# Supplementary Online Content

George DJ, Morgans AK, Constantinovici N, et al. Androgen receptor inhibitors in patients with nonmetastatic castration-resistant prostate cancer. *JAMA Netw Open*. 2024;7(8):e2429783. doi:10.1001/jamanetworkopen.2024.29783



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 ≈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 (≤74, 75-84, ≥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, ≥10 ng/mL), baseline PSA doubling time (PSADT) group (≤6, >6-≤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 ≥0.1 were included as separate covariates in the IPTW model, in addition to the cohort variable.

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

| | Median follow-up (months) | Darolutamide | Enzalutamide | Apalutamide |
|---|---|---|---|---|
| **Clinical trials** | | | | |
| ARAMIS[4] | 17.9 | 9% (vs 9% for placebo) | Not reported | Not reported |
| PROSPER[5] | 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 |

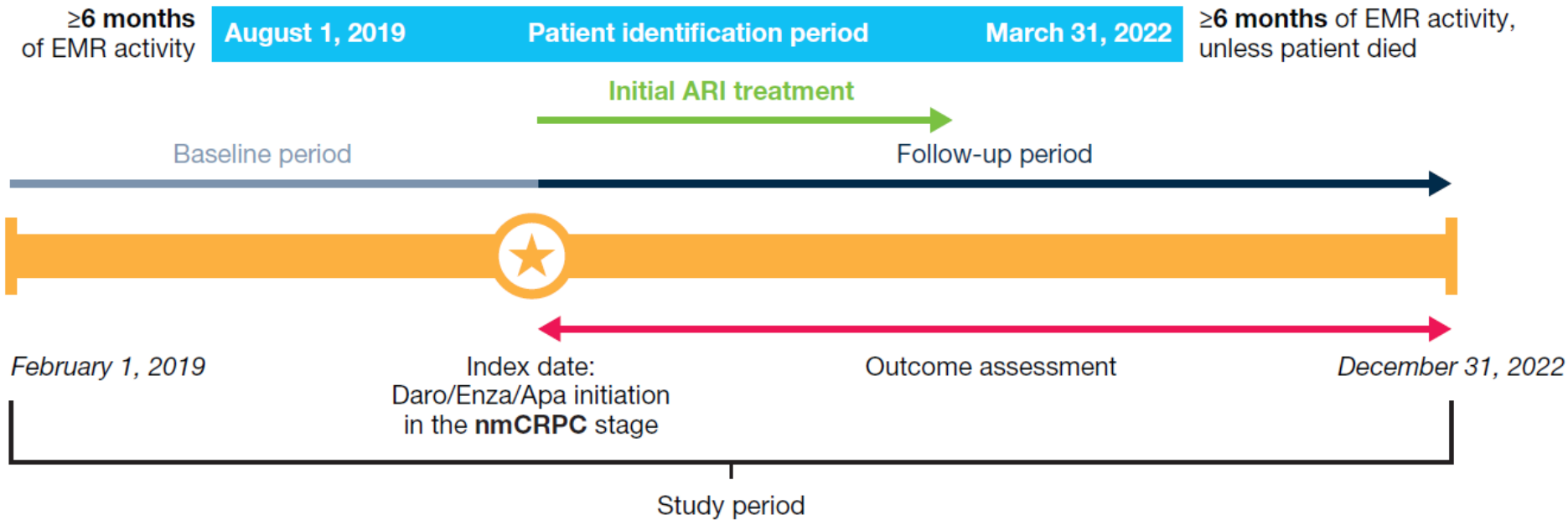
AE, adverse event; ARI, androgen receptor inhibitor.

**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 |

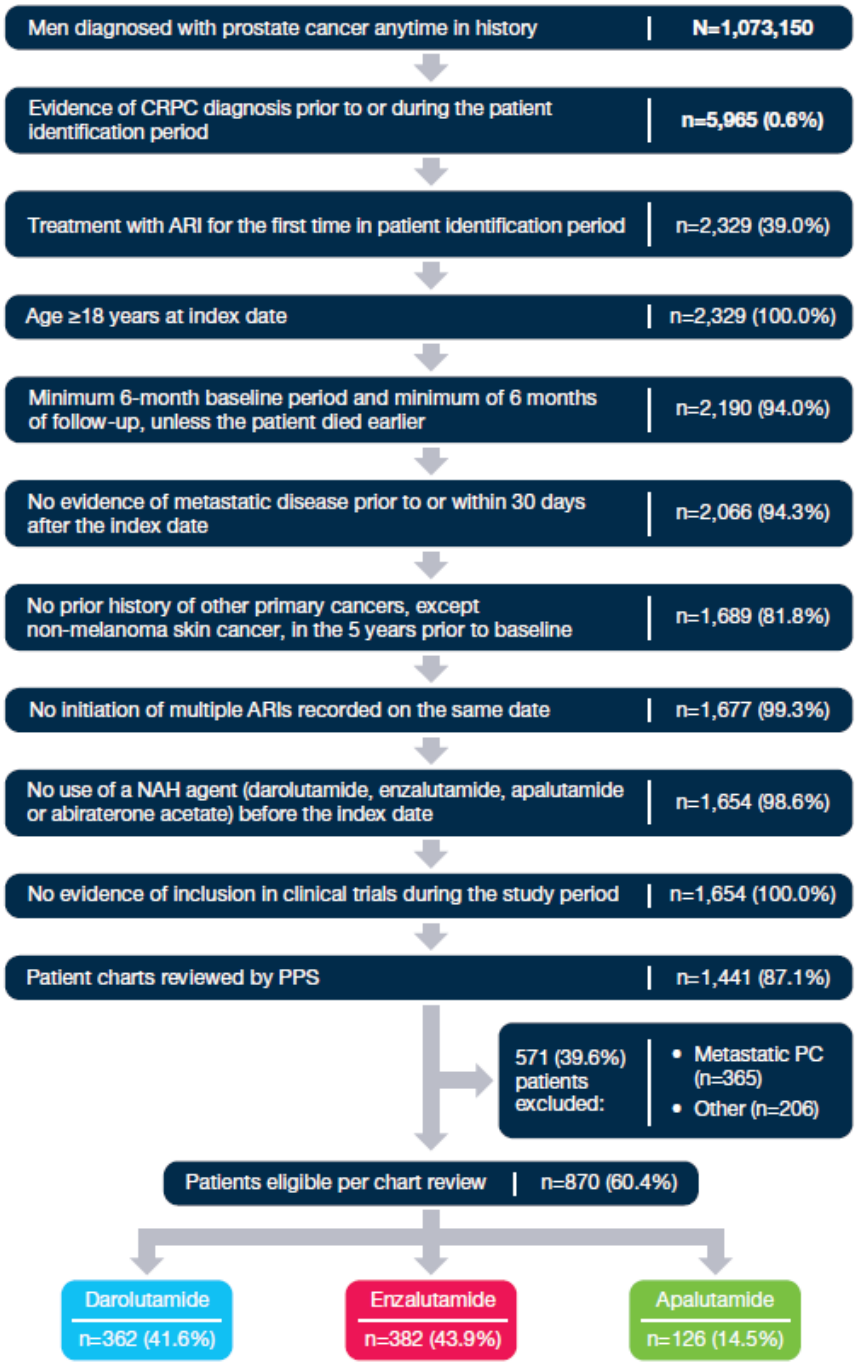
AE, adverse event; ARI, androgen receptor inhibitor.
[a]AEs recorded during each ARI treatment and up to 30 days after discontinuation. Some patients experienced multiple AEs.

**eFigure 1.** Study Design



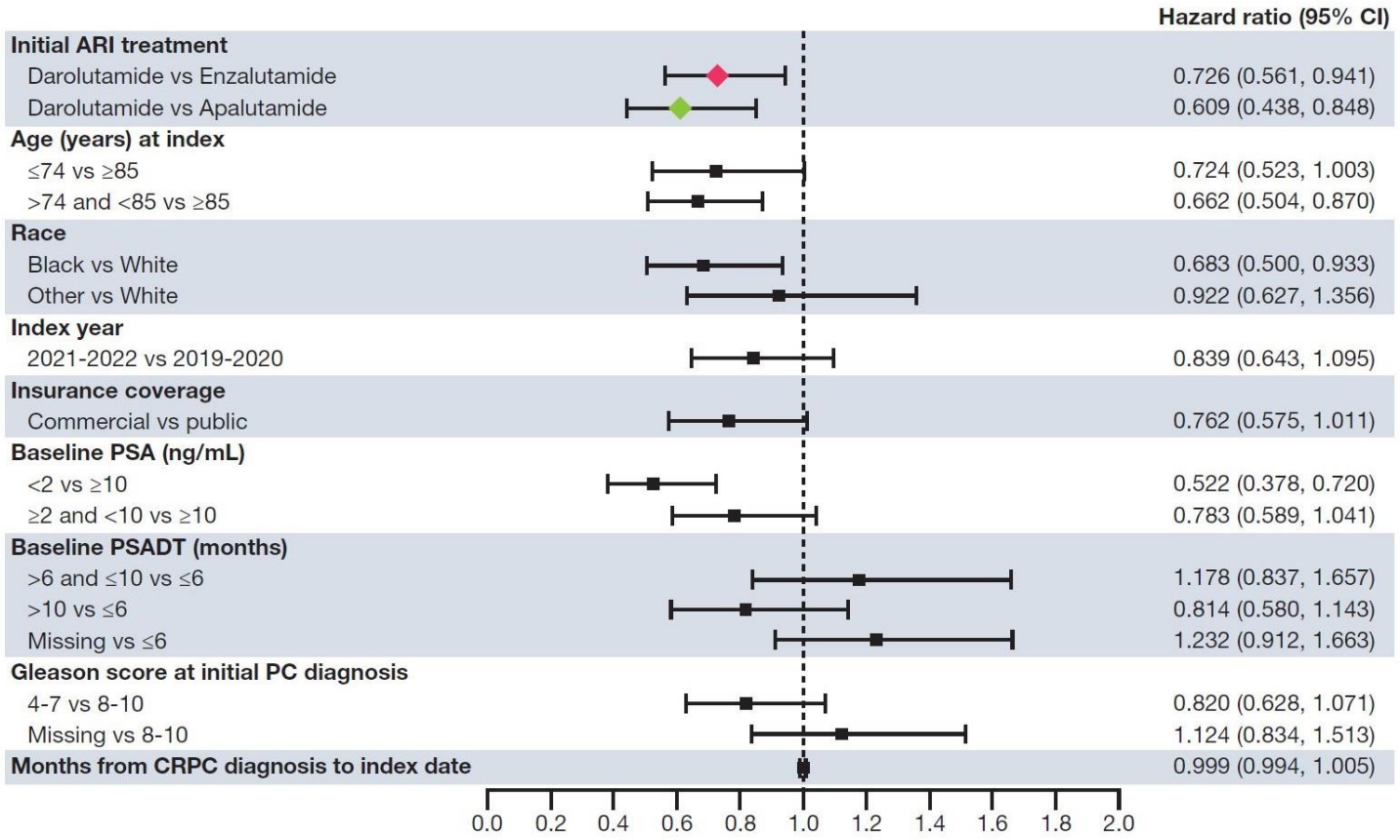

Apa, apalutamide; ARI, androgen receptor inhibitor; Daro, darolutamide; EMR, electronic medical record; Enza, enzalutamide; nmCRPC, nonmetastatic castration-resistant prostate cancer.

**eFigure 2.** Patient Attrition



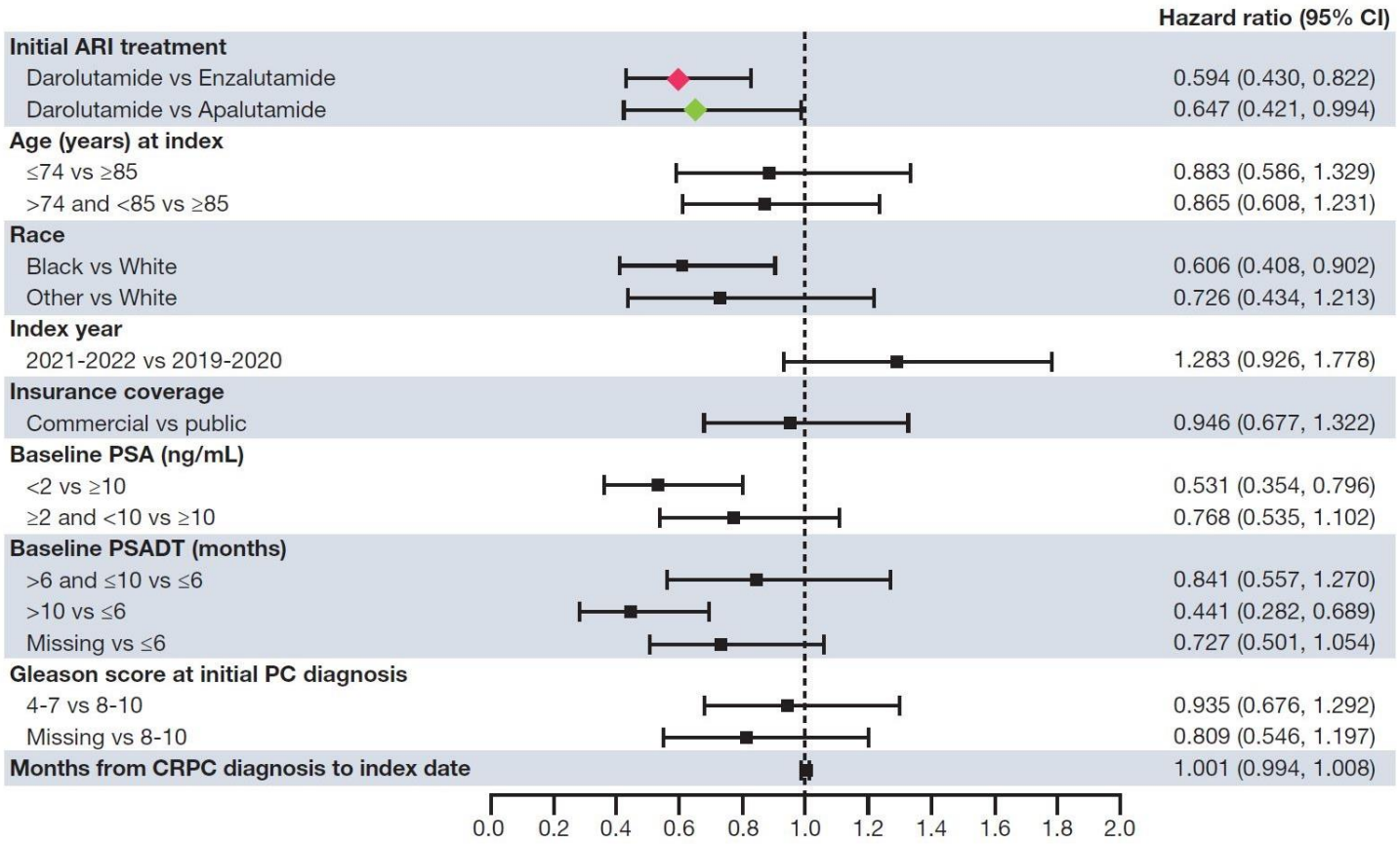

ARI, androgen receptor inhibitor; CRPC, castration-resistant prostate cancer; NAH, novel antihormonal therapy; PC, prostate cancer; PPS, Precision Point Specialty.

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



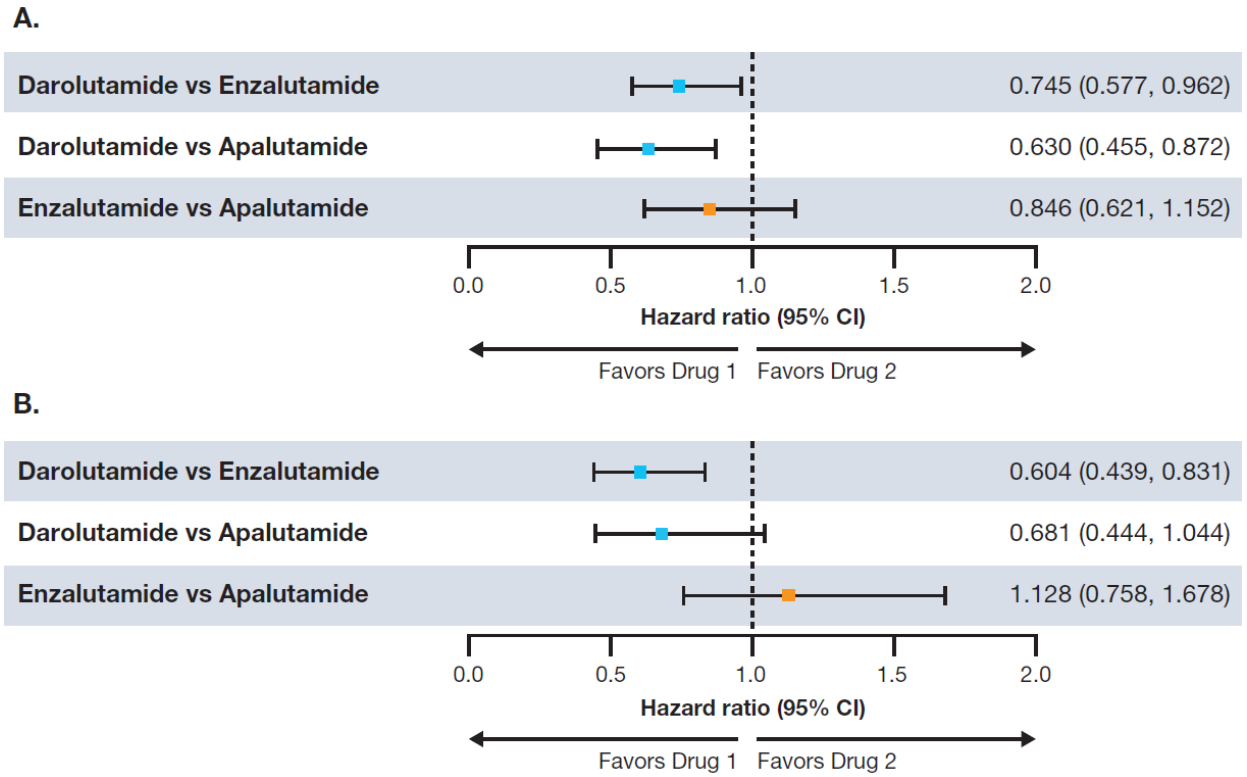

ARI, androgen receptor inhibitor; CI, confidence interval; CRPC, castration-resistant prostate cancer; PC, prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.
Discontinuation of initial ARI treatment was defined as the earliest occurrence of stopping initial 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




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 (≤74, 75-84, ≥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, ≥10 ng/mL), baseline PSA doubling time group (≤6, >6-≤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.

## eReferences.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