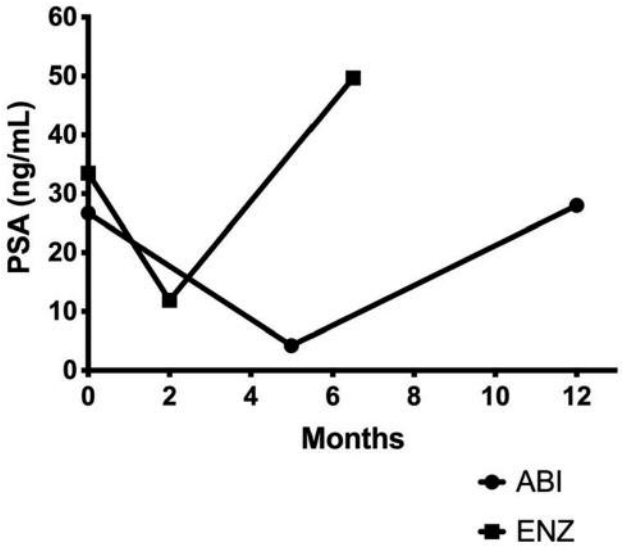

Figure 1. *Median PSA values (ng/ml) at initiation of treatment, at nadir, and at time of treatment discontinuation. Time to nadir and peaks are shown as median values.*

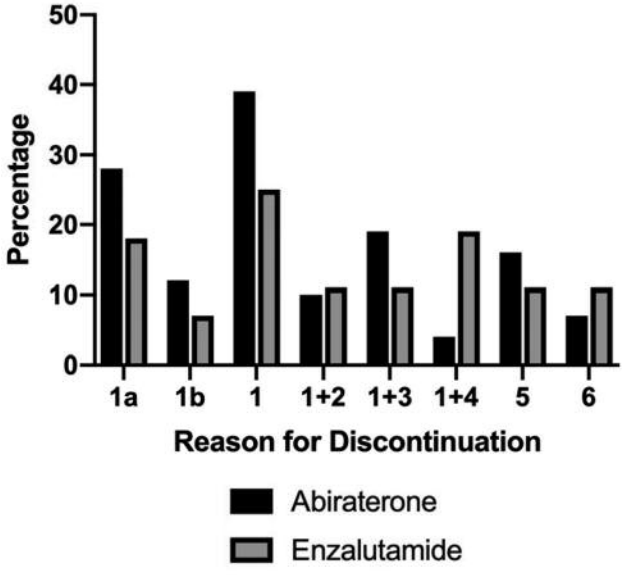

Figure 2. *Reasons for discontinuation of abiraterone and enzalutamide. 1a: PSA increase less than 50 ng/ml. 1b: PSA increase greater than 50 ng/ml 1: PSA change only. 1+2: PSA change and/or radiographic progression. 1+3: PSA change and/or clinical progression. 1+4: PSA change and/or Misc. 5: Death. 6: Patient remained on medication.*

Reasons for change in therapy were PSA progression, radiographic progression, clinical progression, death, poor tolerance of medication, or a combination of these. The most common reason for discontinuation or change of therapy was

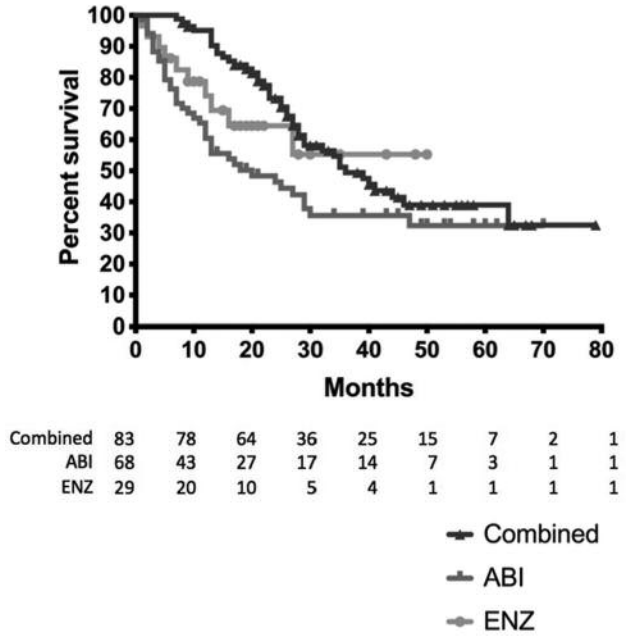

Figure 3. *Kaplan–Meier survival curve showing overall survival of patients treated with abiraterone, enzalutamide, or a combination of both. The table below the survival curve depicts the number at risk at each 10-month interval.*

Table II. *Multivariable logistic regression for receipt of treatment within 30 days prior to death.*

Variable	OR	95%CI	*p*-Value
Age	0.57	0.36-0.91	0.02
Race: black *vs.* white	0.41	0.18-0.93	0.63
Race: other *vs.* white	0.28	0.06-1.40	0.30
Ethnicity: Hispanic *vs.* Not Hispanic	0.26	0.03-2.21	0.22
Presence of bone metastasis	0.45	0.14-1.42	0.17

PSA progression alone (Figure 2). It is interesting to note that despite the common practice of continuation despite PSA progression, PSA progression remains a major reason for change in therapy. Neither the NCCN nor the ASCO guidelines advise that PSA increases warrant changes in therapy (13, 14). In our patient population there appears to be a point at which the treating physician and/or patient will no longer tolerate additional PSA increase. It is noteworthy that patients whose abiraterone was discontinued based on PSA change alone, had a longer duration of abiraterone therapy, medians 394 *vs.* 219 days. It is not clear that this decision is evidence-based. The median increase in PSA among patients for whom PSA increase alone was the reason for change in therapy was 23.7 ng/ml and 34.9 ng/ml for those on abiraterone and enzalutamide,

respectively. The median increase in PSA among patients for whom radiographic, clinical or other reasons warranted therapy change was 19.2 ng/ml and 10.7 ng/ml for those on abiraterone and enzalutamide, respectively. Enza discontinuation for PSA progression only was less common than for abi (25.7% compared to 39.1%). This is likely influenced by the frequent use of enza after failure of abi, thus leaving clinicians and patients with limited additional options, and higher tolerance for PSA increase. Interestingly, radiographic progression was almost always accompanied by PSA progression.

Approximately 20% of patients were continued on either abiraterone or enzalutamide within one month prior to death. Of these, 30% received it while they were in hospice care. In 2012, the American Society of Clinical Oncologists (ASCO) issued recommendations as part of their "Choosing Wisely" campaign to minimize the use of unnecessary antineoplastic therapy at the end of life (15-18). The monthly cost (wholesale acquisition cost) of abiraterone is approximately $8,000 and the monthly cost of enzalutamide is approximately $9,000 (19). Continuation at the end of life consumes resources and should only be considered in the setting of compelling evidence that the drugs are providing symptomatic benefit. In our study alone, this accounted for a cost of approximately $315,000 for 37 patients receiving therapy in the last month of life. Of note, Black patients in our study were less likely than white patients to be treated with abi/enza in the last month of life. In this regard Black patients may have received more evidence-based end of life care, but any differences by race warrant further evaluation. The reasons for this racial association remain unknown. Black patients also had worse survival from the time of abi/enza initiation. Previous studies have established differences in outcomes for Black patients with prostate cancer, likely related to differences in pathology, treatment, and social factors (20-29). We were not able to fully account for these additional variables in our models.

Our study has several significant limitations. A relatively small number of patients were analyzed, and they were treated by a small group of physicians. Patterns may not be representative of larger physician and/or patient samples. PSA levels were not measured at prespecified standard timepoints for all patients, which allowed us to only effectively comment on the peaks and nadirs of PSA for this group of patients. For similar reasons we were unable to calculate the rate of PSA change. There was no uniform standard for PSA- only progression, (as the 25% increase in nadir used in studies), but this may be representative of community care. All-cause mortality was used as our primary survival outcome, and it is possible that non-cancer related deaths contributed.

Nonetheless, the value of the study is that it adds to the remarkably scarce literature on practice patterns after PSA increase, and reasons for therapy change. Physicians are frequently confronted with this situation and lack guideline recommendations to help them to get informed decisions. Our study suggests that there is significant value to extending abi and/or enza treatment past PSA nadir in patients who are otherwise responding. The data also suggests that there comes a point beyond which treating physicians may change therapy based on additional PSA increase, despite other clinical factors reflecting stable disease. More studies are urgently needed for informed clinical decisions in CRPC patients with substantial increases in PSA during abi and enza, and to ensure evidence-based decisions about continued use of costly medications during the end of life care.

Conflicts of Interest

The Authors declare no conflicts of interest relevant to this article.

Authors' Contributions

Conception and design: Daniel J. Becker, Arjun D. Iyengar; Collection and assembly of data: Daniel J. Becker, Arjun D. Iyengar, Jason Ng, Anika Zaman, Salman R. Punekar; Data analysis and interpretation: Daniel J. Becker, Arjun D. Iyengar, Salman R. Punekar, Kevin D. Becker, Danil Makarov, Stacey Loeb; Manuscript writing: Daniel J. Becker, Salman R. Punekar, Stacey Loeb, Jason Ng, Arjun D. Iyengar, Kevin D. Becker, Danil Makarov; Final approval of manuscript: All Authors.

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