



Overall Survival with Apalutamide Versus Enzalutamide in Metastatic Castration-Sensitive Prostate Cancer

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ABSTRACT

Introduction: Survival outcomes associated with different androgen receptor pathway inhibitors (ARPIs) prescribed for the treatment of metastatic castration (hormone)-sensitive prostate cancer (mCSPC) have not been directly compared. The objective of this study was to compare overall survival (OS) by 24 months among ARPI-naïve patients with mCSPC initiating apalutamide or enzalutamide.

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Methods: A retrospective, causal longitudinal inverse probability of treatment weighted analysis was conducted to compare OS between patients initiating apalutamide or enzalutamide between December 2019 and December 2023 using de-identified linked US clinical and insurance claims data. Patients were excluded if they had prior exposure to ARPIs, had evidence of castration resistance, had <12 months of database activity prior to ARPI initiation, were diagnosed with other primary cancers, or were treated with other advanced prostate cancer (PC)-related treatment (except docetaxel). Using an intention-to-treat approach, weighted Cox proportional hazards models were used to compare OS by 24 months between patients treated with apalutamide or enzalutamide (primary analyses; exploratory analyses used all available follow-up).

Results: Overall, 1810 and 1909 ARPI-naïve patients who initiated apalutamide or enzalutamide, respectively, were included. Measured baseline characteristics between cohorts were well balanced after weighting (for both: mean

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age 73.0 years, ~60% white, ~23% black or African American, ~78% Medicare-insured, mean Quan-CCI 8.6, ~20% with visceral metastasis, 56.2% with de novo PC). At 24 months post index, there was a statistically significant 23% reduction in the risk of mortality among patients who initiated apalutamide compared with enzalutamide (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.62, 0.96; $p=0.019$). Results remained consistent when using all available follow-up metrics (HR 0.77; 95% CI 0.64, 0.93; nominal $p=0.008$).

Conclusion: In this head-to-head causal analysis among ARPI-naïve patients with mCSPC, treatment with apalutamide resulted in better survival outcomes at 24 months compared with enzalutamide. Longer follow-up studies are required to fully determine the therapeutic comparator impact of these agents.

Keywords: Androgen receptor pathway inhibitors; Comparative effectiveness; Hormonal antineoplastic agents; Hormone-sensitive; Prostatic neoplasms

Key Summary Points

Why carry out this study?

Apalutamide and enzalutamide are two androgen pathway inhibitors approved for treatment of metastatic castration (hormone)-sensitive prostate cancer (mCSPC)

In combination with androgen deprivation therapy, pivotal phase III clinical trials have shown statistically significant reductions of disease progression and death in patients with mCSPC treated with apalutamide (TITAN) and enzalutamide (ARCHES)

However, no real-world head-to-head studies have assessed the comparative effectiveness of these two medications among patients with mCSPC

What was learned from this study?

Patients with mCSPC treated with apalutamide had a statistically significant 23% reduction in the risk of death by 24 months post treatment initiation compared with those treated with enzalutamide

This survival benefit for apalutamide patients persisted across the overall follow-up period extending past 24 months

INTRODUCTION

Treatment with oral androgen receptor pathway inhibitor (ARPI)-based regimens, such as apalutamide and enzalutamide, are supported by current guidelines for patients with metastatic castration-sensitive prostate cancer (mCSPC), also known as metastatic hormone-sensitive PC [1, 2]. The combination of apalutamide and androgen deprivation therapy (ADT) was approved by the US Food and Drug Administration (FDA) for mCSPC on the basis of the results of the TITAN phase III clinical trial, which demonstrated a 52% reduction in radiographic progression and a 35% reduction in mortality relative to ADT alone [3–5]. Similarly, the combination of

enzalutamide and ADT was also approved by the US FDA on the basis of the results of the ARCHES phase III clinical trial, which demonstrated a 61% reduction in radiographic progression and a 34% reduction in mortality relative to ADT alone [6–8].

Recent causal head-to-head analyses have shown superior early treatment responses for apalutamide versus enzalutamide on the likelihood of achieving a prostate-specific antigen decline of at least 90% (PSA90) by 6 months (hazard ratio [HR] 1.21; 95% confidence interval [CI] 1.05, 1.40; $p=0.008$) [9]. Early, deep prostate-specific antigen (PSA) response has been identified in the TITAN trial, and other phase III ARPI trials, as a clinically important indicator of treatment efficacy and predictive of better long-term survival outcomes [10–14].

Real-world evidence is increasingly informing regulators and health decision-makers about treatment effectiveness in the absence of head-to-head clinical trials [15]. To date, however, rigorous studies to assess overall survival between these ARPIs for mCSPC have not been conducted; hence, clinicians may often consider the survival benefit as equivalent. To better understand the comparative survival benefit of these medications, the objective of this causal analysis was to test the hypothesis that there was no difference in overall survival at 24 months between ARPI-naïve patients with mCSPC initiating apalutamide or enzalutamide.

METHODS

The study was designed taking into account guidance the FDA has issued on real-world evidence [16].

Data Source

This study linked patient-level data from two unique data sources, a clinical urology database (Precision Point Specialty Analytics; PPS) and an administrative claims database (Komodo Research Database; KRD). The PPS proprietary database contains a wide range of demographic and clinical data collected as part of routine

subscribing urology practices in the US, including PSA results, dispensation information, and additional PC-specific medication and procedure data that are not available from traditional administrative databases. KRD is an insurance claims database of over 320 million US patients across commercial, Medicaid, and Medicare insurers, and includes information on insurance eligibility, diagnoses and procedures received in inpatient and outpatient settings, and prescription fills. Notably, mortality data are obtained from multiple third-party sources that aggregate information from national and state governments, public listings, private claims, and obituaries, and are therefore not dependent on data supplied by healthcare providers [17]. On the basis of an external validation assessment, the KRD captures more than 90% of all deaths in oncology settings between 2018 and 2023 identified by the US Centers for Disease Control (CDC) [17]. Mortality data from KRD were thus used to inform the overall survival analysis. The PPS and KRD databases were linked by Datavant using the patent-pending, machine-learning validated, de-identification technology which replaces private patient information with an encrypted token that cannot be reverse-engineered to reveal the original information.

Ethical Approval

This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments and considered exempt research under 45 CFR § 46.104(d)(4) as it involved only the secondary use of data that were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA), specifically, 45 CFR § 164.514.

Study Design

A retrospective, longitudinal causal analyses utilizing propensity score-weighted cohorts of ARPI-naïve patients initiating apalutamide or enzalutamide was conducted and followed an intention-to-treat design (study period 16 December 2018–31 December 2023). Patients were classified into either of the mutually

exclusive treatment cohorts based on the earliest date of the first record for a paid pharmacy claim in the KRD or in-office dispensation in PPS for apalutamide or enzalutamide. Power calculations were performed to pre-specify sufficient sample size to compare overall survival between the cohorts. Patients' index dates were set at the date of the first dispensation or paid prescription for apalutamide or enzalutamide on or after 16 December 2019 [8]. Only patients who initiated treatment after the FDA approval of the most recent of both treatment options were considered (i.e., enzalutamide approval date; apalutamide was approved for use in mCSPC on 17 September 2019 [5]). The baseline period comprised 12 months pre-index, while the observation period spanned from the index date until the latter of open insurance claim activity in the KRD or clinical activity in PPS, both no later than 31 December 2023 (i.e., end of data). Given the use of an intention-to-treat design, patients were not censored if they discontinued the index ARPI, switched to another ARPI, initiated therapy with another advanced PC treatment, or progressed to castration resistance.

Patient Selection Criteria

Adult patients with mCSPC were selected for this study if they (i) initiated either apalutamide or enzalutamide on or after 16 December 2019 (ii) had at least 12 months of KRD insurance claim activity or at least 12 months of PPS clinical activity pre-index, and (iii) had a diagnosis code in KRD or PPS, or clinical indicator in PPS, for bone, nodal, or visceral metastasis on or prior to the index date. Patients were excluded if they (i) initiated the index ARPI prior to 16 December 2019, (ii) initiated two or more different ARPIs on the index date, (iii) had a diagnosis for another primary cancer during the baseline period (iv) had a prescription in PPS for a non-index ARPI, (v) were castration-resistant prior to or on the index date (see Supplementary Table 1), (vi) used estrogens, immunotherapy, poly(ADP-ribose) polymerase inhibitors, radiopharmaceuticals, or etoposide, or (vii) used

either cabazitaxel or carboplatin after docetaxel. Concurrent ADT use was not required for study inclusion.

Study Outcomes

The primary study outcome was overall survival at 24 months post index. Overall survival was defined as the time from the index date to the date of death from any cause, if observed.

Patients' demographic and clinical characteristics were assessed prior to or on the index date. Specifically, the following characteristics were evaluated: age, race, geographic region, payer, time between metastasis and index date, time between PC diagnosis and index date, metastasis location, Quan-Charlson comorbidity index (Quan-CCI), de novo PC, ADT use overlapping the index date, prior first-generation ARPI use, prior chemotherapy, most recent PSA result, and earliest Gleason score. Treatment patterns were observed from the index date for a period spanning up to 24 months.

Statistical Analysis

The null hypothesis was that in ARPI-naïve patients with mCSPC, overall survival at 24 months post apalutamide initiation was not different from overall survival at 24 months post enzalutamide initiation. The alternative hypothesis was that in ARPI-naïve patients with mCSPC, overall survival at 24 months post apalutamide initiation was different from overall survival at 24 months post enzalutamide initiation.

Potentially confounding baseline variables were balanced between treatment cohorts using inverse probability of treatment weighting (IPTW). Propensity scores were generated using probability estimates from a logistic regression model based on dependent (i.e., apalutamide initiation) and independent variables. Patients in the apalutamide and enzalutamide cohorts were attributed a weight of $\frac{1}{PS}$ and $\frac{1}{1-PS}$, respectively, with weights normalized using the mean weight of each respective cohort and truncated to the 95th percentile [18]. The number of patients in each

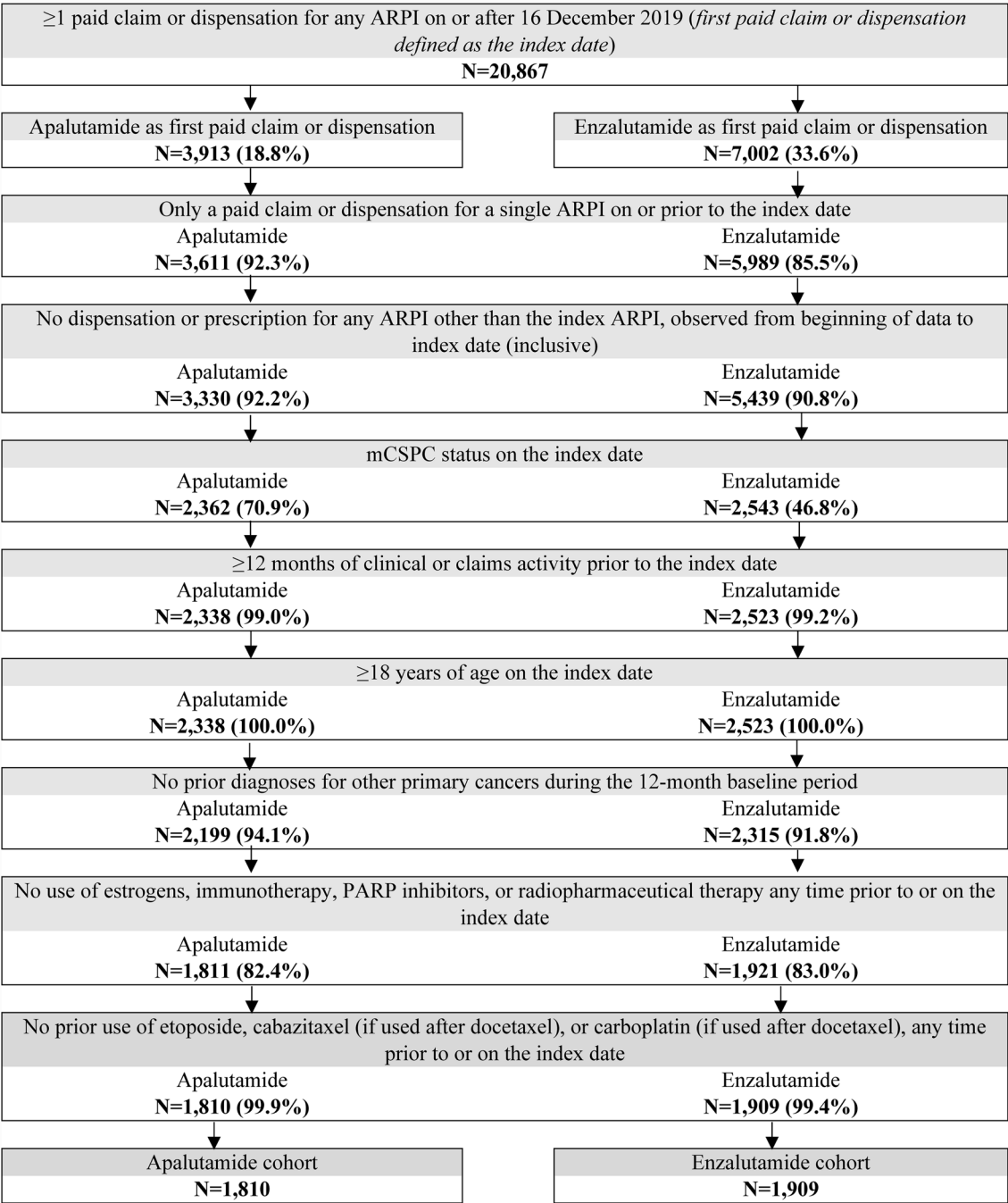


Fig. 1 Sample selection. *ARPI* androgen receptor pathway inhibitor, *mCSPC* metastatic castration-sensitive prostate cancer, *PARP* poly(ADP-ribose) polymerase

cohort remained unchanged following weighting. The weighted cohorts were considered well balanced if individual baseline characteristics had a standardized difference of less than 10% [19]. Weighted Kaplan–Meier (KM) analyses were used to assess overall survival separately for patients treated with apalutamide or enzalutamide. KM rates were reported at 3-month intervals up to a maximum of 48 months post index. Overall survival between the apalutamide and enzalutamide cohorts was compared at 24 months post index (primary) and using all available follow-up data (exploratory; nominal) using a weighted Cox proportional hazards model. HRs and 95% CIs served to compare overall survival between cohorts. In a sensitivity analyses, overall survival was assessed among a subgroup treated with ADT 180 days prior to or within 180 days following the index date.

RESULTS

Patient Characteristics

This study included 1810 ARPI-naïve patients with mCSPC who initiated apalutamide and 1909 patients with mCSPC who initiated enzalutamide (Fig. 1). After IPTW, baseline characteristics were well balanced between the apalutamide and enzalutamide cohorts (i.e., standardized difference < 10%; Table 1). The mean and median age was 73.0 years in both treatment cohorts. The majority of patients in both treatment cohorts were white (apalutamide, 59.8%; enzalutamide, 59.4%), and receiving Medicare insurance (apalutamide, 77.7%; enzalutamide, 77.9%). Of all metastasis types, bone metastasis was the most common in both treatment cohorts (apalutamide, 71.9%; enzalutamide, 72.8%), followed by nodal metastasis (apalutamide, 49.0%; enzalutamide, 48.1%) and visceral metastasis (apalutamide, 19.7%; enzalutamide, 20.8%). The median time between metastasis diagnosis and the index date was 2.6 months for apalutamide patients and 2.7 months for enzalutamide patients.

Overall Survival

Patients who initiated apalutamide were 23% less likely to have died at 24 months post treatment initiation compared to those treated with enzalutamide (HR 0.77, 95% CI 0.62, 0.96, $p=0.019$; Fig. 2). The trend towards a reduction in the risk of mortality among patients who initiated apalutamide versus enzalutamide was maintained when evaluated over the entire follow-up period (HR 0.77, 95% CI 0.64, 0.93, nominal $p=0.008$). The median overall survival was not reached in either the apalutamide or enzalutamide cohort. A total of 87.6% of patients in the apalutamide cohort were alive at 24 months post index compared with 84.6% of patients in the enzalutamide cohort. By 48 months post index, 75.6% of patients in the apalutamide cohort were alive compared with 68.1% of patients in the enzalutamide cohort. Results from the sensitivity analysis of patients with concurrent ADT use was consistent with the primary analysis (HR 0.79, 95% CI 0.64, 0.99, nominal $p=0.039$).

Treatment Patterns

The mean (median) follow-up period was 17.2 (20.1) months among both the apalutamide and enzalutamide cohorts (Table 2). The mean (median) duration of continuous index ARPI use was 9.6 (6.9) months for apalutamide and 8.6 (6.4) months for enzalutamide, with ARPI discontinuation defined by a 90-day gap in treatment.

A numerically higher proportion of patients in the enzalutamide cohort discontinued treatment (63.1%) than the apalutamide cohort (56.6%). Among those who were treated after discontinuation (apalutamide, 19.1%; enzalutamide, 17.0%), the most common classes of medications initiated were a non-index ARPI (apalutamide, 9.2%; enzalutamide, 8.3%), chemotherapy (apalutamide, 3.7%; enzalutamide, 3.9%), and estrogen (apalutamide, 3.0%; enzalutamide, 1.5%). Among the apalutamide cohort, enzalutamide was the most frequently used subsequent non-index ARPI (4.4%). Among the enzalutamide cohort, however, abiraterone

Table 1 Baseline characteristics

	Non-weighted population					IPTW population ^{a,b}				
	Apalutamide <i>N</i> = 1810		Enzalutamide <i>N</i> = 1909		Standardized difference, %	Apalutamide <i>N</i> = 1810		Enzalutamide <i>N</i> = 1909		Standardized difference, %
Age, mean ± SD [Q1, median, Q3]	72.9 ± 9.2	[67.0, 73.0, 80.0]	73.0 ± 9.4	[66.0, 73.0, 80.0]	0.9	73.0 ± 9.2	[67.0, 73.0, 80.0]	73.0 ± 9.3	[66.0, 73.0, 80.0]	0.1
Age group, <i>n</i> (%)										
≤ 60	178	(9.8)	179	(9.4)	1.6	184	(10.2)	173	(9.1)	3.7
61–70	550	(30.4)	593	(31.1)	1.5	540	(29.8)	596	(31.2)	3.0
71–80	689	(38.1)	704	(36.9)	2.5	687	(37.9)	714	(37.4)	1.1
≥ 81	393	(21.7)	433	(22.7)	2.3	400	(22.1)	426	(22.3)	0.6
Race, <i>n</i> (%)										
White	1096	(60.6)	1107	(58.0)	5.2	1083	(59.8)	1135	(59.4)	0.8
Black or African American	400	(22.1)	449	(23.5)	3.4	407	(22.5)	432	(22.7)	0.3
Hispanic or Latino	133	(7.3)	150	(7.9)	1.9	135	(7.5)	146	(7.6)	0.6
Other ^c	68	(3.8)	101	(5.3)	7.4	79	(4.4)	88	(4.6)	1.2
Unknown	113	(6.2)	102	(5.3)	3.9	105	(5.8)	108	(5.7)	0.7
Geographic region, <i>n</i> (%)										
South	1031	(57.0)	975	(51.1)	11.8	986	(54.5)	1021	(53.5)	2.0
Midwest	409	(22.6)	472	(24.7)	5.0	429	(23.7)	458	(24.0)	0.6
Northeast	200	(11.0)	288	(15.1)	12.0	225	(12.4)	250	(13.1)	1.9
West	170	(9.4)	174	(9.1)	1.0	170	(9.4)	181	(9.5)	0.3
Payer type, <i>n</i> (%)										
Medicare	1396	(77.1)	1489	(78.0)	2.1	1406	(77.7)	1487	(77.9)	0.5
Commercial	355	(19.6)	342	(17.9)	4.4	339	(18.7)	354	(18.5)	0.5
Medicaid	54	(3.0)	74	(3.9)	4.9	59	(3.3)	65	(3.4)	0.7
Unknown	5	(0.3)	4	(0.2)	0.0	6	(0.3)	3	(0.2)	0.0

Table 1 continued

	Non-weighted population			IPTW population ^{a,b}		
	Apalutamide <i>N</i> = 1810	Enzalutamide <i>N</i> = 1909	Standard- ardized differ- ence, %	Apalutamide <i>N</i> = 1810	Enzalutamide <i>N</i> = 1909	Standard- ized differ- ence, %
Index year, <i>n</i> (%)						
2019–2020	336 (18.6)	510 (26.7)	19.6	391 (21.6)	434 (22.7)	2.7
2021	447 (24.7)	562 (29.4)	10.7	488 (27.0)	524 (27.5)	1.2
2022	519 (28.7)	469 (24.6)	9.3	493 (27.3)	511 (26.7)	1.2
2023	508 (28.1)	368 (19.3)	20.8	438 (24.2)	440 (23.1)	2.7
Time between metastasis and index date, months, mean ± SD [Q1, median, Q3]	9.2 ± 18.2 [0.9, 2.3, 7.2]	12.1 ± 18.8 [1.2, 3.4, 14.5]	15.8	10.1 ± 18.2 [0.9, 2.6, 8.9]	10.6 ± 18.0 [1.0, 2.7, 10.5]	2.7
Time between PC diagnosis and index date, months, mean ± SD [Q1, median, Q3]	39.5 ± 47.1 [2.9, 15.4, 64.9]	40.9 ± 46.7 [3.8, 21.9, 66.3]	3.0	39.4 ± 46.6 [3.0, 16.8, 64.0]	39.8 ± 46.8 [3.5, 17.8, 65.7]	1.0
Metastasis type ^d , <i>n</i> (%)						
Bone	1258 (69.5)	1448 (75.9)	14.3	1301 (71.9)	1390 (72.8)	2.1
Nodal	936 (51.7)	856 (44.8)	13.8	887 (49.0)	918 (48.1)	1.8
Visceral	324 (17.9)	453 (23.7)	14.4	356 (19.7)	398 (20.8)	2.9
Metastasis in multiple sites	521 (28.8)	445 (23.3)	12.5	485 (26.8)	498 (26.1)	1.6
Quan-CCI, mean ± SD [Q1, median, Q3]	8.5 ± 3.0 [8.0, 8.0, 10.0]	8.7 ± 3.1 [8.0, 9.0, 10.0]	7.2	8.6 ± 3.0 [8.0, 8.0, 10.0]	8.6 ± 3.1 [8.0, 9.0, 10.0]	1.1
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	1800 (99.4)	1889 (99.0)	5.6	1797 (99.3)	1893 (99.2)	1.6

Table 1 continued

	Non-weighted population					IPTW population ^{a,b}				
	Apalutamide N = 1810		Enzalutamide N = 1909		Standardized difference, %	Apalutamide N = 1810		Enzalutamide N = 1909		Standardized difference, %
Metastatic solid tumor	1531	(84.6)	1600	(83.8)	2.1	1538	(84.9)	1577	(82.6)	6.4
Diabetes without chronic complication	433	(23.9)	508	(26.6)	6.2	439	(24.2)	497	(26.0)	4.1
Renal disease	270	(14.9)	358	(18.8)	10.3	276	(15.3)	347	(18.2)	7.8
Peripheral vascular disease	261	(14.4)	373	(19.5)	13.7	275	(15.2)	356	(18.6)	9.2
Diabetes with chronic complication	228	(12.6)	248	(13.0)	1.2	233	(12.9)	240	(12.6)	1.0
Chronic pulmonary disease	221	(12.2)	297	(15.6)	9.7	225	(12.4)	291	(15.3)	8.2
Congestive heart failure	191	(10.6)	203	(10.6)	0.3	201	(11.1)	190	(9.9)	3.8
Mild liver disease	157	(8.7)	196	(10.3)	5.4	157	(8.7)	188	(9.8)	3.9
Cerebrovascular disease	124	(6.9)	173	(9.1)	8.2	124	(6.9)	165	(8.6)	6.7
Myocardial infarction	79	(4.4)	106	(5.6)	5.5	84	(4.6)	100	(5.2)	2.8
Dementia	40	(2.2)	58	(3.0)	5.2	44	(2.5)	56	(2.9)	2.8
Rheumatic disease	35	(1.9)	41	(2.1)	1.5	34	(1.9)	41	(2.2)	2.0
Peptic ulcer disease	19	(1.0)	14	(0.7)	3.4	21	(1.1)	13	(0.7)	4.6
Hemiplegia or paraplegia	10	(0.6)	23	(1.2)	7.0	10	(0.6)	20	(1.0)	5.3
Moderate or severe liver disease	5	(0.3)	10	(0.5)	3.9	4	(0.2)	11	(0.6)	5.2
AIDS/HIV	0	(0.0)	0	(0.0)	0.0	0	(0.0)	0	(0.0)	0.0

Table 1 continued

	Non-weighted population					IPTW population ^{a,b}				
	Apalutamide <i>N</i> = 1810		Enzalutamide <i>N</i> = 1909		Standardized difference, %	Apalutamide <i>N</i> = 1810		Enzalutamide <i>N</i> = 1909		Standardized difference, %
De novo PC ^c , <i>n</i> (%)	1004	(55.5)	1073	(56.2)	1.5	1017	(56.2)	1072	(56.2)	0.1
Concurrent use of ADT with index ARPI ^f , <i>n</i> (%)	1480	(81.8)	1411	(73.9)	19.0	1434	(79.2)	1486	(77.8)	3.3
Duration of ADT episode overlapping with index date, months, mean ± SD [Q1, median, Q3]	4.4 ± 8.6 [0.7, 1.8, 4.4]		5.9 ± 9.4 [0.9, 2.4, 6.8]		15.7	4.5 ± 8.6 [0.7, 1.8, 4.9]		5.5 ± 9.3 [0.8, 2.2, 5.8]		9.6
Prior use of first-generation ARPI ^g , <i>n</i> (%)	279	(15.4)	470	(24.6)	23.2	350	(19.4)	393	(20.6)	3.0
Prior use of chemotherapy ^h , <i>n</i> (%)	29	(1.6)	64	(3.4)	11.3	41	(2.3)	49	(2.6)	2.0
Most recent PSA level, ng/mL, <i>n</i> (%)										
≤ 0.2	309	(17.1)	242	(12.7)	12.4	281	(15.5)	283	(14.8)	2.0
> 0.2 to ≤ 2	298	(16.5)	285	(14.9)	4.2	291	(16.1)	302	(15.8)	0.8
> 2 to ≤ 5	206	(11.4)	156	(8.2)	10.8	180	(9.9)	181	(9.5)	1.5
> 5 to ≤ 10	186	(10.3)	138	(7.2)	10.8	165	(9.1)	165	(8.6)	1.6
> 10	541	(29.9)	544	(28.5)	3.1	541	(29.9)	563	(29.5)	0.8
Unknown	270	(14.9)	544	(28.5)	33.4	352	(19.5)	415	(21.7)	5.6
Initial Gleason score ⁱ , <i>n</i> (%)										
≤ 6	107	(5.9)	101	(5.3)	2.7	101	(5.6)	108	(5.7)	0.3
7	357	(19.7)	282	(14.8)	13.1	323	(17.8)	326	(17.1)	2.1
8	251	(13.9)	259	(13.6)	0.9	256	(14.2)	267	(14.0)	0.4
9	388	(21.4)	403	(21.1)	0.8	383	(21.1)	405	(21.2)	0.1

Table 1 continued

	Non-weighted population					IPTW population ^{a,b}				
	Apalutamide N = 1810		Enzalutamide N = 1909		Standardized difference, %	Apalutamide N = 1810		Enzalutamide N = 1909		Standardized difference, %
10	52	(2.9)	68	(3.6)		60	(3.3)	64	(3.3)	0.1
Unknown	655	(36.2)	796	(41.7)	11.3	687	(37.9)	739	(38.7)	1.6

ADT androgen deprivation therapy, *AIDS* acquired immunodeficiency syndrome, *ARPI* androgen receptor pathway inhibitor, *CCI* Charlson Comorbidity Index, *HIV* human immunodeficiency virus, *IPTW* inverse probability of treatment weighting, *PC* prostate cancer, *PSA* prostate-specific antigen, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

^aPropensity scores were generated using probability estimates from a logistic regression models using the following predictors: age (continuous), race, geographic region, payer, year of index date, time between metastasis and index date (continuous and categorical), time between PC diagnosis and index date (continuous), de novo PC, ADT use overlapping with index date, first-generation antiandrogen use, chemotherapy use, types of metastases (bone, nodal, visceral, and metastasis in multiple sites), Quan-CCI (continuous), most recent PSA level (categorical), and earliest Gleason score (categorical). Each patient was attributed an inverse probability of treatment weight that was defined as follows: 1/(propensity score) for the apalutamide cohort and 1/(1 – propensity score) for the enzalutamide cohort. Normalized inverse probability of treatment weights were truncated at the 95th percentiles

^bOf note, the number of patients reported in this weighted population represents the sum of weights for the corresponding non-weighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated on the basis of rounded numbers

^cThis category includes patients identified as “Other” or “Asian or Pacific Islander” in the Komodo Research Database demographic dataset

^dTypes of metastases were defined at any time prior to (and including) the index date. Types of metastases were not mutually exclusive

^eDe novo PC was defined as ≤ 180 days between first observed PC diagnosis and date of metastasis

^fConcurrent ADT use was defined as an episode of continuous ADT use overlapping with the index date (using a 60-day gap to define discontinuation)

^gPrior use of first-generation ARPI was defined as any prescription for bicalutamide, nilutamide, or flutamide in the 12 months preceding the index date

^hPrior chemotherapy use was defined as an administration any time prior to (and excluding) the index date

ⁱGleason score was evaluated at any time prior to and including the index date

acetate was the most frequently used subsequent non-index ARPI (5.3%).

DISCUSSION

This retrospective study represents the first head-to-head causal analysis of overall survival among ARPI-naïve patients with mCSPC who initiated either apalutamide or enzalutamide using US clinical urology data linked with insurance claims permitting an evaluation of outcomes in

a large sample of over 3700 patients. The combination of the two data sources allowed the use of variables that are highly relevant to the current study but were not readily available from one individual database alone (e.g., castration resistance indicator from PPS, and mortality data from the KRD). Results show that while the median overall survival was not reached by 24 months post treatment initiation in either cohort, apalutamide was associated with a 23% statistically significant reduction in the risk of mortality versus enzalutamide at 24 months.

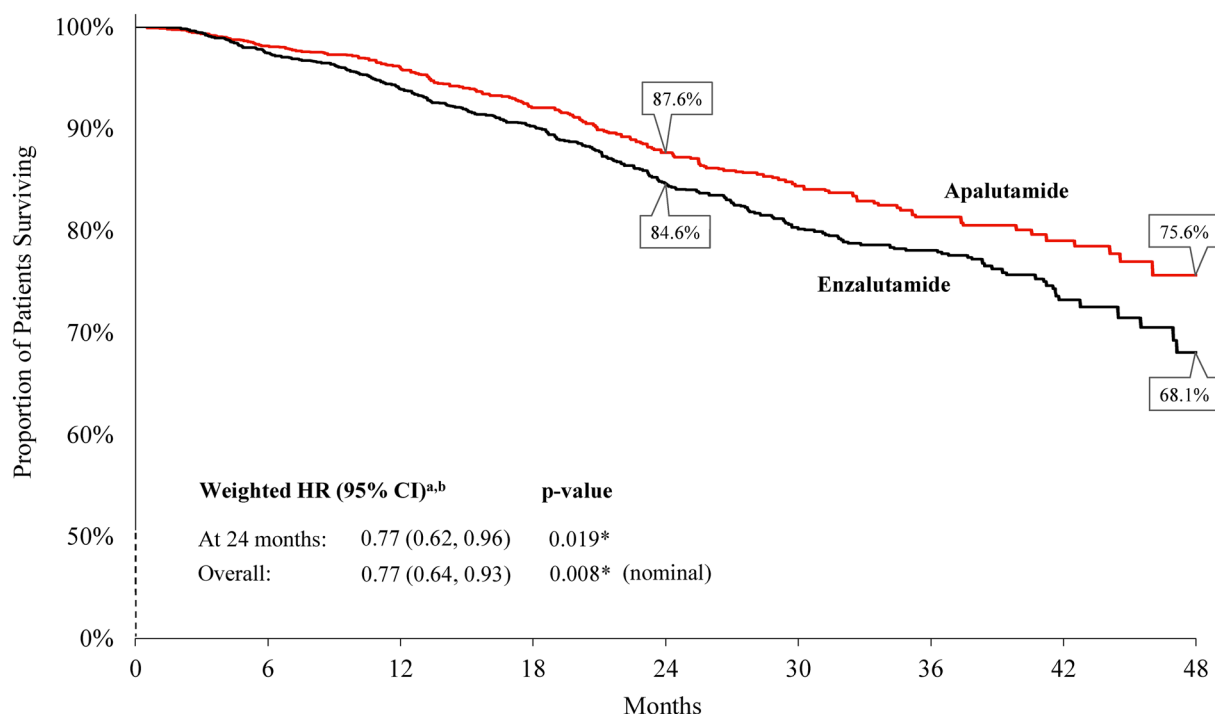


Fig. 2 Overall survival among patients initiating apalutamide versus enzalutamide. *ADT* androgen deprivation therapy, *CI* confidence interval, *HR* hazard ratio, *PC* prostate cancer. *Significant at the 5% level. ^aPropensity scores were generated using probability estimates from a logistic regression models using the following predictors: age (continuous), race, geographic region, payer, year of index date, time between metastasis and index date (continuous and categorical), time between PC diagnosis and index date (continuous), de novo PC, ADT use overlapping with index date, first-generation antiandrogen use, chemotherapy use, types of metastases (bone, nodal, visceral, and

metastasis in multiple sites), Quan-Charlson Comorbidity Index (continuous), most recent prostate-specific antigen level (categorical), and earliest Gleason score (categorical). Each patient was attributed an inverse probability of treatment weight that was defined as follows: $1/(\text{propensity score})$ for the apalutamide cohort and $1/(1 - \text{propensity score})$ for the enzalutamide cohort. Normalized inverse probability of treatment weights were truncated at the 95th percentiles. ^b $HR < 1$ indicates that the apalutamide cohort had a lower rate of death compared to the enzalutamide cohort

The significant overall survival benefit of apalutamide compared with enzalutamide treatment remained consistent over the entire follow-up period. These findings from a demographically and clinically diverse study population are therefore more generalizable to the entire population of patients with mCSPC in the US than the patients assessed in the TITAN [3] or ARCHES [6] trials.

Only one real-world study has reported overall survival following apalutamide initiation in patients with mCSPC [20]. In this prior study, a recent retrospective analysis of electronic medical record data primarily from US community

oncology practices, Lowentritt et al. reported overall survival rates post apalutamide initiation were 91% at 12 months and 88% at 24 months among 176 patients with mCSPC (median follow-up of 11.6 months) [20]. Results from the current analyses are more generalizable, with overall survival assessed among a considerably larger sample of 1810 patients treated with apalutamide who were followed for a median of 20.1 months. Overall survival rates from the current study (96% at 12 months and 88% at 24 months post apalutamide initiation) were consistent with the prior analyses by Lowentritt et al. [20]. To our knowledge, no

Table 2 Treatment patterns by 24 months post index

	Weighted population ^a	
	Apalutamide <i>N</i> = 1810	Enzalutamide <i>N</i> = 1909
Follow-up length ^b , months, mean $\pm$ SD [median]	17.2 $\pm$ 7.3 [20.1]	17.2 $\pm$ 7.2 [20.1]
Duration of continuous use of index ARPI ^c , months, mean $\pm$ SD [median]	9.6 $\pm$ 7.9 [6.9]	8.6 $\pm$ 7.4 [6.4]
Proportion of patients who discontinue index ARPI ^d , <i>n</i> (%)	1025 (56.6)	1205 (63.1)
Proportion of patients with no additional treatment after discontinuation, <i>n</i> (%)	680 (37.6)	880 (46.1)
Proportion of patients who received different advanced PC medication after discontinuation of index ARPI ^e , <i>n</i> (%)	345 (19.1)	325 (17.0)
Time to first advanced PC medication after discontinuation of index ARPI, months, mean $\pm$ SD [median]	4.8 $\pm$ 5.4 [2.4]	4.4 $\pm$ 5.0 [1.8]
First advanced PC medication received after discontinuation of index ARPI, <i>n</i> (%)		
Non-index ARPI ^f	166 (9.2)	159 (8.3)
Enzalutamide	80 (4.4)	–
Abiraterone acetate	66 (3.6)	101 (5.3)
Darolutamide	20 (1.1)	10 (0.5)
Apalutamide	–	48 (2.5)
Chemotherapies	67 (3.7)	74 (3.9)
Estrogens	55 (3.0)	28 (1.5)
Immunotherapies	36 (2.0)	25 (1.3)
Radiotherapy	12 (0.7)	22 (1.2)
PARP inhibitors	9 (0.5)	18 (0.9)

ARPI androgen receptor pathway inhibitor, PARP poly(ADP-ribose) polymerase, PC prostate cancer, PPS Precision Point Specialty, SD standard deviation

^aOf note, the number of patients reported in this weighted population represents the sum of weights for the corresponding non-weighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated on the basis of rounded numbers

^bFollow-up length was defined as the index date until the latter of the end of open insurance claim activity in Komodo, clinical activity in PPS (both no later than 31 December 2023). The observation period was censored such that it is not longer than 24 months

^cContinuous use was reported from the first ARPI episode observed in the observation period. Continuous use of ARPI was defined as the time from the date of the first paid pharmacy or dispensation claims to the last day of supply before a gap > 90 days

^dDiscontinuation of index ARPI was assessed using > 90-day gap in days of supply

^eIncludes patients with a record for an advanced PC medication different from the index ARPI; advanced PC medication use was assessed from the date of index ARPI discontinuation until the end of the observation period

^fDefined as a record for another ARPI than the one initiated on the index date

real-world studies to date have evaluated overall survival following enzalutamide initiation among patients with mCSPC and no clinical trials have directly compared survival outcomes between patients treated with apalutamide versus enzalutamide.

The overall survival rates observed among patients with mCSPC treated with apalutamide or enzalutamide in the current study were also comparable to those reported in the respective pivotal clinical trials for these treatments. In TITAN [4], the overall survival rate by 24 months was 82.4% versus 87.6% in the present analysis, and by 48 months in TITAN was 65% relative to 75.6% in the present analysis. In ARCHES, the overall survival rate by 24 months was 86% and was 84.6% in the present analysis. By 48 months in ARCHES overall survival rate was 71% and 68.1% in the present analysis [7]. In the ENZAMET open-label, randomized, phase III trial evaluating enzalutamide plus nonsteroidal antiandrogen therapy versus nonsteroidal antiandrogen therapy alone among patients with mCSPC, the overall survival rate by 36 months was 80% [21].

Although the causal mechanism between the improved overall survival observed with apalutamide versus enzalutamide remains to be determined, prior comparative studies assessing other clinical outcomes associated with the two treatments among patients with mCSPC have shown similar trends [9, 22]. A number needed to treat analysis using clinical trial data from the TITAN and ENZAMET trials to compare clinical outcomes favored apalutamide over enzalutamide for patients with mCSPC [22]. Specifically, Santoni et al. showed that relative to treatment with ADT alone, in order to prevent one death by 12 months post ARPI initiation, 20 patients would require apalutamide treatment while 33 patients would require enzalutamide treatment [22]. Recent studies by Lowentritt et al. evaluated PSA90 using clinical and administrative data from PPS and KRD showed that a significantly higher proportion of patients with mCSPC initiating apalutamide compared with enzalutamide achieved a PSA90 response by 6 months (69% vs 56%, $p=0.014$ [23]; 63% vs 54%, $p=0.008$ [9]). Considering the growing body of evidence describing the clinical importance of PSA90 as

an indicator of treatment efficacy and long-term survival outcomes [10–14, 24, 25], the earlier and deeper response achieved by patients with mCSPC treated with apalutamide versus enzalutamide may be linked to the associated reduction in mortality observed in the current study.

Limitations

There are certain limitations that should be considered when interpreting findings from this study. Despite efforts to balance the study populations, miscoding or misclassification in the clinical record or through the administrative claims may introduce selection and information biases. Furthermore, as both linked databases were from an open source, the entire patient history may not be captured (e.g., diagnoses, medications, and procedures), as there were no defined periods of continuous insurance eligibility used in this analysis. Relying on data from the US CDC estimates of overall survival, KRD captured more than 90% of all deaths in oncology settings between 2018 and 2023 [17]. However, there is a small but unlikely possibility that some death data were not captured. Regression analyses used to balance the characteristics of patients from both cohorts could only account for documented covariates; unknown confounding could still occur. In phase III trials, overall survival is assessed at pre-specified numbers of events [4, 7]; however, in this study, survival was assessed at 24 months for a statistically comparative evaluation. Studies assessing longer follow-up in these patient cohorts may be needed to estimate the full magnitude of the therapeutic effects of these agents, and additional research on healthcare resource utilization, medical costs, and additional treatment patterns are warranted to further contextualize these findings.

CONCLUSIONS

In this US representative, causal head-to-head analysis of overall survival using linked clinical and administrative claims data, ARPI-naïve

patients with mCSPC who initiated apalutamide had a 23% statistically significant reduction in the risk of mortality compared with enzalutamide at 24 months post ARPI initiation. The reduction in the risk of mortality associated with apalutamide versus enzalutamide treatment remained consistent using all available follow-up extending past 48 months post treatment initiation. While findings suggest that apalutamide may provide a superior treatment option compared with enzalutamide among patients with mCSPC in clinical practice, studies assessing longer follow-up in these patient cohorts may be needed to estimate the full magnitude of the therapeutic effects of these agents.

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draft, writing—review and editing. Shawn Du contributed to the conceptualization, data curation, funding acquisition, methodology, project administration, resources, supervision, writing—original draft, writing—review and editing. Frederic Kinkead contributed to the formal analysis, investigation, software, validation, visualization, writing—original draft, writing—review and editing. Lilian Diaz contributed to the formal analysis, investigation, software, validation, visualization, writing—original draft, writing—review and editing. Dominic Pilon contributed to the conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review and editing. Lorie Ellis contributed to the funding acquisition, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review and editing. Neal D. Shore contributed to the conceptualization, investigation, methodology, writing – original draft, writing – review and editing. All authors have provided final approval of this manuscript to be published and agree to be accountable for all aspects of the work.

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Data Availability. The data that support the findings of this study are available from PPS Analytics and Komodo Health Solutions. Restrictions apply to the availability of these data, which were used under license for this study.

Declarations

Conflict of Interest. Mehmet A. Bilen has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Johnson & Johnson, Calithera Biosciences, Genomic Health, Nektar, EMD Serono, SeaGen, and Sanofi and has received grants to his institution from Merck, Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, SeaGen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer for work performed outside of the current study. Benjamin Lowentritt is an employee of Chesapeake Urology and has received consulting fees from Johnson & Johnson, Dendreon, Astellas Pharma, Bayer, AstraZeneca/MedImmune, Merck, Tolmar, Abbvie, Pfizer, and Myovant Sciences. Ibrahim Khilfeh and, Shawn Du are employees and stockholders of Johnson & Johnson. Lorie Ellis was an employee of Johnson & Johnson at the time the study was conducted. Carmine Rossi, Frederic Kinkad, Lilian Diaz, and Dominic Pilon are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Johnson & Johnson. Neal D. Shore is an employee of the Carolina Urologic Research Center and has received consulting fees from Johnson & Johnson, Bayer, Dendreon, Tolmar, Ferring, Medivation/Astellas, Amgen, Pfizer, AstraZeneca, Astellas Pharma, AbbVie, Merck, Bristol Myers Squibb/Sanofi, Exact Imaging, FerGene, InVita, MDxHealth, Myriad Genetics, Propella Therapeutics, Genzyme, Sanofi, CG Oncology, Genesis Cancer Care, Urogen pharma, Speciality Networks, PeerView, Clarity Pharmaceuticals, Lantheus Medical Imaging, Lilly, Photocure, Telix Pharmaceuticals, Alkido Pharma, Arquer Diagnostics, Asieris Pharmaceuticals, Minomic, Novartis, PlatformQ Health, Promaxo, Protara Therapeutics, Fize Medical, Accord Research, Antev, Aura Biosciences, Bioprotect, and Sumitomo Pharma Oncology. NS has received research funding from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Boston Scientific, Clovis Oncology, Dendreon, Exact Imaging, Ferring, Foundation Medicine, InVita, Johnson & Johnson, MDxHealth, Merck, Myovant Sciences,

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Ethical Approval. This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments and considered exempt research under 45 CFR § 46.104(d)(4) as it involved only the secondary use of data that were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA), specifically, 45 CFR § 164.514.

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