Economic Burden Associated with Adverse Events among Patients with Non-metastatic Prostate Cancer Treated with Bicalutamide, Enzalutamide or Abiraterone Following Androgen Deprivation Therapy (Surgical/Medical Castration)

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INTRODUCTION

- The goal of treating patients with non-metastatic castration-resistant prostate cancer (nmCRPC) is to delay the onset of metastasis while maintaining the quality of a patient's survival.
- Historically, treatment strategies for nmCRPC included the addition of antiandrogens (such as bicalutamide) or watchful waiting and active surveillance.[1,2]
- The treatment landscape has evolved following the recent approval of the second-generation androgen receptor inhibitors (SGARIs), enzalutamide and apalutamide.[3,4]
- Fractures, central nervous system (CNS)-related, and skin rash are frequently reported adverse events (AEs) among patients treated with enzalutamide and apalutamide, respectively, as well as first generation antiandrogens (e.g. bicalutamide).[5]
- It is imperative to be cognizant of the impact these AEs can have on patients' daily lives, both for making treatment as well as coverage decisions.

OBJECTIVES

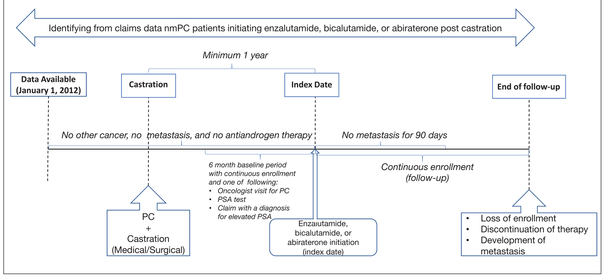
- To describe the healthcare resource use (HCRU) and costs attributable to AEs among previously castrated non-metastatic prostate cancer (nmPC) patients who had possibly developed resistance to androgen deprivation therapy and initiated second line treatment with enzalutamide, bicalutamide, or abiraterone (EBA).

METHODS

Study Design

- This was a retrospective cohort study among previously castrated nmPC patients who initiated second line therapy with EBA ≥1 year after medical or surgical castration.
  - This 1-year gap ensures that EBA treatment was not a part of a first-line androgen deprivation therapy (ADT) and was initiated due to disease progression despite ADT.
- An outline of the study design is found in **Figure 1**.
- Treatment patterns: most common treatments in 1st, 2nd, and 3rd line nmCRPC regimens (1R, 2R, 3R), % of patients receiving SGARis. The dataset contains physician-reported information related to each nmCRPC regimen received by the patients.

Figure 1. Study Design and Patient Inclusion Criteria



Data Source and Measurement

- The IBM Watson MarketScan data from 2012-2017 was used.

Study Population

- Inclusion criteria:
  - Age ≥18 years at the date of first castration therapy.
  - Initiating EBA ≥1 year after medical or surgical castration.
  - ≥ 6 months enrollment pre and ≥ 3 months metastasis-free enrollment post index date.
  - Oncologist visit for prostate cancer, PSA test, or claim with a diagnosis for elevated PSA (ICD-9 code 79093, ICD-10 code R9720) ≥ 6 months pre-initiation of EBA.
- Exclusion criteria:
  - Diagnosis of any other type of cancer (except non-melanoma skin cancer cancers) during the study period.
  - Metastasis or other antiandrogen therapies (i.e., nilutamide, flutamide, EBA) any time prior to initiation of EBA.

Study Cohorts

Patients initiating EBA treatment were stratified into the following cohorts based on the presence or absence of AEs during the follow-up period:

- **CNS AE vs no CNS AE:** Patients with ≥1 claim for a CNS AEs versus those without a claim for a CNS AE.
  - The CNS AEs of interests included in the analysis were: amnesia/memory impairment, anxiety, ataxia, cognitive disorders, confusion, convulsions, disturbance in attention, dizziness, falls, fatigue/asthenia, hallucinations, headaches, insomnia, pain, paresthesia, seizures, weakness, other CNS disorders.[5]
- **Any AE vs no AE:** Patients with ≥1 claim for a CNS AE, skin rash or fracture versus those without a claim for any AE.

Note: Patients could be a part of one or both stratifications.

Outcome Measures

- Patient characteristics: Age, insurance provider, Charlson comorbidity index (CCI), therapy, AE during baseline period, type of castration.
- Per patient per year (PPPY) HCRU and costs: Number of inpatient, outpatient and ER visits, and total costs.

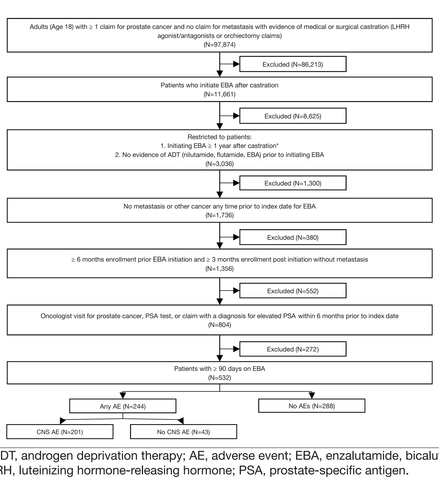
Analysis

- Descriptive statistics were used to compare patient characteristics between CNS AE vs no CNS AE and any AE vs no AE cohorts.
- To account for baseline patient characteristics differences between cohorts, two separate multivariable logistic regression models were utilized to generate the propensity of having a CNS AE and any AE.
- To determine the incremental HCRU and cost burden of CNS AEs and any AEs, propensity score-weighted generalized linear models (GLMs) were used.
- Predicted estimates of adjusted PPPY mean HCRU and costs for patients with a CNS AE vs no CNS AE and any AE vs no AE cohorts were obtained from these models.

KEY FINDINGS

- A total of 532 patients were included, of which 89.7% were treated with bicalutamide, 6.3% were treated with abiraterone, and 4.0% with enzalutamide. The cohort selection flowchart is outlined in the figure below (**Figure 2**).

Figure 2. Patient Selection Flow Chart



Abbreviations: ADT, androgen deprivation therapy; AE, adverse event; EBA, enzalutamide, bicalutamide, or abiraterone; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

- Median follow-up time of these patients was 9 months.
- Out of 532 patients, 37.8% experienced a CNS AE while 45.9% had any AE (i.e., CNS AE, skin rash, or fracture).
- Patients' key characteristics for each cohort are presented in **Table 1**.
- Patients in any AE or CNS AE cohorts were older, had a higher baseline CCI, were more likely to be on Medicare advantage plans, and had higher presence of CNS or any AEs during the baseline period compared to patients in no AE and no CNS AE cohorts.

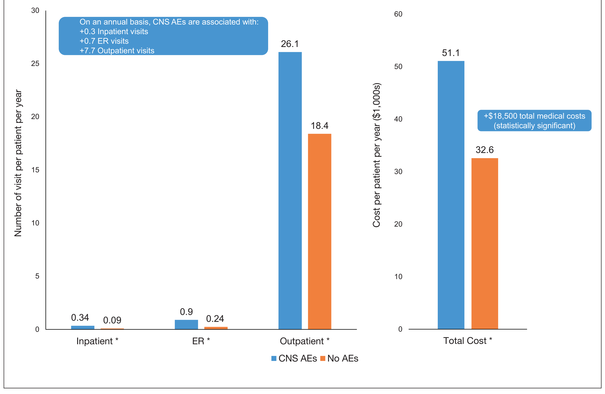
Table 1. Baseline Patient Characteristics

Variable	Statistic or Category	All	By any AE		By CNS AE	
		(N = 532)	any AE (N = 244)	no AE (N = 288)	CNS AE (N =201)	no CNS AE (N =331)
Age, years	Mean (SD)	73.84 (10.98)	75.61 (11.26)	72.34 (10.52)	75.50 (11.22)	72.83 (10.72)
	Median (IQR)	73.5 (64.0 to 82.0)	77.3 (65.4 to 83.7)	70.8 (63.5 to 79.3)	77.3 (65.5 to 83.3)	71.5 (63.5 to 80.5)
CCI score, n (%)	0	76.9%	71.3%	81.6%	69.7%	81.3%
	1	13.3%	15.6%	11.5%	16.9%	11.2%
	2	9.8%	13.1%	6.9%	13.4%	7.6%
Type of castration, n (%)	Medical	82.30%	78.70%	85.40%	78.10%	84.90%
	Surgical and Medical	9.40%	11.50%	7.60%	11.40%	8.20%
	Surgical	8.30%	9.80%	6.90%	10.40%	6.90%
Drug of interest, n (%)	Bicalutamide	89.70%	91.00%	88.50%	90.50%	89.10%
	Abiraterone	6.00%	3.70%	8.00%	3.00%	7.90%
	Enzalutamide	4.30%	5.30%	3.50%	6.50%	3.00%
Insurance provider, n (%)	Medicare Advantage	73.3%	78.3%	69.1%	79.1%	69.8%
	Commercial	26.7%	21.7%	30.9%	20.9%	30.2%
AE during baseline, n (%)	Yes	30.1%	46.7%	16.0%	42.3%	13.9%

A, abiraterone; B, bicalutamide; C, Chi-square test; CCI, Charlson Comorbidity Index; E, enzalutamide; IQR, interquartile range; SD, standard deviation;
V, ANOVA (analysis of variance); W, Wilcoxon rank sum test

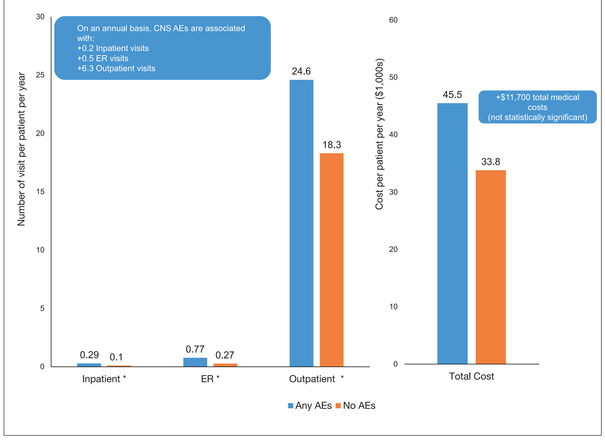
- The adjusted mean and incremental PPPY HCRU and Cost for patients with CNS AEs vs no CNS AEs is shown in **Figure 3**.

Figure 3. PPPY Healthcare resource utilization and total cost among patients with and without CNS AEs



- The adjusted mean and incremental PPPY HCRU and Cost for patients with any AEs vs no AEs are shown in **Figure 4**.

Figure 4. PPPY Healthcare resource utilization and total cost among patients with and without any AEs



LIMITATIONS

- This study is subject to limitations inherent to retrospective claims database studies such as potential misclassification, and under coding of adverse events, Also AEs cannot be linked with drug use in administrative claims data.
- Our sample may not be representative of nmPC patients using enzalutamide or abiraterone since majority of our cohort included patients who initiated second-line therapy with bicalutamide (90%). However, we would not expect extensive use of enzalutamide and abiraterone in nmCRPC to be captured in this analysis, since enzalutamide received FDA approval for the treatment of high-risk nmCRPC on July 13, 2018 whereas abiraterone has still not received approval.

DISCUSSION/CONCLUSIONS

- This is the first real-world study providing estimates of HCRU and cost burden of AEs in a cohort of previously castrated nmPC patients.
- Over 45% (enzalutamide: 56.52%, bicalutamide: 46.54%, abiraterone: 25.71%) experienced at least 1 AE (CNS AE, skin rash, or fracture) and 37% (enzalutamide: 56.52%, bicalutamide: 38.16%, abiraterone: 17.14%) experienced a CNS AE after initiating EBA therapy.
- CNS AEs and any AEs were associated with 34% to 200% increases in the annual number of outpatient, inpatient, and ED visits.
- CNS AEs were associated with 57% increase (~$18,000) in the annual direct costs, independent of patient characteristics.
- Overall, these findings highlight the burden of AEs, and the need for novel agents with better risk-benefit profiles in this population.
- Follow-up studies using a chart review design is necessary to substantiate these findings.

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