Real-World Incidence and Management of Adverse Events (AEs) in Patients with Non-Metastatic Castrate-Resistant Prostate Cancer Receiving Apalutamide or Enzalutamide

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BACKGROUND

- Non-metastatic castrate-resistant prostate cancer (nmCRPC) is a distinct clinical state within the prostate cancer disease spectrum in men on androgen deprivation therapy (ADT) who develop rising prostate-specific antigen (PSA) in the setting of castrate levels of serum testosterone but without evidence of detectable disease on imaging tests.[1]
- The goal of treating nmCRPC patients is to primarily delay metastatic disease.[2]
- Second generation androgen receptor inhibitors (SGARIs) apalutamide, enzalutamide and darolutamide have been approved by the US Food and Drug Administration (FDA) to treat men with nmCRPC, and the adverse event (AE) profiles of these agents have been described in the respective clinical trials.
- Avoiding or minimizing AEs is a key consideration when choosing treatment options for relatively asymptomatic disease states, such as nmCRPC: therefore, it is important to understand the real-world consequences of the newer SGARIs.[3]

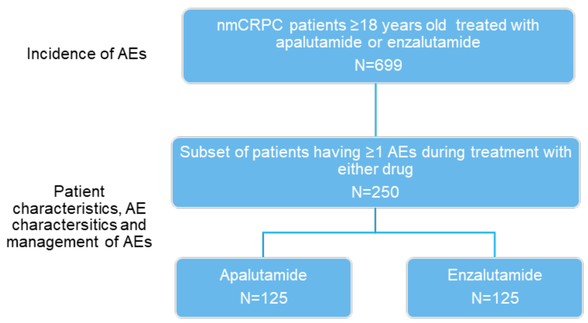
OBJECTIVES

- Objectives of this real-world study were to describe nmCRPC patients and their treatment patterns, and to estimate the frequencies (proportions) and management of AEs in patients receiving apalutamide and enzalutamide (darolutamide was not included due to lack of real-world on-label use for nmCRPC at time of data collection).

METHODS

- A 2-phase non-interventional, retrospective, multi-site medical chart review study was conducted in the US where clinical data was sourced from patient medical charts.
- A geographically dispersed sample of 43 physicians (36 medical oncologists; 6 urologist/urologist-oncologists; 1 radiologist) treating nmCRPC patients were recruited as study investigators to provide relevant data on such patients who met the eligibility for inclusion into the study as defined by the study protocol.
- Patient selection criteria included the following:
  - A total of 699 adult nmCRPC patients initiating treatment with apalutamide between February 1, 2018 and December 31, 2018 or enzalutamide between July 1, 2018 and December 31, 2018 (based on FDA approval dates of the SGARIs for nmCRPC) were included, and any AEs they experienced were recorded (Figure 1).
  - Detailed chart data were collected in a subset of 250 patients with ≥1 AEs to better understand AE severity and management (Figure 1).
  - Patients had to have a minimum of 6 months of follow-up from SGARI treatment initiation and follow-up concluded at the date of last visit, date of death or the end of the study period, whichever occurred first.
  - Patients were excluded if they had a history of metastasis before CRPC diagnosis or other primary cancers; or were currently enrolled in an nmCRPC-related clinical trial.
- AEs included hypertension, rash, pruritus, weight loss, diarrhea, nausea, decreased appetite, hot flushes, arthralgia, hypothyroidism, cardiovascular events and CNS-related events which included fatigue, asthenia, headache, fracture, falls, seizures, dizziness, and cognitive disorders (mental/memory impairment or changes, disturbances in attention).
- Descriptive results were summarized using frequency and percentage for categorical variables and mean and standard deviation for continuous variables.

Figure 1. Distribution of Eligible Patients



RESULTS

Physician Characteristics

- Most physicians were male, specialized in medical oncology or urology, and more than half had been in practice for 15 years or less.
- The physicians currently managed/treated a median of 74 PC patients and 26 nmCRPC patients within their practice.
- On average, physicians reported that within their practice:
  - Nearly half of all their nmCRPC patients were treated with enzalutamide (46%) and more than a third were treated with apalutamide (38%).
  - More than half of the patients treated with either SGARI experienced an AE (apalutamide, 55%; enzalutamide, 57%).
- All physicians reported using PSA to monitor patients with nmCRPC; only ~40% reported using prostate-specific antigen doubling time (PSA-DT).

Incidence of (All Grade) AEs

- Of the 699 patients (apalutamide, 368; enzalutamide, 333; 2 patients received both), 75.1% experienced ≥1 AE and 44.2% experienced ≥1 CNS-related AE.
- The most common adverse events were fatigue/asthenia (34.3%), flush (13.9%), and arthralgia (13.6%) (Figure 2). Cognitive disorders were reported in 6.4% of patients.

Patient and Treatment Characteristics

- On average, the subset of 250 patients with ≥1 AE were 71 years old; three-fourths were Caucasian and covered by Medicare and 86% had an Eastern Cooperative Oncology Group (ECOG) Score of 0-1 at time of nmCRPC diagnosis (Table 1).
- Only 41 (16.4%) patients had at least 2 PSA values that could be used to calculate PSA-DT; of those with known PSA-DT, 32% had PSA-DT ≤6 months.
- The 2 most common physician-reported rationale for initiating treatment with SGARIs were to prevent/delay metastasis (63%) and for a PSA-DT <10 months (40%).
- Median duration of SGARI therapy was 13 months, with 14.4% progressing to metastasis by end of study (median follow-up of 1.1 years).
- Of the 250 patients, grade 3-4 and grade 5 AEs occurred in 14.4% and 0.4% of patients, respectively.

Figure 2. Most Reported AEs Among 699 Patients Treated with SGARI

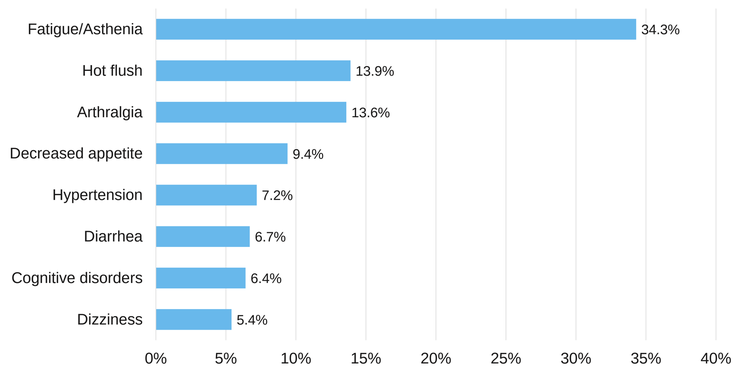


Table 1. Patient Demographic and Clinical Characteristics

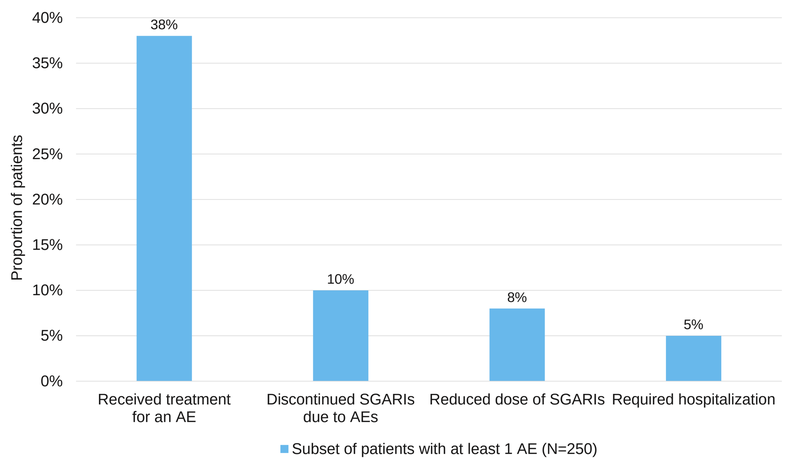
Variables	All Patients (N = 250)
Age (years)	
Mean (SD)	70.84 (7.84)
Median (IQR)	70.0 (66.0 to 76.0)
Race, N (%)	
White or Caucasian	180 (72.0%)
Black or African/Caribbean-origin	65 (26.0%)
Asian	2 (0.8%)
American Indian/Alaska native	1 (0.4%)
Unknown	2 (0.8%)
Healthcare coverage, N (%)	
Medicare	186 (74.4%)
Medicaid	28 (11.2%)
Preferred provider organization	27 (10.8%)
Private	24 (9.6%)
Health maintenance organization	9 (3.6%)
Medigap	5 (2.0%)
Traditional fee for service	5 (2.0%)
Veteran's Affair	2 (0.8%)
Body mass index	
Mean (SD)	27.47 (3.90)
Median (IQR)	26.8 (25.0 to 28.9)
Charlson Comorbidity Index, N (%)	
0	162 (64.8%)
1	60 (24.0%)
2+	28 (11.2%)
ECOG score at nmCRPC diagnosis, N(%)	
0	83 (33.2%)
1	132 (52.8%)
2	25 (10.0%)
3+	2 (0.8%)
Unknown	8 (3.2%)
Gleason score at nmCRPC diagnosis, N (%)	
6 or lower	28 (11.2%)
7	87 (34.8%)
8 to 10	94 (37.6%)
Unknown	41 (16.4%)
PSA at nmCRPC diagnosis	
N	241
Mean (SD)	23.21 (44.15)
Median (IQR)	12.0 (6.7 to 26.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; nmCRPC, non-metastatic castrate-resistant prostate cancer; PSA, prostate specific antigen; SD, standard deviation.

Actions to Address Adverse Events

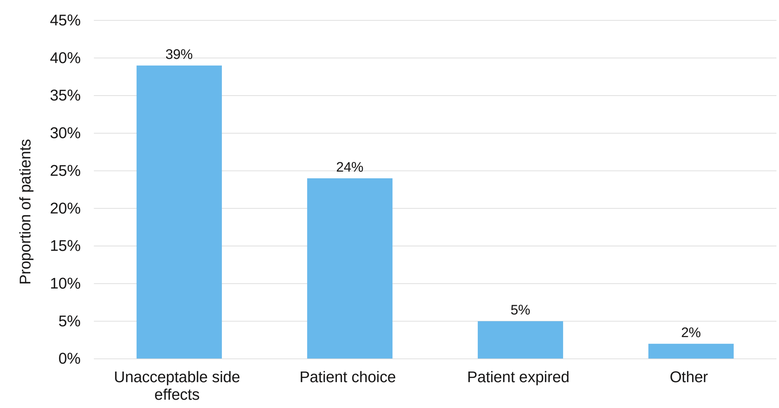
- Of the subset of 250 patients treated with SGARI experiencing AEs:
  - More than a third (38%) required treatment for their AE
  - SGARIs were discontinued due to AEs in 10%
  - Dose of SGARIs were reduced in approximately 8% (Figure 3)

Figure 3. Actions Taken to Address AEs Occurring During SGARI Treatment



- More than a quarter (26.8%) of the 250 patients discontinued their SGARI for different reasons (Figure 4). Among the patients discontinuing for reasons other than disease progression, more than a third discontinued due to AEs.

Figure 4. Physician-Reported Non-Progression Related Reason for SGARI Discontinuation Among Those Who Discontinued

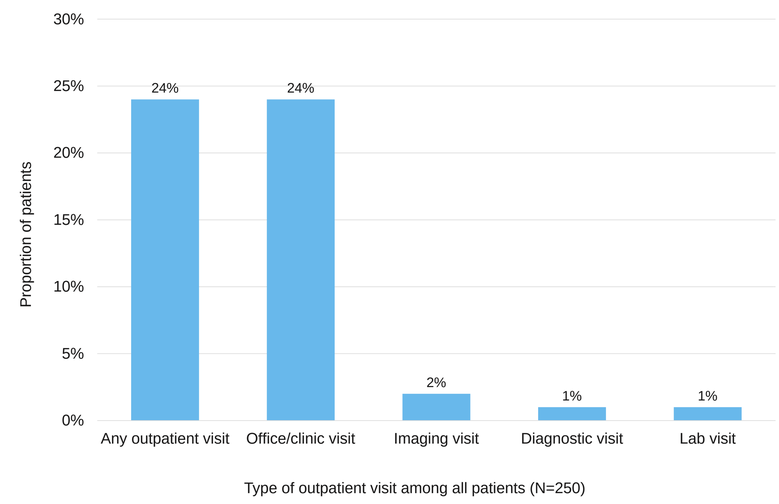


*Categories as reported verbatim in the case-reported form

Resource Utilization

- Approximately 5% required a hospitalization for their AE and spent an average of 5 days in the hospital.
  - AEs requiring hospitalization included seizure, fracture, falls, hypertension and other cardiovascular events.
- A quarter of the patients had at least 1 outpatient visit (including office/clinic visits, lab visits, imagine visits and diagnostic visits) for the management of their AEs (Figure 5).

Figure 5. Outpatient Use of AE Management



LIMITATIONS

- The focus of this study is AEs associated with FDA approved medications for nmCRPC in the US (apalutamide and enzalutamide). Off-label use of other medications was not systematically captured.
- The results are reflective of the practices of participating physicians/sites and may vary from non-participating sites.

DISCUSSION/CONCLUSION

- This is the first real-world study to examine the frequency and burden of AEs amongst a nmCRPC patient population treated with SGARIs using data abstracted directly from patient charts.
- Three-quarters of the treated patients experienced at least 1 AE and almost half experienced a CNS-related AE.
- "Prevention or delay of metastasis" and "PSA-DT ≤10 months" were the 2 most common reasons for prescribing a SGARI.
- The study highlights the downstream consequences of AEs with nearly 40% requiring treatment to manage their AEs, 10% discontinuing SGARI treatment and 5% requiring hospitalization.
- This study highlights the need for effective therapies with a favorable safety profile and the importance of considering the risk-benefit profile of SGARI therapy in nmCRPC.

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