REVIEWS IN UROLOGY

A Comparison of Prostate-Specific Antigen Response in Patients With Metastatic Castration-Sensitive Prostate Cancer Initiated on Apalutamide vs Abiraterone Acetate in Linked Clinical and Claims Databases

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

Abstract

Background: This real-world study compared prostate-specific antigen (PSA) decline of at least 90% from baseline (PSA90 response) among patients with metastatic castration-sensitive prostate cancer (mCSPC) initiated on apalutamide or abiraterone acetate.

Methods: Clinical data from community urology practices in Precision Point Specialty Analytics were linked with administrative claims from the Komodo Research Database. Patients with mCSPC and at least 12 months of preindex clinical activity were included in the apalutamide or abiraterone acetate cohort based on their first dispensation or paid claim on or after September 17, 2019 (ie, the index date). Patients were followed to the earliest of treatment discontinuation or switch, radiopharmaceutical use, end of insurance or clinical activity, or end of data availability (September 30, 2022). Inverse probability of treatment weighting was used to address potential preindex confounding. The PSA90 response (at least 90% PSA decline relative to the most recent value within 13 weeks up to and including the index date) was compared between cohorts using weighted Kaplan-Meier analysis, and time to PSA90 response was compared using a weighted Cox proportional hazards model.

Results: A total of 920 patients treated with apalutamide and 637 treated with abiraterone acetate were included. By 6 months, patients in the apalutamide cohort were 68% more likely to achieve a PSA90 response than patients in the abiraterone acetate cohort ($P < .001$). Median time to PSA90 response was 3.6 months for apalutamide and 10.3 months for abiraterone acetate.

Conclusion: Results from this causal analysis of real-world patients with mCSPC confirmed that patients treated with apalutamide had statistically significantly higher rates of PSA90 response compared with abiraterone acetate. Given the association between early and deep PSA response with overall survival, apalutamide may be an important treatment option to improve prognosis for patients with mCSPC.

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Prostate cancer (PCa) is the second-most common type of cancer affecting men in the United States, with an estimated 299 000 new cases expected in 2024.[1,2] Metastases to bone and other sites, including the lymph nodes, lungs, and liver, are a leading driver of PCa-related mortality.[3] Although androgen-deprivation therapy (ADT), which aims to lower serum testosterone levels, was once the standard of care for metastatic PCa,[4] the majority of patients who have an initial clinical response to ADT (ie, metastatic castration-sensitive PCa [mCSPC]) experience an increase in prostate-specific antigen (PSA) levels despite castration-like testosterone levels, leading to metastatic castration-resistant PCa.[5,6]

Current treatment guidelines for mCSPC recommend that androgen receptor pathway inhibitors (ARPIs) be used in conjunction with ADT based on clinical trial evidence demonstrating the superior efficacy of the combination in delaying disease progression and prolonging overall survival (OS) in this population.[7-10] Apalutamide, a next-generation ARPI approved by the US Food and Drug Administration for the treatment of mCSPC on September 17, 2019,[11] was shown to increase OS when combined with ADT relative to ADT alone in the phase 3, randomized, double-blind TITAN trial.[12] Similarly, patients treated with abiraterone acetate, another next-generation ARPI approved by the Food and Drug Administration for high-risk mCSPC on February 7, 2018,[13] in combination with ADT had greater OS relative to patients treated with ADT alone in the phase 3 randomized, double-blind LATITUDE trial.[14]

Despite the increasing adoption of oral therapies for patients with mCSPC in recent years, no head-to-head randomized trials have been conducted to compare clinical outcomes among patients using apalutamide or abiraterone acetate. In a recent analysis of real-world data based on electronic health records (EHRs) from a consortium of community-based urology practices in the United States, apalutamide use was associated with a statistically significantly greater proportion of patients achieving at least a 90% reduction from the most recent pretreatment PSA level (PSA90 response) compared with abiraterone acetate (64% vs 42% by 6 months after treatment initiation).[15] Given the importance of PSA levels, particularly the attainment of early (ie, by 6 months from treatment initiation) and deep PSA90 response as a biomarker of treatment response and long-term prognosis,[16-18] the goal of this study was to replicate the previous analysis comparing real-world PSA90 response in a larger cohort of ARPI-naive patients with mCSPC who newly initiated apalutamide or abiraterone acetate by verifying medication receipt, either through administrative insurance claims or in-office dispensing data from community-based urology practices in the United States.

SUMMARY OF MAIN POINTS

- This real-world study compared deep PSA response (ie, PSA90) among patients with mCSPC initiating the ARPIs apalutamide and abiraterone acetate.
- By 6 months after apalutamide and abiraterone acetate initiation, 63.9% and 41.7% of the patients, respectively, achieved a PSA90 response.
- Patients with mCSPC treated with apalutamide were 68% more likely to attain a PSA90 response by 6 months after treatment initiation compared with patients treated with abiraterone acetate.
- Patients treated with apalutamide also attained an earlier PSA90 response relative to patients treated with abiraterone acetate by approximately 7 months.
- These results confirm previous findings in a larger sample of patients and warrant clinical consideration given the importance of rapid and deep PSA response attainment on the prognosis of patients with mCSPC.

ABBREVIATIONS

ADT	androgen deprivation therapy
ARPI	androgen receptor pathway inhibitor
EHR	electronic health records
HR	hazard ratio
IPTW	inverse probability of treatment weighting
mCSPC	metastatic castration-sensitive prostate cancer
OS	overall survival
PCa	prostate cancer
PPS	Precision Point Specialty
PSA	prostate-specific antigen
PSA90	prostate-specific antigen decline ≥90%

Methods

DATA SOURCE

Clinical data from EHRs collected as part of routine clinical care at multiple community-based urology practices in the United States were obtained from Precision Point Specialty (PPS) Analytics and used for this study. The practices included in the PPS database treat a large number of patients with mCSPC and are widely representative of the patient distribution in the United States. The EHR data in the PPS database are robust and capture a large amount of valid PSA measurements and other laboratory and vital data that are not available from traditional administrative claims data sources. In addition to patient demographics, the PPS database includes information about dispensations for next-generation ARPIs (ie, fill dates, amount dispensed, dosage), medication and procedure information to identify ADT use, first-generation antiandrogens, other PCa-related medications (ie, chemotherapies, poly ADP-ribose polymerase inhibitors, immunotherapies, estrogens, radiopharmaceuticals, and bone antiresorptive therapy), procedure information to identify imaging tests (ie, bone scan, computed tomography scan, and next-generation imaging), and *International Classification of Diseases, Ninth Revision, Clinical Modification/International Classification of Diseases, Tenth Revision, Clinical Modification* diagnoses and dates of diagnoses.

To supplement PPS information about demographic and clinical variables and to verify medications received that were captured outside the urology setting, insurance claims from the Komodo Research Database were linked to the PPS database. Komodo is a deidentified database sourced from a variety of payers and health care organizations. The Komodo database contains more than 320 million patients from the United States across Medicaid, commercial, and Medicare insurers. This study included data from both the open and closed claims portions of the Komodo database, which consist of information on diagnoses and procedures received in inpatient and outpatient settings, along with prescription fills and billing and reimbursement information. All data were deidentified and comply with the requirements of the US Health Insurance Portability and Accountability Act.

Data from both sources spanned from September 17, 2018 (ie, 12 months preceding the approval date for apalutamide), to September 30, 2022.

STUDY DESIGN AND SAMPLE SELECTION

A retrospective longitudinal cohort design was used for this causal analysis of patients with mCSPC initiated on apalutamide or abiraterone acetate. The earliest dispensation or paid pharmacy claim for apalutamide or abiraterone acetate on or after September 17, 2019 (ie, the approval date of apalutamide for mCSPC), defined the ARPI initiated as the index treatment and the date of initiation as the index date (Figure 1). Patients were assigned to mutually exclusive cohorts based on the treatment received at the index date. The baseline period was defined as the 12 months before the index date. The observation period spanned from the index date to the earliest of index treatment discontinuation (with a 90-day treatment gap used to define treatment discontinuation), initiation of a nonindex ARPI (ie, apalutamide, abiraterone acetate, darolutamide, or enzalutamide) or a radiopharmaceutical agent, end of insurance or clinical activity (including death), or end of data availability (September 30, 2022).

PATIENT SELECTION CRITERIA

Adult patients (at least 18 years old) were required to have metastatic disease on or before the index date. Metastases were identified through derived variables from the PPS database or diagnosis codes for metastasis identified in the PPS and Komodo databases. In addition, patients were required to have at least 12 months of clinical activity (defined as the period from the first to last record in PPS EHR database) before the index date and at least 1 PSA measurement in the 13-week period up to and including the index date. Patients who initiated apalutamide or abiraterone acetate before September 17, 2019; patients with a paid pharmacy claim or a dispensation for a nonindex ARPI before the index date; patients

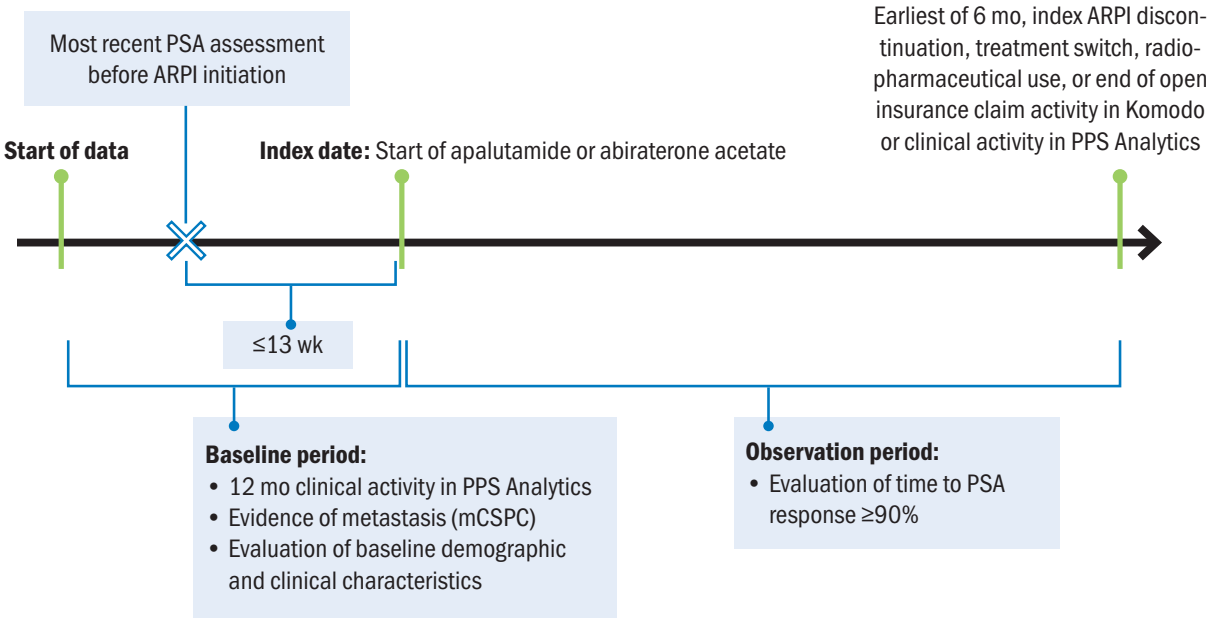

Figure 1. Study Design
Abbreviations: ARPI, androgen receptor pathway inhibitor; mCSPC, metastatic castration-sensitive prostate cancer; PPS, Precision Point Specialty; PSA, prostate-specific antigen.

with a prescription for a nonindex ARPI, observed from the beginning of PPS data to the index date, inclusively; and patients with evidence of castration resistance or radiopharmaceutical use on or before the index date were excluded. Patients who had no measurable observation period after the index date were also excluded.

The concurrent use of ADT was not required for patients to be included in either the apalutamide or abiraterone acetate cohort, and the concurrent use of prednisone was not required for patients to be included in the abiraterone acetate cohort. These proportions, however, were assessed among the patient population.

STUDY MEASURES

The primary outcome was the proportion of patients who achieved PSA90 response by 6 months after index treatment initiation. As an exploratory outcome, PSA90 was assessed during the entire available observation period. The PSA90 response was defined as the first follow-up PSA measurement, obtained from PPS, with at least 90% relative decline from the most recent baseline PSA value observed within 13 weeks up to and including the index date (Figure 1).

The following patient demographics and clinical characteristics were evaluated during the 12-month baseline period: age, race, geographic region, payer type, index year, time between metastasis and the index date, time between the first PCa diagnosis and the index date, de novo PCa (defined as ≤180 days between first PCa diagnosis and the date of metastasis), prior ADT use, first-generation antiandrogen use (ie, bicalutamide, nilutamide, or flutamide), chemotherapy use, metastasis location (bone, nodal, visceral; not mutually exclusive), the most recent PSA level, the most recent testosterone level, and the most recent Gleason score.

The PSA testing patterns were descriptively reported during the observation period, including the proportion of patients with at least 1 PSA test within 3, 6, 9, and 12 months of the index date and the number of follow-up PSA tests per year.

STATISTICAL ANALYSIS

Based on methods appropriate for causal inference, the null hypothesis of this study was that the proportion of patients achieving a PSA90 response by 6 months after index was the same between patients who initiated treatment with apalutamide and patients who initiated abiraterone acetate. The alternative hypothesis was that the proportion of patients achieving PSA90 response differed between those initiating apalutamide and those initiating abiraterone acetate. Inverse probability of treatment weighting (IPTW) was used to adjust for differences in observed baseline characteristics between the apalutamide and abiraterone acetate cohorts based on a propensity score.[19] The propensity score was calculated using probability estimates from a logistic regression model whereby the index treatment was defined as the dependent variable, and the following preindex characteristics were defined as independent variables: age (categorical), race, geographic region, payer type, index year, time between metastasis and the index date (continuous), time between the first PCa diagnosis and the index date (continuous), de novo PCa, prior ADT use, first-generation antiandrogen use, chemotherapy use, metastasis location, the most recent PSA level (continuous), the most recent preindex testosterone level (<1.735 nmol/L [<50 ng/dL] or ≥1.735 nmol/L [≥50 ng/dL]; patients without a testosterone measurement were included in the <1.735 nmol/L [<50 ng/dL] category), and the most recent Gleason score (≤6, 7, 8, 9, 10, or unknown).

Each patient was attributed an IPTW that was defined as 1/propensity score for the apalutamide cohort and 1/(1 – propensity score) for the abiraterone acetate cohort. The normalized IPTWs were truncated at the 95th percentiles to prevent bias from patients with outlier weights. No patients were excluded from the study because of the truncation of outlier weights. The balance of baseline characteristics between the 2 treatment cohorts after IPTW was confirmed by standardized differences less than 10%.[20]

Weighted Kaplan-Meier analyses were used to assess the proportion of patients in the apalutamide and abiraterone acetate cohorts achieving PSA90 response by 6 months after the index date using Kaplan-Meier rates and 95% CIs. Weighted Cox proportional hazards models were used to evaluate the causal relationship between the index treatment and the likelihood of achieving PSA90 response by 6 months (primary objective) and over the duration of the observation period. Results were reported as hazard ratios (HRs) and 95% CIs.

Results

The study sample consisted of 920 patients with mCSPC who initiated apalutamide and 637 who initiated abiraterone acetate (Figure 2).

BASELINE CHARACTERISTICS

After the IPTW was applied, the patients' baseline characteristics were generally well balanced between the weighted cohorts, with standardized differences less than 10% (Table 1). The mean (SD) age was 73.5 (8.7) years [median, 74.0 years] in the weighted apalutamide cohort and 73.2 (8.9) years [median, 73.0 years] in the weighted abiraterone acetate cohort. The proportion of Black patients was 16.3% in the apalutamide cohort and 15.9% in the abiraterone acetate cohort. The most recent mean (SD) baseline PSA level was 23.7 (58.1) µg/L [23.7 (58.1) ng/mL; median, 3.4 µg/L {3.4 ng/mL}] in the apalutamide cohort and 25.0 (57.2) µg/L [25.0 (57.2) ng/mL; median, 3.4 µg/L {3.4 ng/mL}] in the abiraterone acetate cohort. The mean (SD) time between metastasis diagnosis and the index treatment initiation was 9.0 (17.4) months [median, 2.3 months] in the apalutamide cohort and 8.8 (15.2) months [median, 2.3 months] in the abiraterone acetate cohort.

PSA OUTCOMES

By 6 months after the index date, 63.9% of the patients in the apalutamide cohort and 41.7% of patients in the abiraterone acetate cohort achieved a PSA90 response (Figure 3). Patients who were treated with apalutamide were 68% more likely to achieve a PSA90 response than patients who were treated with abiraterone acetate (HR, 1.68

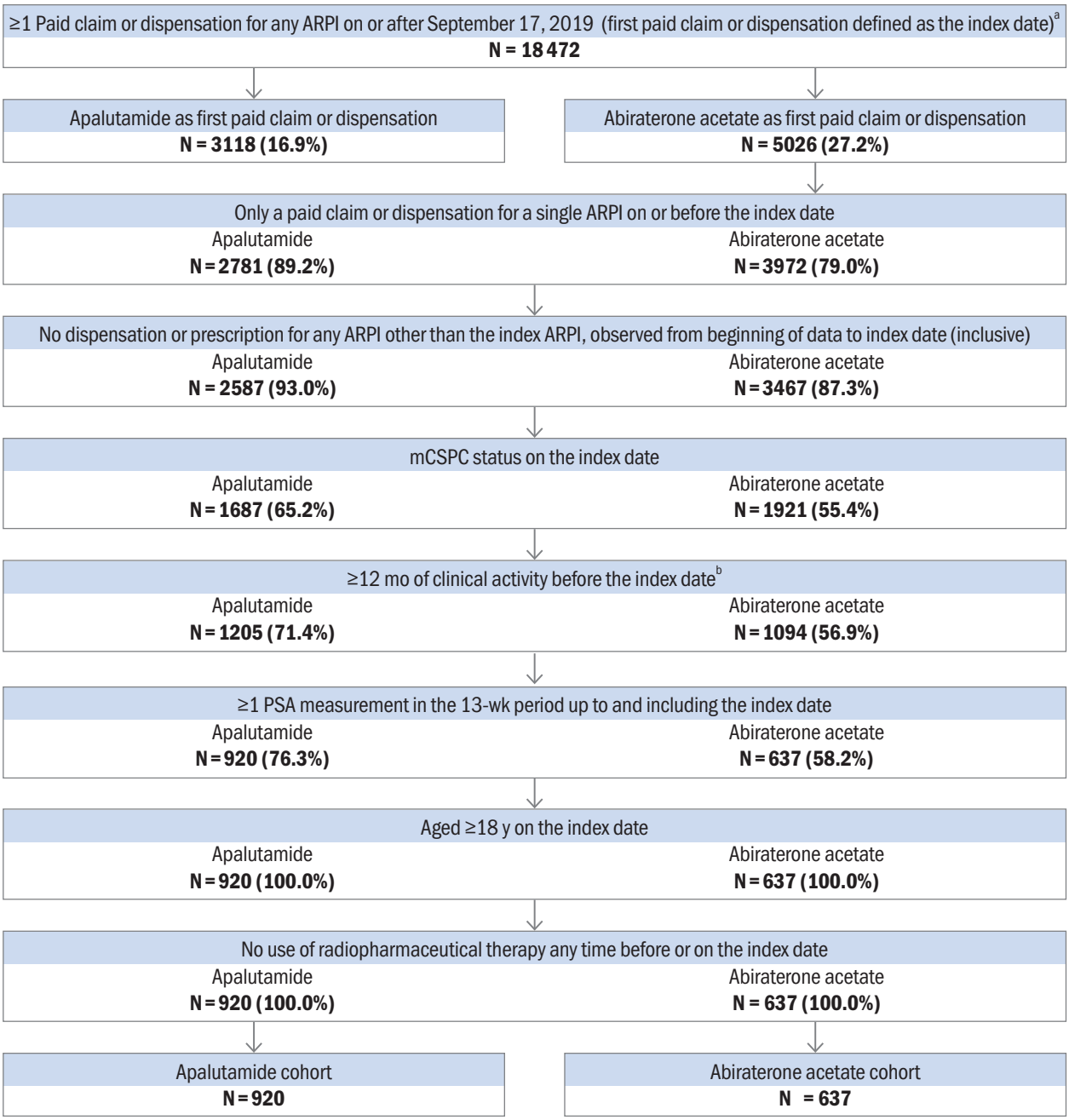

Figure 2. Patient Identification Flowchart

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

[a] The US Food and Drug Administration approved apalutamide as treatment for mCSPC on September 17, 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[a]

	Nonweighted population			IPTW population		
	Apalutamide (n = 920)	Abiraterone acetate (n = 637)	Standardized difference	Apalutamide (n = 920)	Abiraterone acetate (n = 637)	Standardized difference
Age, mean (SD) [median], y	73.9 (8.4) [74.0]	72.4 (9.3) [72.0]	17.2	73.5 (8.7) [74.0]	73.2 (8.9) [73.0]	3.8
Age group, No. (%)						
≤60 y	53 (5.8)	60 (9.4)	13.9	62 (6.7)	46 (7.2)	1.7
61-70 y	265 (28.8)	223 (35.0)	13.3	285 (31.0)	201 (31.5)	1.2
71-80 y	404 (43.9)	216 (33.9)	20.6	371 (40.3)	249 (39.1)	2.4
≥81 y	198 (21.5)	138 (21.7)	0.4	202 (22.0)	141 (22.2)	0.5
Race, No. (%)						
Asian	4 (0.4)	9 (1.4)	10.2	4 (0.4)	8 (1.3)	9.0
Black	164 (17.8)	84 (13.2)	12.8	150 (16.3)	101 (15.9)	1.3
White	668 (72.6)	480 (75.4)	6.3	679 (73.8)	468 (73.4)	0.9
Other/unknown	84 (9.1)	64 (10.0)	3.1	87 (9.4)	60 (9.5)	0.2
Geographic region,[b] No. (%)						
South	503 (54.7)	246 (38.6)	32.6	453 (49.2)	306 (48.0)	2.4
Midwest	218 (23.7)	179 (28.1)	10.1	233 (25.3)	161 (25.3)	0.1
Northeast	108 (11.7)	124 (19.5)	21.4	132 (14.3)	96 (15.0)	2.0
West	91 (9.9)	87 (13.7)	11.7	103 (11.2)	73 (11.5)	1.1
Unknown	0 (0.0)	1 (0.2)	5.6	0 (0.0)	1 (0.1)	4.5
Payer type, No. (%)						
Medicare	673 (73.2)	413 (64.8)	18.1	650 (70.6)	445 (69.9)	1.6
Commercial	166 (18.0)	163 (25.6)	18.4	188 (20.5)	136 (21.3)	2.0
Medicaid	25 (2.7)	22 (3.5)	4.3	27 (3.0)	19 (3.0)	0.4
Unknown	56 (6.1)	39 (6.1)	0.2	55 (6.0)	37 (5.8)	0.8
Year of treatment initiation (index date), No. (%)						
2019	61 (6.6)	47 (7.4)	2.9	63 (6.8)	43 (6.8)	0.2
2020	244 (26.5)	181 (28.4)	4.2	248 (27.0)	172 (27.0)	0.1
2021	324 (35.2)	202 (31.7)	7.4	313 (34.1)	215 (33.8)	0.5
2022	291 (31.6)	207 (32.5)	1.9	296 (32.2)	206 (32.4)	0.5

Continued

Table 1. Baseline Characteristics[a], *Continued*

	Nonweighted population			IPTW population		
	Apalutamide (n = 920)	Abiraterone acetate (n = 637)	Standardized difference	Apalutamide (n = 920)	Abiraterone acetate (n = 637)	Standardized difference
Time between metastasis and treatment initiation, mean (SD) [median], mo	9.3 (17.7) [2.4]	8.4 (14.8) [2.3]	5.9	9.0 (17.4) [2.3]	8.8 (15.2) [2.3]	1.6
Time between PCa diagnosis and treatment initiation, mean (SD) [median], mo	51.6 (49.0) [42.8]	40.1 (46.7) [18.0]	24.1	47.6 (48.2) [34.6]	46.7 (49.6) [31.1]	1.9
Metastasis type,[c] No. (%)						
Bone	618 (67.2)	405 (63.6)	7.6	607 (65.9)	418 (65.6)	0.7
Nodal	469 (51.0)	329 (51.6)	1.3	471 (51.2)	327 (51.3)	0.3
Visceral	163 (17.7)	120 (18.8)	2.9	165 (17.9)	112 (17.6)	0.8
De novo PCa,[d] No. (%)	356 (38.7)	324 (50.9)	24.7	396 (43.1)	283 (44.5)	2.8
Concurrent use of ADT with index ARPI,[e] No. (%)	868 (94.3)	565 (88.7)	20.4	863 (93.8)	575 (90.3)	12.9
Prior use of ADT,[f] No. (%)	815 (88.6)	529 (83.0)	15.9	800 (86.9)	549 (86.2)	2.2
Cumulative duration of prior ADT use, mean (SD) [median], mo	9.4 (12.8) [4.4]	8.7 (12.8) [3.7]	5.4	9.0 (12.4) [4.2]	9.4 (13.8) [4.2]	3.4
Prior use of first-generation androgen receptor inhibitor,[g] No. (%)	132 (14.3)	150 (23.5)	23.6	159 (17.3)	117 (18.3)	2.7
Prior use of chemotherapy,[h] No. (%)	13 (1.4)	17 (2.7)	8.9	17 (1.8)	13 (2.1)	1.9
Baseline PSA level,[i] mean (SD) [median], ng/mL	21.1 (52.8) [3.3]	28.5 (62.3) [4.0]	12.8	23.7 (58.1) [3.4]	25.0 (57.2) [3.4]	2.3
Baseline testosterone tests,[j] No. (%)	572 (62.2)	374 (58.7)	7.1	556 (60.4)	393 (61.7)	2.7
Testosterone <50 ng/dL[k]	383 (67.0)	259 (69.3)	4.9	741 (80.6)	517 (81.2)	1.7
Baseline Gleason score,[l] No. (%)						
≤6	35 (3.8)	17 (2.7)	6.4	32 (3.4)	21 (3.3)	0.6
7	185 (20.1)	84 (13.2)	18.7	161 (17.5)	105 (16.5)	2.8
8	118 (12.8)	81 (12.7)	0.3	118 (12.8)	83 (13.0)	0.5
9	182 (19.8)	146 (22.9)	7.7	192 (20.8)	135 (21.2)	0.8
10	17 (1.8)	25 (3.9)	12.4	22 (2.4)	17 (2.7)	1.9
Unknown	383 (41.6)	284 (44.6)	6.0	396 (43.0)	276 (43.4)	0.8

Abbreviations: ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; IPTW, inverse probability of treatment weighting; 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 rounding and may be slightly different than if they had been 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 d between first observed PCa diagnosis and date of metastasis.
[e] Concurrent ADT use was defined as having a claim for any ADT medication from 180 d before to 180 d 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 administration at any time before (and excluding) the index date.
[i] Baseline PSA was evaluated as the most recent value from 13 wk up to and including the index date.
[j] Testosterone testing was evaluated during the 12-mo baseline period and included the index date, with the most recent value reported.
[k] Patients' mCSPC status was evaluated via their records, and baseline testosterone may not be synchronous with mCSPC designation.
[l] Gleason score was evaluated during the 12-mo baseline period and included the index date, with the most recent value reported.

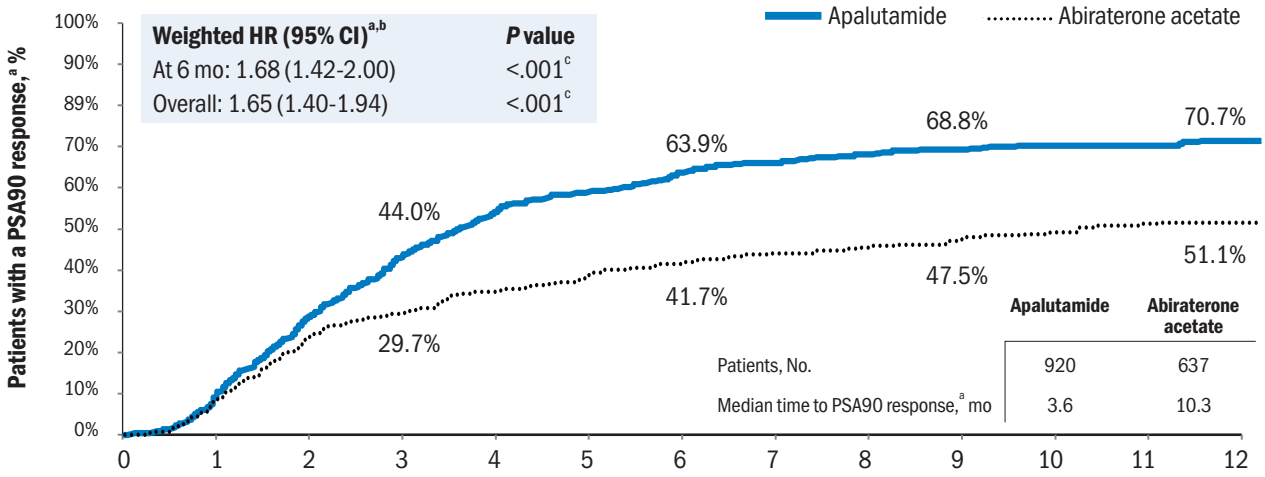

Figure 3. Comparison of Time to PSA90 Response Among Patients With mCSPC
Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen; PSA90, reduction in PSA value from baseline to at least 90%.
[a] PSA90 response was defined as the first decline for a follow-up PSA value of ≥90% relative to the most recent baseline PSA value observed within 13 wk up to and including the index date.
[b] HR >1 indicates that the apalutamide cohort had a higher rate of PSA90 response compared with the abiraterone acetate cohort.
[c] $P < .05$ was considered statistically significant.

[95% CI, 1.42-2.00]; $P < .001$) (Figure 3), a difference that remained consistent over the entire observation period (HR, 1.65 [95% CI, 1.40-1.94]; $P < .001$) (Figure 3). Patients treated with apalutamide also attained an earlier PSA90 response relative to patients treated with abiraterone acetate, with a median time to PSA90 response of 3.6 months for apalutamide and 10.3 months for abiraterone acetate.

PSA-RELATED TESTING

The mean (SD) duration of the observation period was 10.1 (8.8) months [median, 7.3 months] for the apalutamide cohort and 8.6 (8.0) months [median, 5.9 months] for the abiraterone acetate cohort. During the observation period, PSA testing occurred more frequently among patients in the weighted apalutamide cohort than in the weighted abiraterone acetate cohort, with 83.6% and 76.2% of patients, respectively, having at least 1 PSA measurement during the period (Table 2). By 6 months after the index date, 82.1% of the apalutamide cohort and 74.3% of the abiraterone acetate cohort had at least 1 follow-up PSA measurement. The mean (SD) number of PSA tests per year was 4.2 (3.3) [median, 3.8] in the apalutamide cohort and 5.2 (4.8) [median,

Table 2. Follow-Up PSA Testing[a]

	Nonweighted population		IPTW population	
	Apalutamide (n = 920)	Abiraterone acetate (n = 637)	Apalutamide (n = 920)	Abiraterone acetate (n = 637)
Patients with ≥1 PSA test, No. (%)	772 (83.9)	489 (76.8)	769 (83.6)	485 (76.2)
Within 3 mo of observation	681 (74.0)	434 (68.1)	679 (73.8)	430 (67.5)
Within 6 mo of observation	760 (82.6)	476 (74.7)	755 (82.1)	473 (74.3)
No. of follow-up PSA tests/y, mean (SD) [median]	4.2 (3.3) [3.8]	5.2 (4.8) [4.3]	4.2 (3.3) [3.8]	5.2 (4.8) [4.3]
Patients with PSA test on average every 3 mo, No. (%)	433 (47.1)	338 (53.1)	430 (46.7)	340 (53.4)
Patients with PSA test on average every 6 mo, No. (%)	727 (79.0)	446 (70.0)	721 (78.4)	445 (69.8)

Abbreviations: IPTW, inverse-probability of treatment weighting; 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 rounding and may be slightly different than if they had been calculated based on rounded numbers.

4.3] in the abiraterone acetate cohort.

Discussion

This real-world study identified patients with mCSPC in the United States using clinical data linked with administrative claims and showed that as early as 6 months after treatment initiation, patients treated with apalutamide were statistically significantly more likely to attain a deep PSA90 response than patients treated with abiraterone acetate. Furthermore, patients treated with apalutamide attained the PSA90 response nearly 7 months earlier relative to patients treated with abiraterone acetate.

These findings confirm results from a prior study using the PPS EHR database that showed that patients with mCSPC who were treated through community-based urology practices with in-office dispensing were more likely to attain a deep and rapid PSA90 response after initiating apalutamide compared with patients on abiraterone acetate.[15] Specifically, the study by Lowentritt et al[15] reported that in a sample of 364 patients who initiated apalutamide and 147 patients who initiated abiraterone acetate, patients who initiated apalutamide were 53% more likely to achieve the PSA90 response by 6 months after treatment initiation compared with abiraterone acetate. The study population was limited, however, to patients who had a confirmation of medication receipt documented from the in-office dispensing data, which restricted the sample given that some urology practice sites did not document medication receipt. By using clinical data from PPS Analytics linked with administrative claim data from the Komodo Research Database and including an additional year in the study period, the current study identified patients initiating the index treatments through filled prescriptions, which was not possible with the PPS EHR database alone, thus enhancing the sample to contain a larger cohort of patients with mCSPC for inclusion in the analyses (ie, 920 patients who initiated apalutamide and 637 patients who initiated abiraterone acetate). Considering the expanding landscape of treatments available for patients with PCa and the lack of head-to-head comparisons between them, these large comparative studies based on real-world data fill an important gap in knowledge that can help inform clinical decision-making.

The implications of these observations warrant important consideration in clinical practice given existing evidence on the association between the depth and speed of PSA response with survival-related end points among patients with mCSPC.[16-18] A recent post hoc analysis of the phase 3 TITAN study was conducted by Chowdhury et al[16] to evaluate the association between rapid and deep

PSA decline (defined as PSA90 response or undetectable PSA [ie, PSA <0.2 µg/L (<0.2 ng/mL)]) and clinical outcomes among patients with mCSPC who received apalutamide or placebo in combination with ADT. The results show that the higher rate and faster onset of a deep PSA decline in patients treated with apalutamide as early as 3 months after treatment initiation were associated with increased OS (HR, 0.29 [95% CI, 0.20-0.42]; *P* < .0001), radiographic progression-free survival (HR, 0.38 [95% CI, 0.24-0.59]; *P* < .0001), time to PSA progression (HR, 0.34 [95% CI, 0.23-0.52]; *P* < .0001), and time to metastatic castration-resistant PCa (HR, 0.39 [95% CI, 0.27-0.58]; *P* < .0001) compared with the lack of deep PSA response attainment.[16] Importantly, the improvement associated with such response across all outcomes was statistically significant by 3 months after the initiation of apalutamide, underscoring the value of achieving an early treatment response for patients with mCSPC.

Although the results of the current real-world study and the original analysis by Lowentritt et al[15] are not directly comparable to randomized clinical trials because of differences between the study samples with regard to patient experiences, clinical characteristics, and medical management, the proportion of patients attaining a PSA90 response by 12 months after the initiation of apalutamide in this real-world study (70.7%) was consistent with that observed in patients with mCSPC enrolled in the phase 3 TITAN trial (73.3%).[16] The proportion of patients who achieved a PSA90 response 12 months after abiraterone acetate initiation in the present work (51.1% by 12 months), however, was lower than that reported in the phase 3 LATITUDE trial (79.3% by the end of follow-up).[18] In addition, the median time to PSA90 response for patients with mCSPC receiving apalutamide in the TITAN study was 1.9 months,[16] which is shorter than the 3.6 months observed in the current study. These differences may be due to the differences in PSA screening frequency between randomized clinical trials and real-world clinical practice, whereby in the TITAN trial,[8] patients who received apalutamide had a PSA screening conducted once every 28-day treatment cycle, whereas patients in the current study underwent 4.2 tests per year. Nevertheless, the high rate and rapid onset of deep PSA90 response associated with apalutamide over abiraterone acetate observed in the current study among real-world patients with mCSPC undergoing routine clinical care in community-based urology practices in the United States can have meaningful prognostic consequences.

LIMITATIONS

The results of the current study should be interpreted in light of some limitations. Miscoding or misclassification in the clinical records or administrative claims may have introduced selection and information biases, despite efforts to balance baseline characteristics in the study cohorts. In addition, abiraterone acetate is indicated only for high-risk mCSPC, which may have resulted in residual differences relative to the apalutamide cohort after IPTW was applied. Because IPTW was used to account for differences in the baseline characteristics between cohorts, it is unclear how variability in the frequency and timing of PSA testing between the cohorts during the observation period may have affected the findings of the study through potential surveillance bias. Although the findings of this study are expected to have prognostic value, this study did not directly evaluate whether they represent a clinically meaningful difference or whether they translate into differences in longer-term outcomes (eg, OS). Finally, the PPS database reflects the community urology perspective and may not be representative of the entire population of patients with mCSPC in the United States.

Conclusions

Given the association between rapid and deep PSA response attainment and the survival outcomes of patients with mCSPC, early PSA90 response may be an important factor to consider in frontline treatment selection. This study represents the second causal real-world analysis of patients with mCSPC demonstrating that patients treated with apalutamide were statistically significantly more likely to attain a deep PSA90 response than patients treated with

abiraterone acetate by 6 months after treatment initiation. Moreover, PSA90 response was attained earlier in patients treated with apalutamide than in patients treated with abiraterone acetate.

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