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Real-World Assessment of New-Onset Central Nervous System Conditions in Patients With Non-Metastatic Castration-Resistant Prostate Cancer Treated With Apalutamide, Darolutamide, or Enzalutamide

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Key Takeaway

Patients with nmCRPC initiated on apalutamide had numerically lower incidence and delayed onset of CNS-related conditions relative to the darolutamide and enzalutamide cohorts

Conclusions

In a real-world setting, patients with nmCRPC initiated on apalutamide experienced numerically fewer and later CNS-related events relative to those treated with darolutamide or enzalutamide

These findings suggest a clinical difference in the real-world incidence of CNS-related conditions among patients treated with different ARPIs, suggesting that apalutamide may have a more favorable profile that minimizes the risk of CNS-related conditions in patients with nmCRPC

Ongoing research and long-term monitoring are needed to further characterize CNS-related outcomes and guide optimal treatment selection in this patient population

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Disclosures

D. Sentana Lledo is an employee of the Dana-Farber Cancer Institute. C. Patel and S. Burbage are employees and stockholders of Johnson & Johnson. K. Joshi was an employee of Johnson & Johnson at the time the study was conducted. C. Rossi, F. Kinkead, G. Wong, A. Palladino, and D. Pilon are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Johnson & Johnson. M.A. Bilen is an employee of the Winship Cancer Institute of Emory University and has received consulting fees from Johnson & Johnson.

Background

- Apalutamide, darolutamide, and enzalutamide are androgen receptor pathway inhibitors (ARPIs), approved for use in combination with androgen deprivation therapy (ADT) for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC)[1-3]
- Central nervous system (CNS) conditions, such as cognitive impairment, falls, seizures, fatigue, pain, or headaches, are important clinical considerations among nmCRPC patients treated with an ARPI due to either pre-existing patient medical history or potential for treatment-related adverse events[4,5]
- Despite the growing use of ARPIs, real-world evidence on CNS-related clinical outcomes in patients with nmCRPC remains limited[6]

Objective

- To describe CNS outcomes among patients with nmCRPC treated with apalutamide, darolutamide, or enzalutamide in a US real-world setting

Methods

Data sources

- Electronic medical record (EMR) data from Precision Point Specialty (PPS) Analytics, collected as part of routine clinical care from private, community-based urology practices in the US, linked with administrative claims data from the Komodo Research Database (KRD+) was used (study period: 1 January 2016 - 31 August 2024)
- Data were de-identified and Health Insurance Portability and Accountability Act (HIPAA) compliant

Study design

- Patients were assigned to mutually exclusive treatment cohorts based on the first dispensation or paid pharmacy claim for apalutamide, darolutamide, or enzalutamide
- The index date was defined as the first dispensation or paid pharmacy claim for apalutamide, darolutamide, or enzalutamide on or after 30 July 2019 (the US Food and Drug Administration approval date for darolutamide[2] in nmCRPC which followed apalutamide approval on 14 February 2018[1] and enzalutamide approval on 13 July 2018[3])
- The baseline period was defined as 12 months of clinical activity in PPS or claims activity prior to the index date
- The on-treatment observation period was defined as the index date until the earliest of index ARPI discontinuation or switch, initiation of an advanced PC-related medication (i.e., chemotherapy, radiopharmaceuticals, poly ADP-ribose polymerase [PARP] inhibitors, or immunotherapy), or end of clinical activity/data availability (i.e., 31 August 2024)

Patient selection criteria

- Concurrent use of ADT was not required for patients to be included in the apalutamide, darolutamide, or enzalutamide cohorts

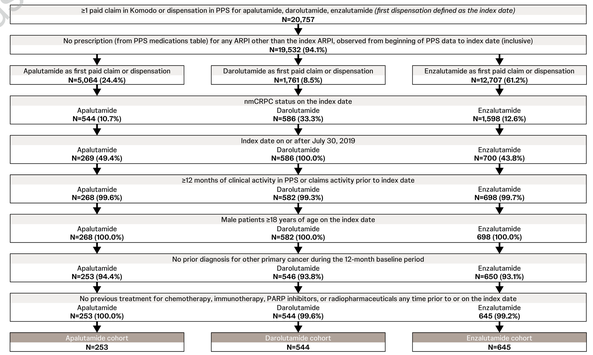
Study outcomes

- Newly diagnosed CNS-related conditions that were not observed during the 12-month baseline period were described among patients who initiated apalutamide, darolutamide, or enzalutamide during the on-treatment observation period

Statistical analysis

- The proportion of patients with new onset of any CNS-related condition by 12- and 24-months post-index was described separately for each treatment cohort using a Kaplan-Meier analysis
- All analyses were descriptive, and no confidence intervals or p-values were generated

Figure 1: Patient flowchart



Abbreviations: ARPI: androgen receptor pathway inhibitor; nmCRPC: non-metastatic castration-resistant prostate cancer; PARP: poly ADP-ribose polymerase; PC: prostate cancer; PPS: Precision Point Specialty.

Results

Baseline characteristics

- Overall, the following patients with nmCRPC were included (**Figure 1 and Table 1**):
  - 253 patients treated with apalutamide (mean age 77.6, 61.3% White, 24.5.% Black, 87.0% Medicare-insured, 97.2% prior ADT use)
  - 544 patients treated with darolutamide (mean age 78.7, 65.8% White, 21.5% Black, 93.6% Medicare-insured, 97.2% prior ADT use)
  - 645 patients treated with enzalutamide (mean age 77.7, 62.8% White, 24.2% Black, 92.4% Medicare-insured, 96.1% prior ADT use)

Table 1: Baseline characteristics

	Apalutamide N=253	Darolutamide N=544	Enzalutamide N=645
Age, mean ± SD [median]	77.6 ± 7.8 [80.0]	78.7 ± 7.3 [81.0]	77.7 ± 7.2 [79.0]
Race, n (%)			
White	155 (61.3)	358 (65.8)	405 (62.8)
Black or African American	62 (24.5)	117 (21.5)	156 (24.2)
Other[a]	27 (10.7)	51 (9.4)	68 (10.5)
Unknown	9 (3.6)	18 (3.3)	16 (2.5)
Geographic region, n (%)			
South	167 (66.0)	243 (44.7)	350 (54.3)
Midwest	39 (15.4)	169 (31.1)	162 (25.1)
Northeast	31 (12.3)	84 (15.4)	92 (14.3)
West	16 (6.3)	48 (8.8)	41 (6.4)
Payer type, n (%)			
Medicare	220 (87.0)	509 (93.6)	596 (92.4)
Commercial	29 (11.5)	29 (5.3)	40 (6.2)
Medicaid	2 (0.8)	4 (0.7)	8 (1.2)
Unknown	2 (0.8)	2 (0.4)	1 (0.2)
Index year, n (%)			
2019-2020	85 (33.6)	130 (23.9)	274 (42.5)
2021-2022	76 (30.0)	257 (47.2)	241 (37.4)
2023-2024	92 (36.3)	157 (28.9)	130 (20.2)
Time between castration resistance[b] and index date, months, mean ± SD [median]	20.5 ± 27.0 [6.6]	17.6 ± 23.9 [8.1]	18.8 ± 27.3 [7.1]
Prior use of ADT[c], n (%)	246 (97.2)	529 (97.2)	620 (96.1)
Quan-CCI, mean ± SD [median]	3.7 ± 2.2 [3.0]	3.8 ± 2.1 [3.0]	3.8 ± 2.2 [3.0]
PSA level[d], ng/mL, n (%)			
≤0.2	34 (13.4)	62 (11.4)	50 (7.8)
>0.2 to ≤2	62 (24.5)	172 (31.6)	147 (22.8)
>2 to ≤10	64 (25.3)	164 (30.1)	180 (27.9)
>10 to <20	23 (9.1)	37 (6.8)	62 (9.6)
≥20	24 (9.5)	37 (6.8)	88 (13.6)
Unknown	46 (18.2)	72 (13.2)	118 (18.3)
Initial Gleason score[e], n (%)			
≤6	17 (6.7)	64 (11.8)	52 (8.1)
7	60 (23.7)	165 (30.3)	130 (20.2)
8	31 (12.3)	74 (13.6)	77 (11.9)
9	41 (16.2)	89 (16.4)	108 (16.7)
10	6 (2.4)	7 (1.3)	12 (1.9)
Unknown	98 (38.7)	145 (26.7)	266 (41.2)

Abbreviations: ADT: androgen deprivation therapy; CCI: Charlson Comorbidity Index; PSA: prostate-specific antigen; SD: standard deviation.

Notes:

a. Other race category included Hispanic, Asian, and other races.

b. Castration resistance evaluated at any time prior to and including the index date.

c. Prior use of ADT medication evaluated at any time prior to and excluding the index date. Prior use was determined based on ≥90 days of continuous ADT use.

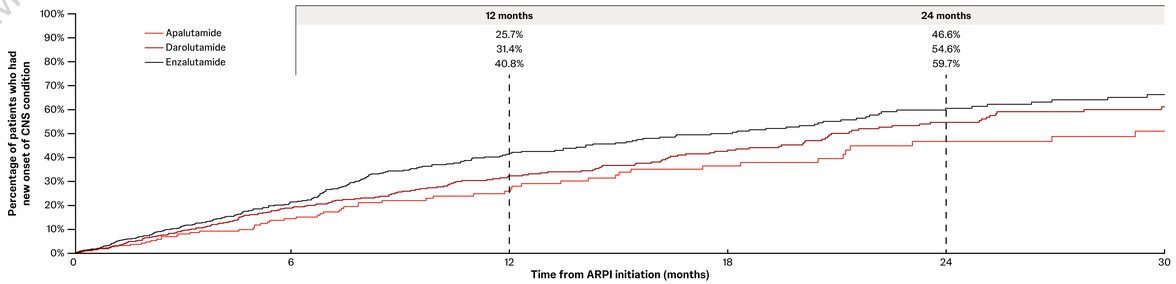
d. PSA testing was evaluated during the 12-month baseline period, including the index date.

e. Gleason score was evaluated at any time prior to and including the index date.

Incidence of CNS-related conditions

- The mean (median) duration of the on-treatment observation period was 12.4 (7.4) months for the apalutamide cohort, 14.0 (9.3) months for the darolutamide cohort, and 12.3 (7.7) months for the enzalutamide cohort
- New onset CNS-related conditions were experienced by a numerically lower proportion of patients in the apalutamide cohort at both 12 months (apalutamide: 25.7%, darolutamide: 31.4%, enzalutamide: 40.8%) and 24 months post-index (apalutamide: 46.6%, darolutamide: 54.6%, enzalutamide: 59.7%) (**Figure 2**)
- Patients in the apalutamide cohort had a numerically longer median time-to-new onset of CNS-related conditions (29.2 months) relative to those in the darolutamide (21.3 months) and enzalutamide (18.1 months) cohorts (**Figure 3**)
- The rates of commonly observed new onset CNS-related conditions (i.e., fatigue, falls, dizziness, pain, and weakness) were numerically lower in apalutamide cohort, relative to the enzalutamide and darolutamide cohorts (**Figure 4**)

Figure 2: Kaplan-Meier analysis for time-to-new onset of any CNS-related condition[a]



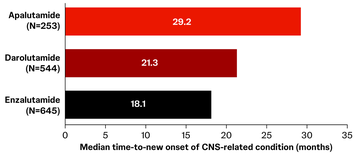
Abbreviations: ARPI: androgen receptor pathway inhibitor; CNS: central nervous system.

Notes:

a. CNS-related conditions were defined as the following: amnesia/memory impairment, anxiety, ataxia, confusion, cognitive disorders, convulsions, depression, dizziness, disturbance in attention, falls, fatigue/asthenia, hallucinations, headaches, insomnia, nausea, pain, paresthesia, posterior reversible encephalopathy syndrome (PRES), psychosis, schizophrenia, seizures, vertigo, weakness, and other CNS disorders.

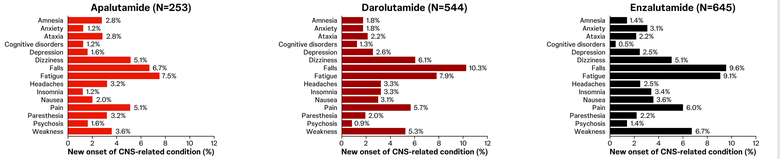
b. New onset of CNS-related conditions were only reported among patients who did not experience the same CNS-related condition in the 12 months prior to (and excluding) the index date (baseline period). If a patient has a CNS-related condition (e.g., falls) during the baseline period, then that specific condition would not be counted as "new onset of CNS" in the observation period; however, the patient would still be at risk of having other incident CNS-related conditions in the observation period (e.g., nausea), as long as these conditions have not been observed during the baseline period.

Figure 3: Time-to-new onset of any CNS-related condition



Abbreviations: CNS: central nervous system.

Figure 4: New-onset CNS-related conditions



Abbreviations: CNS: central nervous system.

Limitations

- This observational study relied on administrative claims and clinical data, which may contain coding inaccuracies or omissions
- Additionally, while the linkages between the PPS and KRD data sources are comprehensive, any mis-linkages may lead to misclassification and potential information bias

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1. FDA approves apalutamide for non-metastatic castration-resistant prostate cancer. 2018. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-non-metastatic-castration-resistant-prostate-cancer. 2. FDA approves darolutamide for non-metastatic castration-resistant prostate cancer. 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-darolutamide-non-metastatic-castration-resistant-prostate-cancer. 3. FDA approves enzalutamide for castration-resistant prostate cancer. 2018. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enzalutamide-castration-resistant-prostate-cancer. 4. Bubendorf L, et al. *Hum Pathol*. 2000;31(5). 5. Markman M. *Cleve Clin J Med*. 1999;66(10):629–631. 6. Pilon D, et al. *Am Health Drug Benefits*. 2017;10(3):143.

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