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Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

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Abstract

IMPORTANCE Novel androgen receptor inhibitors (ARIs; darolutamide, enzalutamide, and apalutamide) are standard-of-care treatments for nonmetastatic castration-resistant prostate cancer (nmCRPC). However, there are sparse data comparing their clinical use and tolerability.

OBJECTIVE To compare clinical use and outcomes for darolutamide, enzalutamide, and apalutamide in patients with nmCRPC.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study reviewed electronic medical records from the Precision Point Specialty network of US urology practices. Eligible patients had nmCRPC and no prior novel hormonal therapy and initiated novel ARI treatment between August 1, 2019, and March 31, 2022. Data were analyzed from February 1, 2019, to December 31, 2022.

EXPOSURES Patients were prescribed darolutamide, enzalutamide, or apalutamide as their first novel ARI for nmCRPC.

MAIN OUTCOMES AND MEASURES The main outcome was a composite of 2 end points, treatment discontinuation and progression to metastatic CRPC (mCRPC), whichever occurred first. Both end points were also assessed separately.

RESULTS All 870 patients meeting eligibility criteria were included (362 receiving darolutamide [41.6%]; 382, enzalutamide [43.9%]; 126, apalutamide [14.5%]); mean (SD) age was 78.8 (8.7) years. Self-reported race was Black or African American in 187 patients (21.5%), White in 585 (67.2%), and other or unknown in 98 (11.3%). The darolutamide cohort had lower proportions of patients with a composite end point event (134 [37.0%] vs 201 [52.6%] for enzalutamide and 66 [52.4%] for apalutamide), discontinuation (110 [30.4%] for darolutamide vs 156 [40.8%] for enzalutamide and 58 [46.0%] for apalutamide), and progression to mCRPC (64 [17.7%] for darolutamide vs 108 [28.3%] for enzalutamide and 35 [27.8%] for apalutamide) during the study period. After adjusting for baseline covariates, patients receiving darolutamide had a lower risk of a composite end point event compared with enzalutamide (risk reduction, 33.8%; hazard ratio [HR], 0.66 [95% CI, 0.53-0.84]) and apalutamide (risk reduction, 35.1%; HR, 0.65 [95% CI, 0.48-0.88]). Similarly, patients receiving darolutamide had a lower risk of discontinuation compared with enzalutamide (risk reduction, 27.4%; HR, 0.73 [95% CI, 0.56-0.94]) and apalutamide (risk reduction, 39.1%; HR, 0.61 [95% CI, 0.44-0.85]) and a lower risk of progression to mCRPC compared with enzalutamide (risk reduction, 40.6%; HR, 0.59 [95% CI, 0.43-0.82]) and apalutamide (risk reduction, 35.3%; HR, 0.65 [95% CI, 0.42-0.99]). There was no difference between enzalutamide and apalutamide treatment across outcomes.

(continued)

Key Points

Question What are the clinical use and outcomes of the androgen receptor inhibitors (ARIs) darolutamide, enzalutamide, and apalutamide in US patients with nonmetastatic castration-resistant prostate cancer (nmCRPC)?

Findings In this cohort study of 870 patients with nmCRPC, darolutamide as initial ARI treatment was associated with significantly lower risks of discontinuation and progression to metastatic CRPC compared with enzalutamide and apalutamide, even after adjusting for patient baseline characteristics.

Meaning These findings suggest that darolutamide has a better tolerability profile compared with enzalutamide and apalutamide, which may be associated with an effectiveness advantage in routine clinical practice in men with nmCRPC.

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this large cohort study of patients with nmCRPC treated with novel ARIs, results suggest better tolerability for darolutamide compared with enzalutamide and apalutamide, which may be associated with a clinical effectiveness advantage. Comparative clinical studies are needed to guide treatment decisions in the absence of head-to-head clinical trials.

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Introduction

Castration resistance is a lethal disease state for prostate cancer and consists of both metastatic and nonmetastatic stages.[1,2] For patients who develop nonmetastatic castration-resistant prostate cancer (nmCRPC), 3 novel androgen receptor inhibitors (ARIs; darolutamide, enzalutamide, and apalutamide) are approved standard-of-care treatment options[3] based on randomized, double-blinded, placebo-controlled clinical trials demonstrating improved metastasis-free and overall survival.[3-8] However, nmCRPC usually develops in older men with significant prior exposure to androgen deprivation therapy, potentially increasing patient frailty beyond physiologic age.[9] Consequently, treatment discontinuations among patients receiving ARIs are common due to adverse events (AEs) (eTable 1 in Supplement 1), with discontinuation rates due to AEs in pivotal phase 3 trials ranging from 9% to 17% in treatment groups compared with 7% to 9% in placebo groups.[4,7,8]

Since regulatory approvals of ARIs in 2019, scant data are available to describe the use and tolerability profiles of the 3 ARIs in clinical practice. In the absence of head-to-head randomized clinical trials, comparative clinical experience can inform expectations and treatment choice for clinicians managing a broad spectrum of patients, who may differ from clinical trial participants. Herein, we describe, to our knowledge, the first large, retrospective cohort study using electronic medical records (EMRs) to compare treatment use and clinical outcomes for the 3 ARIs indicated for nmCRPC.

Methods

Study Design

DEAR (Darolutamide, Enzalutamide, and Apalutamide in Nonmetastatic Castration-Resistant Prostate Cancer [NCT05362149]) is a retrospective cohort study reviewing EMRs from the Precision Point Specialty (PPS) network of urology practices in the US. Additional information about PPS can be found in eMethods in Supplement 1.

The study population included 3 cohorts, defined according to the first ARI (darolutamide, enzalutamide, or apalutamide) prescribed for nmCRPC. The index date was defined as the initiation date of the first ARI treatment (eFigure 1 in Supplement 1). Patient demographic and clinical characteristics were collected during the baseline period (≥6 months before the index date). Outcomes were evaluated during a follow-up period of at least 6 months (unless patients died earlier), starting from the index date until last date of EMR activity, end of study period, or death, whichever occurred first.

The study protocol was approved by the Advarra Institutional Review Board. This report adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This retrospective data analysis used anonymized data, ensuring patients could not be reidentified; therefore, the Advarra Institutional Review Board did not require informed consent.

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Patients

Eligible patients were men 18 years or older at the index date who started treatment with darolutamide, enzalutamide, or apalutamide for the first time between August 1, 2019 (when all 3 ARIs were available in the US market), and March 31, 2022 (eFigure 1 in Supplement 1), and had evidence of nmCRPC before the index date. Diagnosis of CRPC was defined per the castration-resistance flag set by PPS as the earliest date of (1) 2 consecutive rises in prostate-specific antigen (PSA) levels more than 6 months after orchiectomy or while undergoing continuous luteinizing hormone–releasing hormone therapy for more than 6 months; (2) the presence of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, diagnosis code Z19.2 (hormone-refractory malignant status) in conjunction with C61 (malignant neoplasm of prostate); or (3) manual entry of CRPC in the patient's EMR or parsable encounter note. Patients were excluded if they had any of the following: evidence of metastatic disease before or up to 30 days after the index date (to ensure nmCRPC status at ARI initiation); history of other primary cancers, except nonmelanoma skin cancer, within 5 years before the index date; or evidence of inclusion in clinical trials during the study period.

Outcomes

A composite end point of ARI discontinuation or progression to metastatic CRPC (mCRPC) was used to evaluate use of initial ARI treatment strictly during the nonmetastatic disease stage. This end point was determined as the earliest occurrence of any of the following: evidence of stopping initial ARI treatment, switch to another ARI, diagnosis of mCRPC, drug treatment initiated specifically for mCRPC (ie, abiraterone acetate, docetaxel, cabazitaxel, sipuleucel-T, mitoxantrone hydrochloride, radium RA 223 dichloride), or death.

Discontinuation of ARI therapy was also assessed as a separate end point, regardless of disease progression, as the earliest occurrence of initial ARI treatment stop, switch to another ARI, or death. The separate end point of progression to mCRPC was defined as the earliest evidence of diagnosis of mCRPC or drug treatment initiated specifically for mCRPC, as noted previously. Other outcomes included reasons for discontinuation of initial ARI treatment (obtained through manual EMR review), incidence of AEs (recorded in patient EMR during initial ARI treatment and ≤30 days after discontinuation), and AEs of special interest (fatigue, falls, fractures, rash, cognitive and memory impairment, and hypertension).

Statistical Analysis

All statistical analyses were performed in SAS, version 9.4 (TS1M7; SAS Institute, Inc) using deidentified data without access to patients' personal identifying information. Data were analyzed from February 1, 2019, to December 31, 2022.

Counts and percentages were calculated for each cohort to describe baseline categorical variables and the frequency of each end point during the follow-up period; median, range, mean, and SD values were calculated for continuous variables. Statistically significant differences among the 3 cohorts were checked by χ^2 tests for categorical variables, 1-way analysis of variance parametric comparisons of means for continuous variables, and 2-sided Wilcoxon-Mann-Whitney test for nonparametric comparisons of medians for continuous variables with skewed distributions. *P* values should be interpreted in the context of a descriptive analysis; 2-sided $P < .05$ indicated statistical significance.

Kaplan-Meier estimates of times to composite end point, ARI therapy discontinuation, and progression to mCRPC were calculated. Cox proportional hazards regression models were used to assess the association between treatment and outcomes, after controlling for the following observed factors (covariates): age group at index date (≤74, 75-84, or ≥85 years), self-reported race or ethnicity (Black or African American, White, or other or unknown [including American Indian or Alaska Native, Asian, Hispanic or Latino, other, and not reported]), insurance coverage (commercial or public), index period (2019-2020 or 2021-2022), time from nmCRPC diagnosis to index date

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(months), baseline PSA group (<2, 2 to <10, or ≥10 ng/mL [to convert to µg/L, multiply by 1.0]), baseline PSA doubling time (PSADT) group (≤6, >6 to ≤10, or >10 months or missing), and Gleason score at initial prostate cancer diagnosis (4-7, 8-10, or missing). These covariates were included in the model because they have been known to be associated with treatment assignment and outcomes. Baseline PSA level was the value recorded closest to the index date, and baseline PSADT was calculated using the Sloan Kettering method,[10] based on at least 3 PSA values of 0.2 ng/mL or greater taken at least 1 month apart within 12 months before the index date; PSADT values of greater than 100 months were capped at 100. Patients with missing values for insurance coverage and baseline PSA level were excluded from the multivariate models; missing PSADT values and Gleason scores were used as separate categories to handle the relatively higher proportion of missing values. Hazard ratios (HRs) and 95% CIs were reported for key cohort comparisons. Percentage of risk reduction was calculated as 100 × (1 − HR), using the HR for each cohort comparison. A significant risk reduction was suggested when both HR 95% CI limits were less than 1.00. Inverse probability of treatment weighting (IPTW) sensitivity analyses were performed for the separate outcomes, ARI discontinuation and progression to mCRPC, using propensity scores to weight patients, as described in eMethods in Supplement 1.

Results

Patients

All 870 eligible patients with nmCRPC found in the PPS network database were included in the analysis (eFigure 2 in Supplement 1). Of these patients, 362 (41.6%) initiated ARI treatment with darolutamide; 382 (43.9%), with enzalutamide; and 126 (14.5%), with apalutamide.

Demographic and baseline characteristics and duration of follow-up were relatively similar across the 3 cohorts (**Table**). Mean (SD) age was 78.8 (8.7) years. In terms of race and ethnicity, 187 patients (21.5%) self-identified as Black or African American; 585 (67.2%), as White; and 98 (11.3%), as other or unknown. Two hundred twenty-three patients (25.6%) had commercial insurance. Almost all patients (835 [96.0%]) started treatment at the approved ARI dose. Median time from nmCRPC diagnosis to the index date varied between 3.4 (range, 0-130.0) and 6.5 (range, 0-131.2) months for the 3 cohorts. Statistically significant differences were only found for the index period (more patients initiating enzalutamide therapy in the first 2 years compared with the other cohorts) and PSADT group (more patients initiating enzalutamide had a missing PSADT). Follow-up from the index date to the time of data cutoff was similar between treatment cohorts (median, 22.2 [range, 2.2-40.3] to 23.3 [range, 2.6-41.7] months).

Composite End Point of ARI Discontinuation or Progression to mCRPC

The proportion of patients with the composite end point of ARI discontinuation or progression to mCRPC was greater than 15 percentage points lower for darolutamide (134 [37.0%]) compared with enzalutamide (201 [52.6%]) and apalutamide (66 [52.4%]). Based on Kaplan-Meier estimates, darolutamide treatment was associated with a longer time to the composite end point than enzalutamide or apalutamide (**Figure 1**A). The unadjusted Cox proportional hazards regression models suggested a significantly lower risk of meeting the composite end point associated with darolutamide (Figure 1B). After adjusting for baseline covariates, darolutamide was associated with a lower risk of meeting the composite end point compared with enzalutamide (risk reduction, 33.8%; HR, 0.66 [95% CI, 0.53-0.84]) and apalutamide (risk reduction, 35.1%; HR, 0.65 [95% CI, 0.48-0.88]). There was no difference between enzalutamide and apalutamide in adjusted and unadjusted analyses of the composite end point (HRs, 0.97 [95% CI, 0.73-1.29] and 0.98 [95% CI, 0.73-1.31], respectively).

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Table. Patient Demographic and Baseline Characteristics

Characteristic	ARI treatment cohort[a]			*P* value[b]
	Darolutamide (n = 362)	Enzalutamide (n = 382)	Apalutamide (n = 126)	
Age, y				
Median (range)	80 (53-98)	79 (55-99)	80 (52-96)	.77
Mean (SD)	79.0 (8.5)	78.6 (8.9)	79.2 (8.8)	
Age group, y				
≤74	109 (30.1)	118 (30.9)	36 (28.6)	.99
75-84	154 (42.5)	160 (41.9)	56 (44.4)	
≥85	99 (27.3)	104 (27.2)	34 (27.0)	
Race and ethnicity				
Black or African American	80 (22.1)	82 (21.5)	25 (19.8)	.36
White	238 (65.7)	254 (66.5)	93 (73.8)	
Other or unknown[c]	44 (12.2)	46 (12.0)	8 (6.3)	
Insurance coverage				
Commercial	103 (28.5)	88 (23.0)	32 (25.4)	.07
Public	247 (68.2)	287 (75.1)	94 (74.6)	
Unknown	12 (3.3)	7 (1.8)	0	
Index period				
2019-2020	203 (56.1)	255 (66.8)	73 (57.9)	.009
2021-2022	159 (43.9)	127 (33.2)	53 (42.1)	
Time from nmCRPC to index date, mo				
Median (range)	5.3 (0-247.9)	3.4 (0-130.0)	6.5 (0-131.2)	.08
Mean (SD)	14.8 (24.6)	13.3 (22.2)	14.9 (21.5)	
Patients starting at approved ARI dose[d]				
Yes	351 (97.0)	360 (94.2)	124 (98.4)	.05
No	11 (3.0)	22 (5.8)	2 (1.6)	
PSA level, ng/mL[e]				
Median (range)	3.3 (0-321.4)	3.6 (0-417.0)	3.4 (0-114.2)	.85
Mean (SD)	9.4 (24.9)	12.4 (38.5)	8.7 (16.8)	
PSA group, ng/mL[e]				
<2.0	127 (35.1)	134 (35.1)	47 (37.3)	.17
≥2.0 and <10.0	148 (40.9)	135 (35.3)	48 (38.1)	
≥10.0	65 (18.0)	76 (19.9)	27 (21.4)	
Missing	22 (6.1)	37 (9.7)	4 (3.2)	
PSADT, mo[f]				
Median (range)	6.8 (0-100.0)	6.4 (0.6-100.0)	7.4 (1.2-100.0)	.19
Mean (SD)	9.9 (11.3)	13.4 (21.4)	11.8 (17.2)	
PSADT group, mo[f]				
≤6	120 (33.1)	119 (31.2)	37 (29.4)	.02
>6 and ≤10	64 (17.7)	51 (13.4)	31 (24.6)	
>10	85 (23.5)	81 (21.2)	28 (22.2)	
Missing	93 (25.7)	131 (34.3)	30 (23.8)	
Gleason score at initial PC diagnosis[g]				
4-7	161 (44.5)	139 (36.4)	45 (35.7)	.08
8-10	133 (36.7)	153 (40.1)	58 (46.0)	
Missing	68 (18.8)	90 (23.6)	23 (18.3)	
Follow-up, mo				
Median (range)	22.2 (2.2-40.3)	22.7 (0.9-41.5)	23.3 (2.6-41.7)	.80
Mean (SD)	22.8 (8.7)	23.1 (10.2)	23.5 (10.9)	

Abbreviations: ARI, androgen receptor inhibitor; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

SI conversion factor: To convert PSA to µg/L, multiply by 1.0.

[a] Unless otherwise indicated, data are expressed as No. (%) of patients. Percentages have been rounded and may not total 100.

[b] Statistically significant differences among the 3 treatment cohorts were checked by χ^2 tests for categorical variables and 1-way analysis of variance parametric comparisons for continuous variables. Nonparametric tests (Wilcoxon-Mann-Whitney) were used to compare median values across the 3 cohorts for continuous variables with a highly skewed distribution (PSA level, PSADT, and time from nmCRPC to index date).

[c] Includes self-reported American Indian or Alaska Native, Asian, Hispanic or Latino, other race, and not reported.

[d] Indicates 1200 mg for darolutamide, 160 mg for enzalutamide, and 240 mg for apalutamide.

[e] Indicates value closest to index date (340 patients for darolutamide, 345 for enzalutamide, and 122 for apalutamide).

[f] Calculated using the Sloan Kettering method, which is based on at least 3 PSA values of at least 0.2 ng/mL taken at least 1 month apart, within the 12 months prior to index date (269 patients for darolutamide, 251 for enzalutamide, and 96 for apalutamide). Values after 100 months were capped at 100 for 13 patients.

[g] Higher scores indicate higher cancer grade.

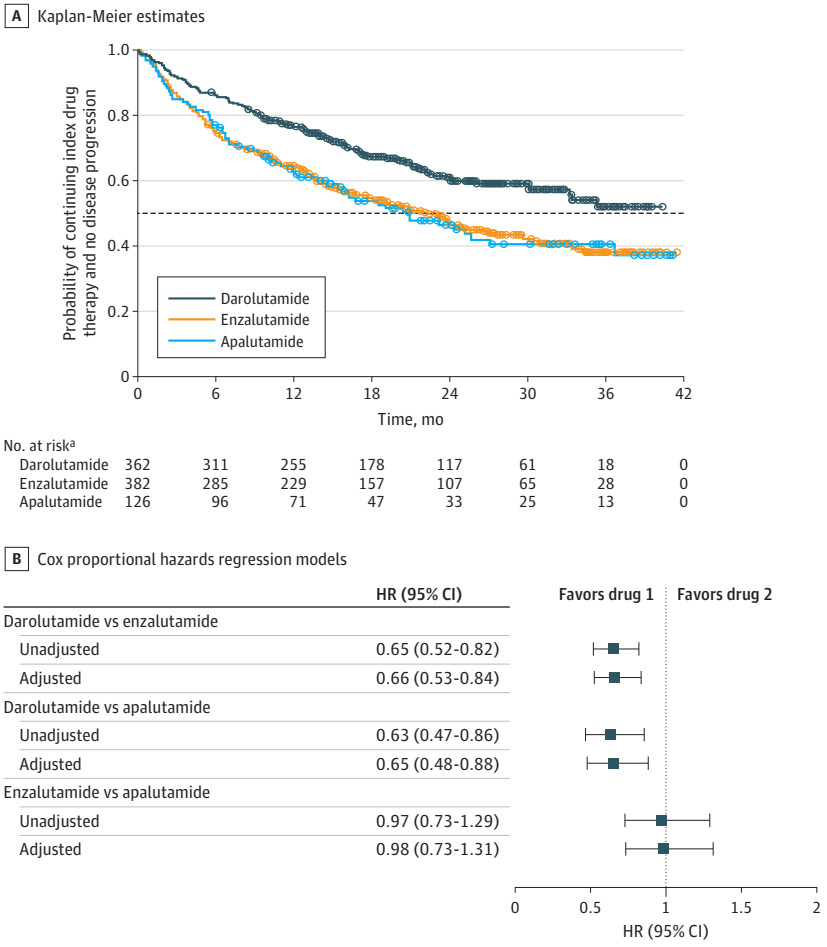
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Discontinuation of ARI Therapy

When analyzing ARI therapy discontinuations separately, darolutamide was associated with a 10.4% lower rate (110 [30.4%]) compared with enzalutamide (156 [40.8%]) and a 15.6% lower rate compared with apalutamide (58 [46.0%]). Based on Kaplan-Meier estimates, darolutamide was associated with longer treatment duration vs enzalutamide and apalutamide (**Figure 2**A). The unadjusted Cox proportional hazards regression model suggested a significantly lower treatment discontinuation risk associated with darolutamide (Figure 2B). After adjusting for baseline covariates, darolutamide was associated with a lower risk of discontinuation vs enzalutamide (risk reduction, 27.4%; HR, 0.73 [95% CI, 0.56-0.94]) and apalutamide (risk reduction, 39.1%; HR, 0.61 [95% CI, 0.44-0.85]). There was no difference in ARI therapy discontinuation between enzalutamide and apalutamide in the unadjusted and adjusted analyses (HRs, 0.82 [95% CI, 0.60-1.11] and 0.84 [95% CI, 0.61-1.15], respectively). Apart from treatment with darolutamide, characteristics associated with a lower discontinuation risk included younger age, Black or African American race, and PSA level of less than 2 ng/mL (eFigure 3 in Supplement 1).

The 2 most commonly documented reasons for ARI therapy discontinuation indicated by physicians in patient EMRs were AEs (darolutamide, 37 [10.2%]; enzalutamide, 55 [14.4%]; apalutamide, 19 [15.1%]) and progression to mCRPC or death (darolutamide, 30 [8.3%]; enzalutamide, 46 [12.0%]; apalutamide, 17 [13.5%]) (**Figure 3**). Many patients continued receiving

Figure 1. Composite End Point of Time to Initial Androgen Receptor Inhibitor (ARI) Therapy Discontinuation or Progression to Metastatic Castration-Resistant Prostate Cancer (mCRPC)



Composite end point was defined as the earliest occurrence of evidence of stopping initial ARI treatment, switch to another ARI, evidence of metastatic lesion(s), diagnosis of mCRPC, drug treatment initiated specifically for mCRPC (ie, abiraterone acetate, docetaxel, cabazitaxel, sipuleucel-T, mitoxantrone hydrochloride, or radium RA 223 dichloride), or death. The dashed line indicates posterior probability of 0.5. A total of 791 patients (328 receiving darolutamide, 341 receiving enzalutamide, and 122 receiving apalutamide) were included in the Cox proportional hazards regression model after excluding 79 patients with unknown insurance coverage and/or missing baseline prostate-specific antigen (PSA) values. The following observed baseline characteristics were included in the adjusted Cox proportional hazards regression models: age group at index (≤74, 75-84, or ≥85 years), race (Black or African American, White, or other or unknown), insurance coverage (commercial or public), index period (2019-2020 or 2021-2022), baseline PSA group (<2, 2 to <10, or ≥10 ng/mL), baseline PSA doubling time group (≤6, >6 to ≤10, or >10 months or missing), time from non-mCRPC diagnosis to index date (months), and Gleason score at initial prostate cancer diagnosis (4-7, 8-10, or missing). HR indicates hazard ratio.

[a] Numbers of patients at risk were calculated at the start of each time point.

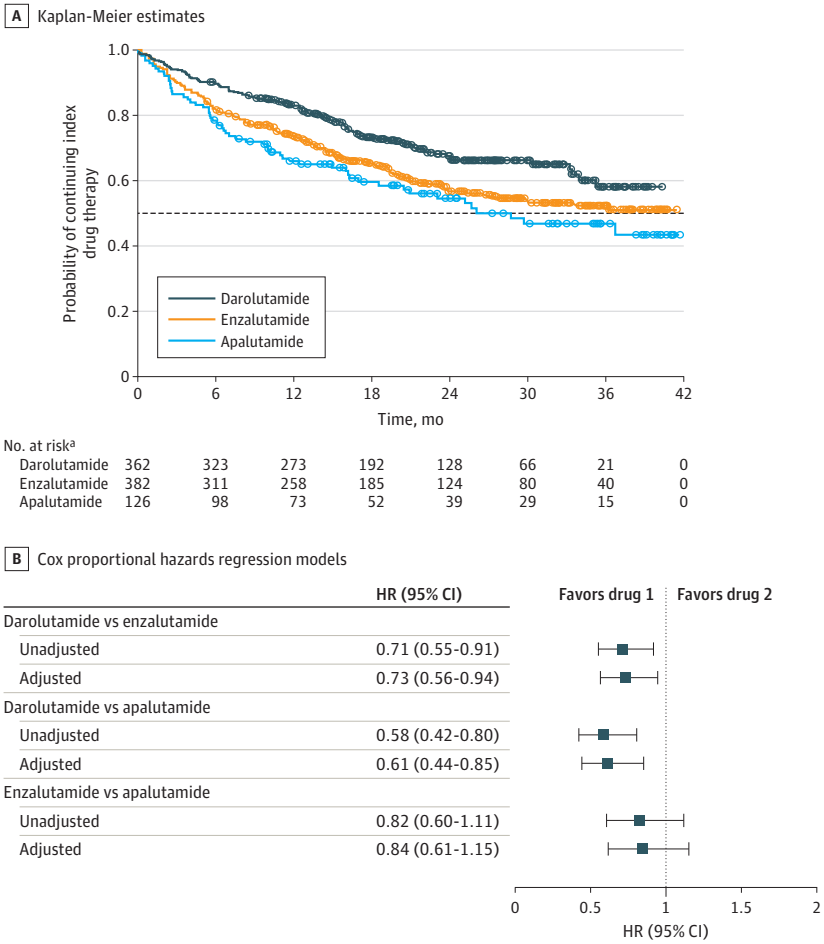
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their initial ARI treatment for 30 days or more after progression to mCRPC was recorded (darolutamide, 38 [59.4%]; enzalutamide, 70 [64.8%]; apalutamide, 17 [48.6%]).

Progression to mCRPC

The proportion of patients who progressed to mCRPC was more than 10 percentage points lower for darolutamide (64 [17.7%]) compared with enzalutamide (108 [28.3%]) and apalutamide (35 [27.8%]). Based on Kaplan-Meier estimates, darolutamide was associated with a longer time to progression to mCRPC compared with enzalutamide and apalutamide (**Figure 4**A). The unadjusted Cox proportional hazards regression models suggested a significantly lower risk of disease progression associated with darolutamide (Figure 4B). After adjusting for baseline covariates, darolutamide was associated with a lower risk of disease progression compared with enzalutamide (risk reduction, 40.6%; HR, 0.59 [95% CI, 0.43-0.82]) and apalutamide (risk reduction, 35.3%; HR, 0.65 [95% CI, 0.42-0.99]). There was no difference between enzalutamide and apalutamide in the unadjusted and adjusted analyses (HRs, 1.05 [95% CI, 0.71-1.56] and 1.09 [95% CI, 0.73-1.63], respectively). Apart from treatment with darolutamide, characteristics associated with a lower progression risk included Black or African American race, PSA level of less than 2 ng/mL, and PSADT of greater than 10 months (eFigure 4 in Supplement 1).

Figure 2. Time to Initial Androgen Receptor Inhibitor (ARI) Therapy Discontinuation



Discontinuation of initial ARI treatment was defined as the earliest occurrence of stopping initial ARI treatment, switch to another ARI, or death. The dashed line indicates posterior probability of 0.5. A total of 791 patients (328 receiving darolutamide, 341 receiving enzalutamide, and 122 receiving apalutamide) were included in the Cox proportional hazards regression model after excluding 79 patients with unknown insurance coverage and/or missing baseline prostate-specific antigen (PSA) values. The following observed baseline characteristics were included in the adjusted Cox proportional hazards regression models: age group at index (≤74, 75-84, or ≥85 years), race (Black or African American, White, or other or unknown), insurance coverage (commercial or public), index period (2019-2020 or 2021-2022), baseline PSA group (<2, 2 to <10, or ≥10 ng/mL), baseline PSA doubling time group (≤6, >6 to ≤10, or >10 months or missing), time from non-mCRPC diagnosis to index date (months), and Gleason score at initial prostate cancer diagnosis (4-7, 8-10, or missing).

[a] Numbers of patients at risk were calculated at the start of each time point.

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Incidence of AEs and AEs of Special Interest

At least 1 AE was found in the EMRs for 90 patients (24.9%) receiving darolutamide, 112 (29.3%) receiving enzalutamide, and 38 (30.2%) receiving apalutamide, while AEs of special interest were recorded in 54 patients (14.9%) receiving darolutamide, 67 (17.5%) receiving enzalutamide, and 28 (22.2%) receiving apalutamide (eTable 2 in Supplement 1). Fatigue was the most common AE of special interest, reported in 41 patients (11.3%) receiving darolutamide, 53 (13.9%) receiving enzalutamide, and 14 (11.1%) receiving apalutamide. The only other AE of interest occurring in at least 3% of patients across cohorts was rash (reported more frequently for apalutamide in 10 patients [7.9%]).

Sensitivity Analyses

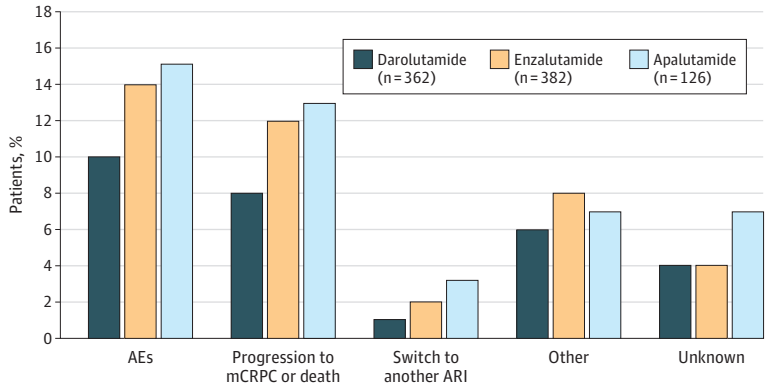
The IPTW analysis (eMethods in Supplement 1) of ARI therapy discontinuation confirmed a significantly lower risk of discontinuation associated with darolutamide compared with enzalutamide (risk reduction, 25.5%; HR, 0.75 [95% CI, 0.58-0.96]) and apalutamide (risk reduction, 37.0%; HR, 0.63 [95% CI, 0.46-0.87]) (eFigure 5A in Supplement 1). Similarly, the IPTW analysis of disease progression showed that darolutamide was associated with a lower risk of progression to mCRPC compared with enzalutamide (risk reduction, 39.6%; HR, 0.60 [95% CI, 0.44-0.83]) and apalutamide (risk reduction, 31.9%; HR, 0.68 [95% CI, 0.44-1.04]). The only HR 95% CI to include 1 was for the darolutamide vs apalutamide IPTW comparison of progression to mCRPC (eFigure 5B in Supplement 1).

Discussion

To our knowledge, DEAR is the first large cohort study of patients with nmCRPC treated with an approved ARI, using the same method (retrospective EMR review) and data source (PPS urology network) to assess and compare treatment discontinuation and underlying reasons, progression to mCRPC, and incidence of AEs in routine clinical practice. An established, representative network of urology practices, PPS represents approximately 80% of US community urologists. The study sample is relatively large (N = 870) and includes all patients meeting the eligibility criteria, irrespective of which ARI treatment was first initiated for nmCRPC. A recent retrospective study[11] also assessed treatment discontinuation and underlying reasons for the 3 ARIs, but darolutamide was underrepresented (n = 10) and the study did not assess time to disease progression or incidence of AEs.

A 2020 meta-analysis of phase 3 trial data[12] showed a more favorable tolerability profile for darolutamide vs enzalutamide and apalutamide. Darolutamide had a similar rate of discontinuation due to AEs vs placebo, whereas enzalutamide and apalutamide were associated with higher rates of

Figure 3. Reasons for Initial Androgen Receptor Inhibitor (ARI) Therapy Discontinuation as Assessed by the Treating Physician



All percentages are rounded to the nearest integer. Other includes additional miscellaneous reasons, such as cost, physician decision, patient decision or withdrawal, rise in prostate-specific antigen level, and moved to oncology practice. AE indicates adverse event; mCRPC, metastatic castration-resistant prostate cancer.

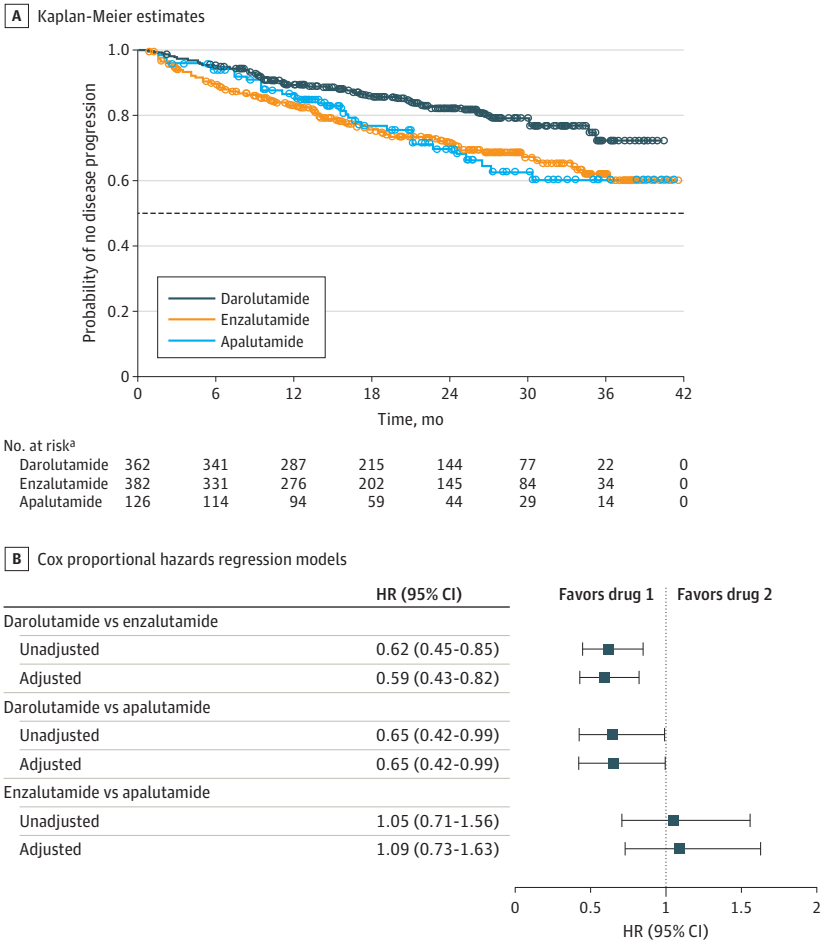
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discontinuation than placebo. In the open-label extension of the pivotal darolutamide trial in nmCRPC, approximately one-third of patients continued taking darolutamide for more than 4 years, suggesting tolerability and long-term clinical benefit; furthermore, the safety profile of darolutamide remained favorable over time.[13]

In DEAR, observed baseline patient characteristics were similar across cohorts. Moreover, median follow-up (range, 22.2-23.3 months) was consistent between cohorts, allowing for robust outcome comparisons across ARIs. The main end point was the composite event of ARI discontinuation or progression to mCRPC, whichever occurred first, to evaluate treatment use strictly during the nmCRPC stage. This end point demonstrated the greatest difference between ARIs favoring darolutamide (>15% lower rate vs both enzalutamide and apalutamide). Of note, most patients meeting criteria for progression to mCRPC continued to receive their initial ARI for at least 30 days after the recorded progression date; hence, results were also presented for discontinuation and progression as separate end points.

The discontinuation rate for darolutamide therapy was 10.4% lower than enzalutamide and 15.6% lower than apalutamide, suggesting potentially better tolerability for darolutamide. Consistent differences (>10%) were also found between the rate of progression to mCRPC for darolutamide vs the other cohorts. The Kaplan-Meier curves for both end points suggest a separation of darolutamide vs enzalutamide as early as 6 months from treatment initiation and continuing throughout the follow-up period. A similar result was observed for discontinuation of darolutamide vs apalutamide therapy, whereas the progression to mCRPC curves separated at 12 months. This observed delay in

Figure 4. Time to Progression to Metastatic Castration-Resistant Prostate Cancer (mCRPC)



Progression to mCRPC was defined as the earliest occurrence of a clear diagnosis of mCRPC, evidence of metastasis in patient medical records or radiology reports, or drug treatment initiated specifically for mCRPC (ie, abiraterone acetate, docetaxel, cabazitaxel, sipuleucel-T, mitoxantrone hydrochloride, or radium RA 223 dichloride). The dashed line indicates posterior probability of 0.5. A total of 791 patients (328 receiving darolutamide, 341 receiving enzalutamide, and 122 receiving apalutamide) were included in the Cox proportional hazards regression model after excluding 79 patients with unknown insurance coverage and/or missing baseline prostate-specific antigen (PSA) values. The following observed baseline characteristics were included in the adjusted Cox proportional hazards regression models: age group at index (≤74, 75-84, or ≥85 years), race (Black or African American, White, or other or unknown), insurance coverage (commercial or public), index period (2019-2020 or 2021-2022), baseline PSA group (<2, 2 to <10, or ≥10 ng/mL), baseline PSA doubling time group (≤6, >6 to ≤10, or >10 months or missing), time from non-mCRPC diagnosis to index date (months), and Gleason score at initial prostate cancer diagnosis (4-7, 8-10, or missing).

[a] Numbers of patients at risk were calculated at the start of each time point.

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separation for progression to mCRPC may be associated with the delayed onset of progressive disease, which does not occur immediately following treatment cessation.

Although a causal link cannot be established between the better tolerability profile of darolutamide and its clinical effectiveness advantage compared with enzalutamide and apalutamide, this association was observed across multiple outcomes and appears consistent. Because the 3 ARIs demonstrated similar efficacy in their respective phase 3 trials, extended treatment durations in clinical practice may confer a benefit in delaying mCRPC progression.

The observed frequencies of overall treatment discontinuation and discontinuation due to AEs in DEAR are higher than those reported in phase 3 trials for all 3 ARIs.[4-6] One difference is the older age (median of 78.8 years in DEAR vs 73-74 years in clinical trials[4,6,7]) of patients with nmCRPC in routine clinical practice; these patients may have more frailty and relatively lower tolerance for therapy. Furthermore, clinical trials are protocol driven with rigorously monitored patients, which may lead to fewer treatment discontinuations compared with routine medication use. These differences highlight the complementary nature of clinical studies and clinical trials and underscore the need for robust comparative real-world evidence.

DEAR results also largely align with those of other observational studies investigating these ARIs. A retrospective medical record review study in patients with nmCRPC[14] found that the most common reasons for discontinuation of enzalutamide or apalutamide therapy were disease progression and AEs. Results from an interim analysis of a prospective study investigating the clinical safety of darolutamide in patients with nmCRPC (DAROL [Darolutamide Observational Study])[15] found a 37% AE rate for darolutamide, which is higher than that observed in DEAR (24.9%).[16]

While DEAR adjusted for observed differences in baseline characteristics between cohorts, unobserved confounding factors may also affect treatment duration and clinical outcomes in the absence of randomization. For example, EMR data may not contain detailed information on comorbidities and treatments not related to prostate cancer and, as such, drug interactions are difficult to assess.

Limitations

This study has some limitations. In contrast to clinical trial efficacy data that depend on rigorous radiologic assessments of tumor progression, treatment effectiveness in PPS was estimated using routine disease progression assessment data from structured and unstructured patient records. Such events may not be recorded promptly and accurately in patient records, there is no blinded independent review, follow-up is usually shorter, and assessments such as laboratory tests and imaging studies are not standardized. It is therefore possible that certain progression events (as assessed in DEAR) were not identified correctly or at their earliest occurrence. However, this limitation is inherent to clinical studies and not unique to this analysis. Another limitation is the possibility of incomplete safety data collection, with retrospective analyses using EMR commonly associated with lower AE rates due to underreporting by patients and clinicians.[17] However, limitations related to the mismeasurement or missingness of study variables would only impact results to the extent that treatment cohorts were affected differently, which appears unlikely given the balance of patient characteristics across cohorts in this study.

While patients seen in academic urology or oncology clinics may have a different profile prior to ARI initiation, most patients with nmCRPC in the US are treated by urologists on an outpatient basis. The DEAR population included all eligible patients with nmCRPC treated with ARIs in a large network of community urology clinics, representing a large portion of the target US population with nmCRPC.

Conclusions

Despite limitations inherent to retrospective data collection, DEAR is the first large cohort study, to our knowledge, to use a single data source to assess prescription of all 3 ARIs approved for nmCRPC in routine clinical practice. Results suggest darolutamide is associated with longer treatment duration and time to progression to mCRPC compared with enzalutamide and apalutamide in a routine care

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setting, while no differences in either outcome were found between enzalutamide and apalutamide. The most common reasons for discontinuation (AEs, disease progression, and death) were numerically less frequent with darolutamide. Further studies are needed to confirm these results in different health care settings and geographies, using data sources linked with mortality statistics, and following up patients for longer periods. In the absence of head-to-head randomized clinical trials, comparative medical record review cohort studies like DEAR are needed to guide treatment decisions by clinicians faced with a difficult selection among medications with similar clinical trial efficacy.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: All authors.

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Data Sharing Statement: See Supplement 2.

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SUPPLEMENT 1.

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eTable 1. Discontinuation Rates Due to AEs in Clinical Trials and Observational Studies of the 3 ARIs
eTable 2. Frequency of All AEs and AEs of Special Interest
eFigure 1. Study Design
eFigure 2. Patient Attrition
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eFigure 5. IPTW Sensitivity Analyses for (A) Time to Initial ARI Discontinuation and (B) Time to Progression to mCRPC
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SUPPLEMENT 2.
Data Sharing Statement

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