REVIEWS IN UROLOGY

Real-World Comparison of Deep Prostate-Specific Antigen Response in Patients With Metastatic Castration-Sensitive Prostate Cancer Treated With Apalutamide or Enzalutamide

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KEYWORDS:
Androgen receptor antagonists; castration; prostate-specific antigen; prostatic neoplasms; treatment effectiveness

Abstract

Background: Deep prostate-specific antigen reduction of at least 90% (PSA90 response) after androgen receptor pathway inhibitor initiation to treat metastatic castration-sensitive prostate cancer (mCSPC) is associated with longer survival. This real-world study evaluated the proportion of androgen receptor pathway inhibitor–naive patients with mCSPC who achieved PSA90 response 6 months after initiating apalutamide or enzalutamide.

Methods: Linked electronic health record and administrative data were used. Patients with mCSPC were assigned to apalutamide or enzalutamide cohorts based on their first pharmacy claim or dispensation on or after the index date. Patients were followed until the earliest among index androgen receptor pathway inhibitor discontinuation or switch, radiopharmaceutical initiation, end of open claim or electronic health record activity, or end of data availability. Earliest PSA90 response relative to the most recent pre–index PSA level was compared between cohorts using inverse probability of treatment weighting.

Results: In total, 862 apalutamide and 871 enzalutamide patients were identified. Preindex characteristics were well balanced after weighting. Six months after the index date, 62.5% of apalutamide patients and 53.8% of enzalutamide patients had achieved PSA90 response (hazard ratio, 1.21; $P = .008$). The median time to PSA90 response was 3.7 months for apalutamide patients and 5.1 months for enzalutamide patients.

Conclusion: This causal real-world analysis is the second such study to demonstrate that a statistically significantly higher proportion of patients with mCSPC achieved an early PSA90 response when treated with apalutamide compared with enzalutamide. Early and deep PSA response may be an important factor to consider in treatment selection, given its association with overall survival.

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Prostate cancer (PCa) is the second-leading cause of cancer death in US men, behind only lung cancer.[1] An estimated 299 000 new PCa cases and 35 250 PCa-related deaths are expected in 2024 in the United States.[1] Although approximately 70% of new patients with PCa are diagnosed with localized disease, the incidence of advanced or metastatic PCa (ie, cancer that has spread to the lungs, liver, or bones) has increased in the past decade.[2] Advanced PCa changes the objectives of clinical management because curative treatment is no longer possible and has a relative survival rate of approximately 30% at 5 years and less than 20% at 10 years.[3,4]

Androgen-deprivation therapy (ADT), which aims to reduce testosterone to castration levels, has long been a key component of the standard of care for patients with metastatic PCa, but the introduction of androgen receptor pathway inhibitors (ARPIs)—used in combination with ADT—has demonstrated that androgen-deprivation monotherapy delivers suboptimal outcomes to men with metastatic PCa.[5] Apalutamide and enzalutamide are 2 ARPIs approved for the treatment of metastatic castration-sensitive PCa (mCSPC); both have been shown to improve clinical outcomes in combination with ADT.[6-9] Specifically, apalutamide plus ADT improved radiographic progression-free survival (PFS) and overall survival (OS) compared with placebo plus ADT in patients with mCSPC in the TITAN phase 3 trial.[6,7] Enzalutamide plus ADT was similarly shown to improve radiographic PFS and OS compared with placebo plus ADT in patients with mCSPC in the ARCHES phase 3 trial.[8,9]

Early and deep prostate-specific antigen (PSA) response (≥90% reduction in PSA [PSA90] or having an undetectable PSA [PSA ≤0.2 µg/L (≤0.2 ng/mL)] by 6 months) has been associated with radiographic PFS and OS in patients with mCSPC.[10,11] Though post hoc analyses of clinical trial data and multiple other independent studies have shown an association between an early and deep PSA response and improved long-term outcomes in patients with advanced PCa,[10-15] there is limited real-world evidence of PSA response in patients with mCSPC.[16,17] One previous real-world study evaluating a cohort of patients from US community-based urology practices reported that the majority (70%) of patients with mCSPC who initiated apalutamide achieved a PSA90 response within 6 months of therapy initiation.[16] Another real-world study using data from US community-based urology practices found that apalutamide was associated with higher PSA90 response rates that were statistically significant than enzalutamide at 6 months after treatment initiation among patients with mCSPC who initiated ARPI therapy through in-office dispensing.[17] The current study aimed to replicate findings from this previous comparative analysis by comparing real-world PSA90 response in a larger cohort of patients with mCSPC by using linked clinical electronic health records (EHRs) and administrative claims data,

SUMMARY OF MAIN POINTS

- Apalutamide and enzalutamide are 2 ARPIs used to treat patients with mCSPC.
- Early and deep PSA response (ie, PSA90) is associated with longer survival and radiographic PFS in patients with mCSPC.
- The current real-world study compared the proportion of ARPI-naive patients with mCSPC and PSA90 response within 6 months after initiating apalutamide vs enzalutamide.
- Using an inverse probability of treatment weighting approach, by 6 months after index, 62.5% of patients who initiated apalutamide and 53.8% of patients who initiated enzalutamide had a PSA90 response (HR, 1.21 [95% CI, 1.05-1.40]; *P* = .008).
- Considering the association between deep PSA response and OS, early PSA90 response may be an important factor to consider in treatment selection for patients with mCSPC.

ABBREVIATIONS

ADT	androgen deprivation therapy
ARPI	androgen receptor pathway inhibitor
EHR	electronic health record
HR	hazard ratio
mCSPC	metastatic castration-sensitive prostate cancer
OS	overall survival
PCa	prostate cancer
PFS	progression-free survival
PSA	prostate-specific antigen
PSA90	reduction of PSA level from baseline of at least 90%

including data for patients who did not necessarily fill their medication through in-office dispensing.

Methods

DATA SOURCES

Clinical EHR data from PPS Analytics software (Precision Point Specialty LLC), collected as part of routine clinical care from US community-based urology practices, were linked with administrative claims data from the Komodo Research Database from December 16, 2018, to September 30, 2022. The PPS Analytics clinical data included patient demographic and clinical variables, such as ARPI dispensations, prescriptions for other medications to treat advanced PCa, PSA measurements, information about metastasis, and assessment of castration resistance. Data from the Komodo Health research database included patient demographics and mortality information, inpatient and outpatient medical claims with diagnosis and procedure codes, and paid pharmacy claims. These linked data were deidentified and compliant with the Health Insurance Portability and Accountability Act. Institutional review board approval was not required for the study.

STUDY DESIGN

A causal analysis using a retrospective longitudinal cohort of patients with mCSPC initiated on apalutamide or enzalutamide was conducted. Patients were assigned to 2 mutually exclusive cohorts for apalutamide or enzalutamide treatment based on their first paid pharmacy claim, as identified in administrative claims, or first pharmacy dispensation, as identified in the clinical data, for apalutamide or enzalutamide. The index date was defined as the first dispensation or paid pharmacy claim for apalutamide or enzalutamide on or after December 16, 2019 (ie, the approval date for enzalutamide,[18] the more recently US Food and Drug Administration approved of the 2 medications, which followed approval of apalutamide[19] on September 17, 2019). The baseline period

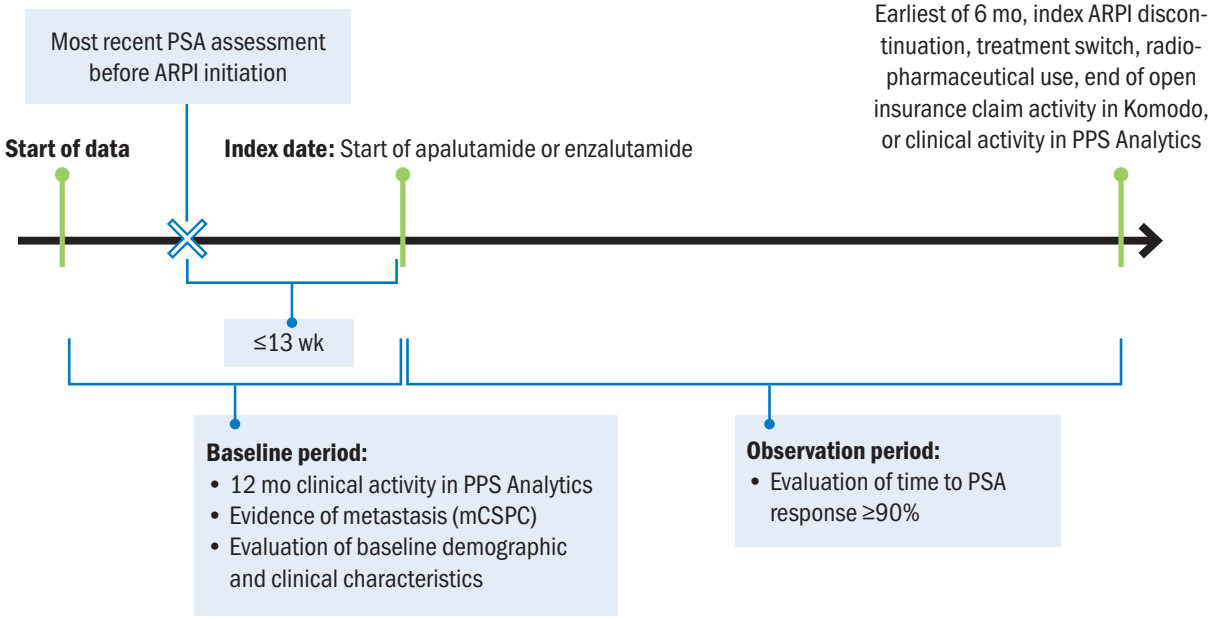

Figure 1. Study Design

Abbreviations: ARPI, androgen receptor pathway inhibitor; mCSPC, metastatic castration-sensitive prostate cancer; PPS, Precision Point Specialty; PSA, prostate-specific antigen.

was defined as the 12 months before the index date (Figure 1). The observation period spanned from the index date to the earliest among index treatment discontinuation (using a ≥90-day treatment gap in days of supply), initiation of a new ARPI that was not used on the index date (ie, apalutamide, abiraterone acetate, darolutamide, or enzalutamide) or a radiopharmaceutical agent, end of clinical or claims activity (including death), or end of data availability (September 30, 2022).

PATIENT SELECTION

Adult patients (≥18 years old) were included if they had at least 1 paid pharmacy claim or dispensation for apalutamide or enzalutamide. Patients were required to have a diagnosis code for metastatic PCa as identified in administrative claims or recorded in the clinical EHR on or before the index date. Patients were also required to have at least 12 months of clinical activity (from PPS Analytics) before the index date and at least 1 PSA measurement in the 13-week period up to and including the index date. Patients were excluded if they had a paid pharmacy claim or dispensation for more than 1 ARPI on the index date; had a paid pharmacy claim or dispensation for a nonindex ARPI before the index date; or had a prescription, as identified in the clinical data, for a nonindex ARPI on or before the index date. Patients were also excluded if they had evidence of castration resistance on or before the index date or had used radiopharmaceuticals at any time on or before the index date. Concurrent use of ADT was not required for patients to be included in either cohort; however, the proportion of patients on ADT concurrently with their index ARPI was assessed.

STUDY MEASURES

The primary outcome was the proportion of patients who achieved PSA90 response by 6 months after treatment initiation. As an exploratory outcome, the median time to PSA90 response over the entire observation period as its time frame was assessed. A PSA90 response was defined as having a PSA measurement that had at least a 90% relative decline from the most recent baseline PSA value observed within 13 weeks of the index date; it was assessed while the patient remained on the index ARPI (Figure 1).

During the 12-month baseline period, the following characteristics were evaluated: age, race, geographic region, payer type, year of index ARPI initiation, time between metastasis and ARPI initiation, time between initial PCa diagnosis and ARPI initiation, metastasis type (ie, bone, nodal, or visceral), de novo PCa (ie, ≤180 days between initial PCa diagnosis and metastasis date), concurrent use of ADT, prior use of ADT, prior use of a first-generation androgen receptor inhibitor, chemotherapy use, baseline PSA level, baseline testosterone level, and baseline Gleason score. During the observation period, postindex PSA measurement patterns were also evaluated.

STATISTICAL ANALYSIS

The null hypothesis was that the proportion of patients achieving a PSA90 response by 6 months would be the same between the apalutamide and enzalutamide cohorts; the alternative hypothesis was that the proportion of patients achieving a PSA90 response would not be the same between the 2 cohorts. This study applied statistical methods appropriate for causal inference. Inverse probability of treatment weighting, based on the propensity score, was used to minimize differences in measured baseline characteristics between the cohorts.[20] The propensity score was generated using probability estimates from a logistic regression model in which the dependent variable was the index treatment (ie, apalutamide or enzalutamide) and the following independent variables were used to predict treatment assignment: age (continuous), race, geographic region, payer type, index year, time between metastasis and index date (continuous), time between initial PCa diagnosis and index date (continuous), de novo PCa, previous ADT use, first-generation androgen receptor inhibitor use, chemotherapy use, metastasis type (ie, bone, nodal, or visceral), most recent baseline PSA level (continuous), most recent baseline testosterone level (categorized as <1.735 nmol/L (<50 ng/dL) or ≥1.735 nmol/L (≥50 ng/dL); patients without a testosterone measurement were grouped into the <1.735 nmol/L

[<50 ng/dL] category), and most recent baseline Gleason score (scores categorized as ≤6, 7, 8, 9, 10, and missing). Patient weights were calculated as 1/propensity score for the apalutamide cohort and 1/(1 – propensity score) for the enzalutamide cohort. Weights were truncated at the 95th percentile to prevent bias as a result of extreme weights and were normalized by the mean weight in each cohort to maintain the overall sample size for the apalutamide and enzalutamide cohorts. No patients were dropped from the analysis as part of the weight truncation.

For both the unweighted and weighted cohorts, demographic and baseline clinical characteristics were compared using standardized differences. The balance of baseline characteristics between treatment cohorts after weighting was confirmed by standardized differences less than 10%, indicating balance.[21] Weighted Kaplan-Meier analysis was used to describe the proportion of patients achieving PSA90 response by 6 months after index. Weighted Cox proportional hazards models were used to generate hazard ratios (HRs) and 95% CIs to evaluate the causal relationship between index treatment and the probability of achieving PSA90 response by 6 months (primary objective) and over the entire follow-up period (exploratory objective).

Results

BASELINE CHARACTERISTICS

Overall, 862 patients with mCSPC who initiated apalutamide and 871 patients with mCSPC who initiated enzalutamide were identified (Figure 2). Cohorts were well balanced after inverse probability of treatment weighting, with standardized differences generally below 10% for all baseline characteristics between the weighted cohorts (Table 1). The mean (SD) age was 74.1 (8.4) years for the apalutamide cohort and 74.1 (8.9) years for the enzalutamide cohort (median age for both cohorts, 74.0 years). Black patients represented 18.5% of the apalutamide cohort and 18.8% of the enzalutamide cohort. Most patients were from the American South (apalutamide, 51.3%; enzalutamide, 50.3%) and had Medicare (apalutamide, 73.5%; enzalutamide, 73.6%). The apalutamide cohort had a mean (SD) time between metastasis and ARPI initiation of 10.6 (20.0) months (median, 2.4 months); the enzalutamide cohort had a mean (SD) time between metastasis and ARPI initiation of 11.0 (17.3) months (median, 3.2 months). The apalutamide cohort mean (SD) baseline PSA value was 22.7 (55.2) µg/L [22.7 (55.2) ng/mL] (median, 3.3 µg/L [3.3 ng/mL]), while the enzalutamide cohort's mean (SD) baseline PSA value was 23.3 (55.8) µg/L [23.3 (55.8) ng/mL] (median, 3.0 µg/L [3.0 ng/mL]). The proportion of patients with de novo PCa was 41.3% in the apalutamide cohort and 42.0% in the enzalutamide cohort (Table 1).

PSA OUTCOMES

Six months after index, 62.5% of patients with mCSPC who initiated apalutamide and 53.8% of patients who initiated enzalutamide had a PSA90 response (HR, 1.21 [95% CI, 1.05-1.40]; *P* = .008) (Figure 3). A PSA90 response was attained earlier in patients treated with apalutamide (median time to PSA90, 3.7 months) than for those treated with enzalutamide (median time to PSA90, 5.1 months). Rates of PSA90 response remained consistently higher for apalutamide patients than for enzalutamide patients over the entire observation period (HR, 1.20 [95% CI, 1.05-1.38]; *P* = .008).

PSA-RELATED MEASUREMENTS

Overall, 83.2% of patients in the apalutamide cohort and 78.4% of patients in the enzalutamide cohort had at least 1 PSA measurement during the observation period (Table 2). By 6 months after index, 81.4% of apalutamide patients and 77.5% of enzalutamide patients had a PSA measurement. Overall PSA testing frequency was similar between patients in the apalutamide and enzalutamide cohorts (mean [SD] number of PSA tests per year: apalutamide, 4.1 [3.2]; enzalutamide, 3.8 [3.4]) (median number of PSA tests per year: apalutamide, 3.8; enzalutamide, 3.6).

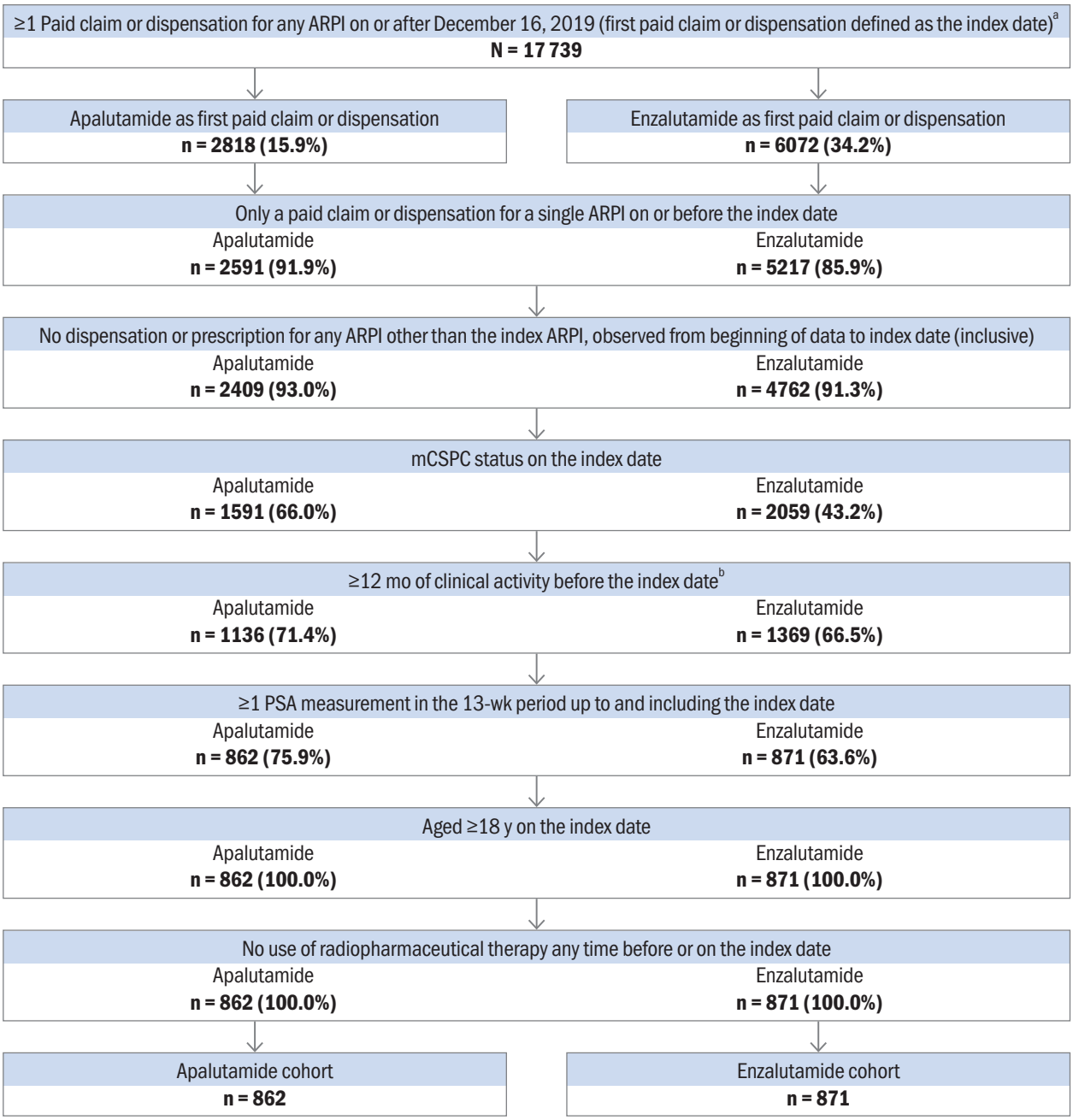

Figure 2. Patient Identification Flowchart

Abbreviations: ARPI, androgen receptor pathway inhibitor; mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen.

[a] The US Food and Drug Administration approved enzalutamide as treatment for mCSPC on December 16, 2019.

[b] Clinical activity was defined as the period from the first to the last record in the Precision Point Specialty Analytics electronic health record database. Patients with no observation period after the index date were excluded.

Table 1. Baseline Characteristics

	Nonweighted population			Inverse probability of treatment weighting population[a]		
	Apalutamide (n = 862)	Enzalutamide (n = 871)	Standardized difference	Apalutamide (n = 862)	Enzalutamide (n = 871)	Standardized difference
Age, mean (SD) [median], y	73.9 (8.4) [74.0]	74.1 (8.8) [74.0]	2.3	74.1 (8.4) [74.0]	74.1 (8.9) [74.0]	0.2
Age group, No. (%)						
≤60 y	51 (5.9)	53 (6.1)	0.7	50 (5.8)	56 (6.4)	2.7
61-70 y	245 (28.4)	248 (28.5)	0.1	240 (27.9)	247 (28.3)	1.0
71-80 y	377 (43.7)	360 (41.3)	4.9	380 (44.1)	359 (41.2)	5.8
≥81 y	189 (21.9)	210 (24.1)	5.2	192 (22.3)	210 (24.1)	4.3
Race, No. (%)						
Asian	4 (0.5)	7 (0.8)	4.3	4 (0.5)	7 (0.8)	4.1
Black	156 (18.1)	179 (20.6)	6.2	160 (18.5)	164 (18.8)	0.8
White	628 (72.9)	574 (65.9)	15.1	606 (70.4)	604 (69.4)	2.2
Other/unknown	74 (8.6)	111 (12.7)	13.5	92 (10.6)	96 (11.0)	1.2
Geographic region,[b] No. (%)						
South	473 (54.9)	405 (46.5)	16.8	442 (51.3)	438 (50.3)	2.1
Midwest	202 (23.4)	269 (30.9)	16.8	226 (26.2)	237 (27.2)	2.2
Northeast	102 (11.8)	113 (13.0)	3.5	109 (12.7)	108 (12.4)	1.0
West	85 (9.9)	79 (9.1)	2.7	84 (9.8)	84 (9.7)	0.3
Unknown	0 (0.0)	5 (0.6)	10.8	0 (0.0)	4 (0.5)	10.1
Payer type, No. (%)						
Medicare	629 (73.0)	644 (73.9)	2.2	633 (73.5)	641 (73.6)	0.2
Commercial	154 (17.9)	160 (18.4)	1.3	156 (18.1)	158 (18.2)	0.3
Medicaid	25 (2.9)	16 (1.8)	7.0	20 (2.3)	19 (2.2)	1.1
Unknown	54 (6.3)	51 (5.9)	1.7	53 (6.1)	53 (6.1)	0.1
Year of treatment initiation (index date), No. (%)						
2019-2020	247 (28.7)	296 (34.0)	11.5	263 (30.5)	272 (31.2)	1.5
2021	324 (37.6)	353 (40.5)	6.0	338 (39.2)	344 (39.5)	0.5
2022	291 (33.8)	222 (25.5)	18.2	260 (30.2)	255 (29.3)	2.0
Time between metastasis and treatment initiation, mean (SD) [median], mo	9.6 (18.1) [2.4]	12.0 (18.6) [3.4]	13.2	10.6 (20.0) [2.4]	11.0 (17.3) [3.2]	2.0
Time between PCa diagnosis and treatment initiation, mean (SD) [median], mo	52.1 (49.2) [44.0]	47.1 (45.5) [36.0]	10.7	49.0 (47.4) [41.0]	48.5 (46.4) [37.5]	1.2
Metastasis type,[c] No. (%)						
Bone	577 (66.9)	605 (69.5)	5.4	590 (68.4)	598 (68.6)	0.4
Nodal	442 (51.3)	391 (44.9)	12.8	419 (48.6)	417 (47.9)	1.4
Visceral	152 (17.6)	177 (20.3)	6.9	156 (18.1)	161 (18.5)	1.2

Continued

Table 1. Baseline Characteristics, *Continued*

	Nonweighted population			Inverse probability of treatment weighting population[a]		
	Apalutamide (n = 862)	Enzalutamide (n = 871)	Standardized difference	Apalutamide (n = 862)	Enzalutamide (n = 871)	Standardized difference
De novo PCa,[d] No. (%)	332 (38.5)	383 (44.0)	11.1	356 (41.3)	365 (42.0)	1.3
Concurrent use of ADT with index ARPI,[e] No. (%)	812 (94.2)	791 (90.8)	12.9	808 (93.8)	799 (91.7)	7.9
Prior use of ADT,[f] No. (%)	760 (88.2)	738 (84.7)	10.1	748 (86.8)	753 (86.5)	1.0
Cumulative duration of prior ADT use, mean (SD) [median], mo	9.5 (13.0) [4.5]	10.7 (12.9) [6.0]	9.0	9.8 (13.6) [4.5]	10.4 (12.6) [6.0]	4.2
Prior use of first-generation androgen receptor inhibitor,[g] No. (%)	119 (13.8)	199 (22.8)	23.5	151 (17.5)	161 (18.5)	2.6
Prior use of chemotherapy,[h] No. (%)	13 (1.5)	18 (2.1)	4.2	15 (1.7)	16 (1.8)	0.8
Baseline PSA level,[i] mean (SD) [median], ng/mL	20.9 (50.9) [3.3]	25.9 (59.9) [3.3]	9.0	22.7 (55.2) [3.3]	23.3 (55.8) [3.0]	1.1
Baseline testosterone tests,[j] No. (%)	543 (63.0)	481 (55.2)	15.9	513 (59.5)	511 (58.6)	1.8
Testosterone <50 ng/dL,[k] No. (%)	359 (66.1)	367 (76.3)	22.6	713 (82.7)	728 (83.6)	2.5
Baseline Gleason score,[l] No. (%)						
≤6	71 (8.2)	61 (7.0)	4.7	68 (7.9)	63 (7.2)	2.7
7	228 (26.5)	165 (18.9)	18.0	208 (24.2)	184 (21.1)	7.4
8	111 (12.9)	132 (15.2)	6.6	112 (13.0)	135 (15.5)	7.2
9	174 (20.2)	155 (17.8)	6.1	166 (19.2)	163 (18.8)	1.2
10	21 (2.4)	29 (3.3)	5.3	25 (2.9)	25 (2.8)	0.6
Unknown	257 (29.8)	329 (37.8)	16.9	282 (32.8)	302 (34.6)	4.0

Abbreviations: ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; mCSPC, metastatic castration-sensitive prostate cancer; PCa, prostate cancer; PSA, prostate-specific antigen.

SI conversion factor: To convert ng/mL to µg/L, multiply by 1. To convert ng/dL to nmol/L, multiply by 0.0347.

[a] Of note, the number of patients reported in this weighted population represents the sum of weights for the corresponding nonweighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated based on rounded numbers.

[b] Geographic region was defined by US Census areas.

[c] Types of metastases were defined at any time up to and including the index date. Types of metastases were not mutually exclusive.

[d] De novo PCa was defined as ≤180 days between first observed PCa diagnosis and date of metastasis.

[e] Concurrent ADT use was defined as having claims data for any ADT medication from 180 days before to 180 days after the index date.

[f] Prior use of ADT medication was defined as any ADT administration at any time before (and excluding) the index date.

[g] Prior use of first-generation androgen receptor inhibitor was defined as any prescription for bicalutamide, nilutamide, or flutamide at any time before (and excluding) the index date.

[h] Prior chemotherapy use was defined as any chemotherapy administration at any time before (and excluding) the index date.

[i] Baseline PSA was evaluated as the most recent PSA value from 13 weeks before index, up to and including the index date.

[j] Testosterone testing was evaluated during the 12-month baseline period and included the index date, with the most recent value reported.

[k] Patients' mCSPC status was evaluated using their health records, and baseline testosterone may not be synchronous with mCSPC designation.

[l] Gleason score was evaluated during the 12-month baseline period and included the index date, with the most recent value reported.

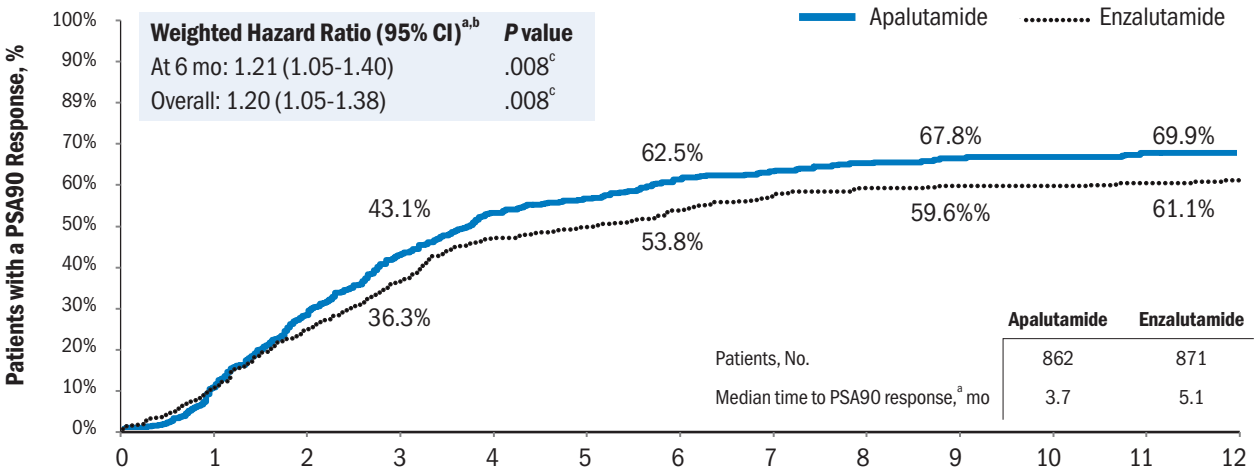

Figure 3. Comparison of Time to PSA90 Response Among Patients With mCSPC

Abbreviations: mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen; PSA90, reduction in PSA value from baseline of at least 90%.

[a] A PSA90 response was defined as the first decline for a follow-up PSA value of 90% or more relative to the most recent baseline PSA value observed within 13 weeks up to and including the index date.

[b] A hazard ratio >1 indicates that the apalutamide cohort had a higher rate of PSA90 response compared with the enzalutamide cohort.

[c] $P < .05$ was considered statistically significant.

Table 2. Follow-Up PSA Testing

	Nonweighted population		Inverse probability of treatment weighting population[a]	
	Apalutamide (n = 862)	Enzalutamide (n = 871)	Apalutamide (n = 862)	Enzalutamide (n = 871)
Patients with ≥1 PSA test, No. (%)	720 (83.5)	677 (77.7)	717 (83.2)	683 (78.4)
Within 3 mo of observation	637 (73.9)	564 (64.8)	632 (73.3)	575 (66.0)
Within 6 mo of observation	708 (82.1)	668 (76.7)	702 (81.4)	675 (77.5)
No. of follow-up PSA tests/y, mean (SD) [median]	4.2 (3.3) [3.8]	3.7 (3.3) [3.5]	4.1 (3.2) [3.8]	3.8 (3.4) [3.6]
Patients with PSA test on average every 3 mo, No. (%)	406 (47.1)	352 (40.4)	394 (45.7)	366 (42.1)
Patients with PSA test on average every 6 mo, No. (%)	677 (78.5)	629 (72.2)	670 (77.7)	638 (73.3)

Abbreviation: PSA, prostate-specific antigen.

[a] Of note, the number of patients reported in this weighted population represents the sum of weights for the corresponding nonweighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated based on rounded numbers.

Discussion

The current study found that a higher proportion of patients with mCSPC initiating apalutamide vs enzalutamide had a PSA90 response by 6 months (62.5% vs 53.8%) in a representative patient population with mCSPC. The study employed causal analyses using the PPS Analytics EHR database and supplemented this information with claims data from the Komodo Health research database to identify a large number of patients with mCSPC initiating apalutamide or enzalutamide. In a prior

causal analysis using clinical EHR data from the PPS Analytics database alone, 69.3% of patients with mCSPC who initiated apalutamide achieved a PSA90 response at 6 months compared with 55.6% of patients who initiated enzalutamide.[17] The findings from the current study build on and support a growing body of evidence that apalutamide therapy has a greater likelihood of producing a PSA90 response by 6 months than other ARPIs.[17,22]

Results from the current study, which found that 62.5% of apalutamide patients achieved a PSA90 response by 6 months, were also aligned with those reported among apalutamide patients in the TITAN post hoc analysis, in which 68% of patients achieved a response by 6 months.[10] Although real-world evidence describing PSA90 response in patients initiating apalutamide is limited, a recent study prospectively enrolling patients with mCSPC or with nonmetastatic castration-resistant PCa in Barcelona, Spain, found that the median time to PSA response end points (including PSA50, PSA90, and PSA ≤0.2 µg/L [≤0.2 ng/mL]) was less than 3 months for all patients.[23] A clinical study of 212 Black patients and patients of other races with mCSPC who initiated apalutamide in the United States similarly reported that 70% of patients achieved PSA90 response by 6 months (Black patients, 77%; patients of other races, 70%), with a median time to PSA90 response of 2.7 months.[16] These findings are comparable to the current study's median time to PSA90 response of 3.7 months for patients with mCSPC who initiated apalutamide.

A sizeable and growing body of evidence, including data from a post hoc analysis of phase 3 ARPI clinical trials, indicates that an early PSA response in patients with advanced PCa may serve as an early indicator of treatment efficacy because it is strongly associated with improvements in PFS and OS.[10-14,24,25] Management and treatment guidelines for patients with mCSPC have also recommended regular monitoring of PSA levels (eg, baseline before treatment and every 3-6 months), given its usefulness in evaluating patients with metastatic disease.[26,27] Real-world evidence has also demonstrated the clinical importance of PSA response regarding disease progression in this setting, with patients achieving suboptimal PSA responses after starting advanced PCa treatments having poorer clinical outcomes.[15,28,29] This evidence provides a clinical context for the current research findings, which report an increased proportion and faster time to PSA90 response in patients with mCSPC who initiate apalutamide vs enzalutamide.

LIMITATIONS

The findings from the current study are subject to several limitations. First, linked administrative claims data were available only for patients who were seen at community-based urology practices and therefore may not be representative of the entire US patient population with mCSPC, which may limit the generalizability of the study. Baseline characteristics of the study population were nevertheless representative of a patient population with mCSPC, with a high proportion of Black patients observed.[3] Second, despite the use of a comprehensive linking and tokenization process between PPS Analytics and Komodo Health, incorrect patient linking between the 2 data sources may have occurred. To mitigate this error, however, we excluded patients with inconsistent birth and death vital records between the 2 data sources in the rare instances that inconsistency occurred. Third, miscoding or omissions in the EHR or administrative claims data may have introduced selection and information biases, despite efforts to match the study populations. Efforts were made to exclude patients with castration-resistant disease, but it is possible that the linked data lacked the complete information required to identify these patients. Fourth, the study may also be subject to surveillance bias. As noted, although the overall PSA testing frequency was similar between the weighted cohorts, more apalutamide patients had a PSA assessment in the first 6 months of treatment, which may have increased the likelihood of observing an early PSA90 response in this cohort. Fifth, despite access to several important baseline and clinical characteristics, which were balanced through inverse probability of treatment weighting, residual and unmeasured confounding may have remained. Though a robust methodology was applied to this analysis, this study did not address whether

these findings represent a clinically meaningful difference or translate to differences in longer-term outcomes (eg, OS, time to disease progression).

Conclusions

This causal analysis of real-world patients with mCSPC is the second such study to demonstrate that a statistically significant higher proportion of patients achieved an early, deep PSA response when treated with apalutamide vs enzalutamide. In light of the association between early, deep PSA response and OS, early PSA response may be an important factor to consider in early treatment selection. These findings confirm results from a previous study that reported higher rates of PSA90 response for apalutamide initiators than for enzalutamide initiators who were treated through community-based urology practices with in-office dispensing.[17]

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