Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Data Source and Additional Statistical Methods

Data Source. Approximately 4,000 urologists from >700 urology group practices participate in the Precision Point Specialty (PPS) network, which corresponds to \approx 80% of all US private community urologists. Additionally, the PPS network contains >35 electronic medical record, practice management, radiology-oncology, and dispensing systems from commercially insured patients, self-paid patients, and those with Medicare or Medicaid coverage, and has been frequently used in retrospective data analyses in the prostate cancer setting.¹⁻³

Additional Statistical Methods

Sensitivity analyses were performed using a propensity score–based inverse probability of treatment weighting (IPTW) method adjusting for: age group at index (\leq 74, 75-84, \geq 85 years), race (White, Black/African American, other/unknown), insurance coverage (commercial, public), index period (2019-2020, 2021-2022), baseline prostate-specific antigen (PSA) group (<2, 2-<10, \geq 10 ng/mL), baseline PSA doubling time (PSADT) group (\leq 6, >6- \leq 10, >10 months, missing), time from diagnosis of nmCRPC to index date (months), and Gleason score at initial prostate cancer diagnosis (4-7, 8-10, missing). A balance assessment was performed between the compared treatment cohorts calculating the absolute standardized mean difference (SMD) for each baseline characteristic, after propensity score weighting. Absolute SMD values <0.2 were considered indicative of a good balance of patient characteristics across treatment cohorts. Factors with SMD \geq 0.1 were included as separate covariates in the IPTW model, in addition to the cohort variable.

	Median follow-up (months)	Darolutamide	Enzalutamide	Apalutamide
Clinical trials				
ARAMIS ^₄	17.9	9% (vs 9% for placebo)	Not reported	Not reported
PROSPER⁵	Enzalutamide: 18.5; Placebo: 15.1	Not reported	17% (vs 9% for placebo)	Not reported
SPARTAN ⁶	20.3	Not reported	Not reported	15% (vs 9% for placebo)
Observational studies				
Hussain et al, 2022 ⁷	Enzalutamide: 12.0; Apalutamide: 14.4	Not reported	13%	8%
Gangwish et al, 2023 ⁸	12.0	10%	11%	17%
DAROL ⁹	14.8	6%	Not reported	Not reported

eTable 1. Discontinuation Rates Due to AEs in Clinical Trials and Observational Studies of the 3 ARIs

AE, adverse event; ARI, androgen receptor inhibitor.

eTable 2. Frequency of All AEs and AEs of Special Interest

	Darolutamide (n=362)	Enzalutamide (n=382)	Apalutamide (n=126)
Any AE,ª n (%)	90 (24.9)	112 (29.3)	38 (30.2)
AEs of special interest, n (%)	54 (14.9)	67 (17.5)	28 (22.2)
Fatigue	41 (11.3)	53 (13.9)	14 (11.1)
Rash	8 (2.2)	3 (0.8)	10 (7.9)
Cognitive and memory impairment	5 (1.4)	8 (2.1)	3 (2.4)
Fall	3 (0.8)	5 (1.3)	1 (0.8)
Hypertension	1 (0.3)	3 (0.8)	0
Fracture	0	0	0

AE, adverse event; ARI, androgen receptor inhibitor. ^aAEs recorded during each ARI treatment and up to 30 days after discontinuation. Some patients experienced multiple AEs.

eFigure 1. Study Design



Apa, apalutamide; ARI, androgen receptor inhibitor; Daro, darolutamide; EMR, electronic medical record; Enza, enzalutamide; nmCRPC, nonmetastatic castration-resistant prostate cancer.

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eFigure 2. Patient Attrition

Men diagnosed with prostate cancer anytime in history	N=1,073,150
+	
Evidence of CRPC diagnosis prior to or during the patient identification period	n=5,965 (0.6%)
+	
Treatment with ARI for the first time in patient identification period	n=2,329 (39.0%)
+	
Age ≥18 years at index date	n=2,329 (100.0%)
+	
Minimum 6-month baseline period and minimum of 6 months of follow-up, unless the patient died earlier	n=2,190 (94.0%)
+	
No evidence of metastatic disease prior to or within 30 days after the index date	n=2,066 (94.3%)
+	
No prior history of other primary cancers, except non-melanoma skin cancer, in the 5 years prior to baseline	n=1,689 (81.8%)
+	
No initiation of multiple ARIs recorded on the same date	n=1,677 (99.3%)
+	
No use of a NAH agent (darolutamide, enzalutamide, apalutamide or abiraterone acetate) before the index date	n=1,654 (98.6%)
+	
No evidence of inclusion in clinical trials during the study period	n=1,654 (100.0%)
+	
Patient charts reviewed by PPS	n=1,441 (87.1%)
571 (39.6%) patients excluded:	 Metastatic PC (n=365) Other (n=206)
Patients eligible per chart review n=870 (60	0.4%)
DarolutamideEnzalutamiden=362 (41.6%)n=382 (43.9%)	Apalutamide n=126 (14.5%)

ARI, androgen receptor inhibitor; CRPC, castration-resistant prostate cancer; NAH, novel antihormonal therapy; PC, prostate cancer; PPS, Precision Point Specialty.

eFigure 3. Hazard Ratio Estimates From Adjusted Cox Proportional Hazards Models for Time to Discontinuation of Initial

ARI Treatment

		Hazard ratio (95% CI)
Initial ARI treatment		
Darolutamide vs Enzalutamide		0.726 (0.561, 0.941)
Darolutamide vs Apalutamide		0.609 (0.438, 0.848)
Age (years) at index		
≤74 vs ≥85	┝──■──┤	0.724 (0.523, 1.003)
>74 and <85 vs ≥85		0.662 (0.504, 0.870)
Race		
Black vs White		0.683 (0.500, 0.933)
Other vs White		0.922 (0.627, 1.356)
Index year		
2021-2022 vs 2019-2020	<u>⊢_</u> ∎_;-i	0.839 (0.643, 1.095)
Insurance coverage		
Commercial vs public	⊢ ∎!	0.762 (0.575, 1.011)
Baseline PSA (ng/mL)		
<2 vs ≥10		0.522 (0.378, 0.720)
≥2 and <10 vs ≥10	⊢ = ji	0.783 (0.589, 1.041)
Baseline PSADT (months)		
>6 and ≤10 vs ≤6	<u>⊢;</u>	1.178 (0.837, 1.657)
>10 vs ≤6		0.814 (0.580, 1.143)
Missing vs ≤6	↓ ↓ ■ − − − 1	1.232 (0.912, 1.663)
Gleason score at initial PC diagnosis		
4-7 vs 8-10		0.820 (0.628, 1.071)
Missing vs 8-10		1.124 (0.834, 1.513)
Months from CRPC diagnosis to index da	te 🍦	0.999 (0.994, 1.005)
	0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.	0

ARI, androgen receptor inhibitor; CI, confidence interval; CRPC, castration-resistant prostate cancer; PC, prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

Discontinuation of initial ARI treatment was defined as the earliest occurrence of stopping initial ARI treatment, switch to another ARI, or death.

A total of 791 patients (darolutamide, n=328; enzalutamide, n=341; apalutamide, n=122) were included in the Cox proportional hazards model after excluding 79 patients with unknown insurance coverage and/or missing baseline PSA values.

eFigure 4. Hazard Ratio Estimates From Adjusted Cox Proportional Hazards Models for Time to Progression to mCRPC

		Hazard ratio (95% CI)
Initial ARI treatment		
Darolutamide vs Enzalutamide		0.594 (0.430, 0.822)
Darolutamide vs Apalutamide	⊢	0.647 (0.421, 0.994)
Age (years) at index		
≤74 vs ≥85		0.883 (0.586, 1.329)
>74 and <85 vs ≥85	F = ;	0.865 (0.608, 1.231)
Race		
Black vs White		0.606 (0.408, 0.902)
Other vs White		0.726 (0.434, 1.213)
Index year		
2021-2022 vs 2019-2020		1.283 (0.926, 1.778)
Insurance coverage		
Commercial vs public		0.946 (0.677, 1.322)
Baseline PSA (ng/mL)		
<2 vs ≥10		0.531 (0.354, 0.796)
≥2 and <10 vs ≥10		0.768 (0.535, 1.102)
Baseline PSADT (months)		
>6 and ≤10 vs ≤6		0.841 (0.557, 1.270)
>10 vs ≤6		0.441 (0.282, 0.689)
Missing vs ≤6	⊢ ■ i	0.727 (0.501, 1.054)
Gleason score at initial PC diagnosis		
4-7 vs 8-10	⊢	0.935 (0.676, 1.292)
Missing vs 8-10		0.809 (0.546, 1.197)
Months from CRPC diagnosis to index date	•	1.001 (0.994, 1.008)
		0
	0.0 0.2 0.4 0.0 0.0 1.0 1.2 1.4 1.0 1.6 2.	0

ARI, androgen receptor inhibitor; CI, confidence interval; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

Progression to mCRPC was defined as the earliest occurrence of a clear diagnosis of mCRPC, evidence of metastasis in patient charts or radiology reports, or drug treatment initiated specifically for mCRPC (ie, abiraterone acetate, docetaxel, cabazitaxel, sipuleucel-T, mitoxantrone, radium-223).

A total of 791 patients (darolutamide, n=328; enzalutamide, n=341; apalutamide, n=122) were included in the Cox proportional hazards model after excluding 79 patients with unknown insurance coverage and/or missing baseline PSA values.

eFigure 5. IPTW Sensitivity Analyses for (A) Time to Initial ARI Discontinuation and (B) Time to Progression to mCRPC



ARI, androgen receptor inhibitor; CI, confidence interval; IPTW, inverse probability of treatment weighting; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

Discontinuation of initial ARI treatment was defined as the earliest occurrence of stopping initial ARI treatment, switch to another ARI, or death.

A total of 791 patients (darolutamide, n=328; enzalutamide, n=341; apalutamide, n=122) were included in the Cox proportional hazards model after excluding 79 patients with unknown insurance coverage and/or missing baseline PSA values.

The following covariates were used in the balance assessment: age group at index (\leq 74, 75-84, \geq 85 years), race (White, Black/African American, other/unknown), insurance coverage (commercial, public), index period (2019-2020, 2021-2022), baseline PSA group (<2, 2-<10, \geq 10 ng/mL), baseline PSA doubling time group (\leq 6, >6- \leq 10, >10 months, missing), time from nmCRPC diagnosis to index date (months), and Gleason score at initial prostate cancer diagnosis (4-7, 8-10, missing).

Gleason score remained unbalanced after weighting and was therefore included as a separate covariate in the final IPTW mode.

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