

Real-world outcomes associated with enzalutamide vs apalutamide in metastatic castration-sensitive prostate cancer: Analysis of United States oncology electronic health record data

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Objective

- This real-world study of US Flatiron electronic health record (EHR) data compared outcomes in patients with metastatic castration-sensitive prostate cancer (mCSPC) who initiated first-line (1L) treatment with enzalutamide or apalutamide.

Key Findings

- Patients with mCSPC who initiated 1L enzalutamide vs apalutamide had a comparable risk of treatment discontinuation (adjusted hazard ratio [aHR] 0.95; 95% confidence interval [CI]: 0.81, 1.12; *P*=0.53), initiation of subsequent antineoplastic treatment (aHR 0.98; 95% CI: 0.78, 1.22; *P*=0.84), and progression to metastatic castration-resistant prostate cancer (mCRPC; aHR 1.03; 95% CI: 0.81, 1.32; *P*=0.80).

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Plain Language Summary

- References:**
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Background and Objectives

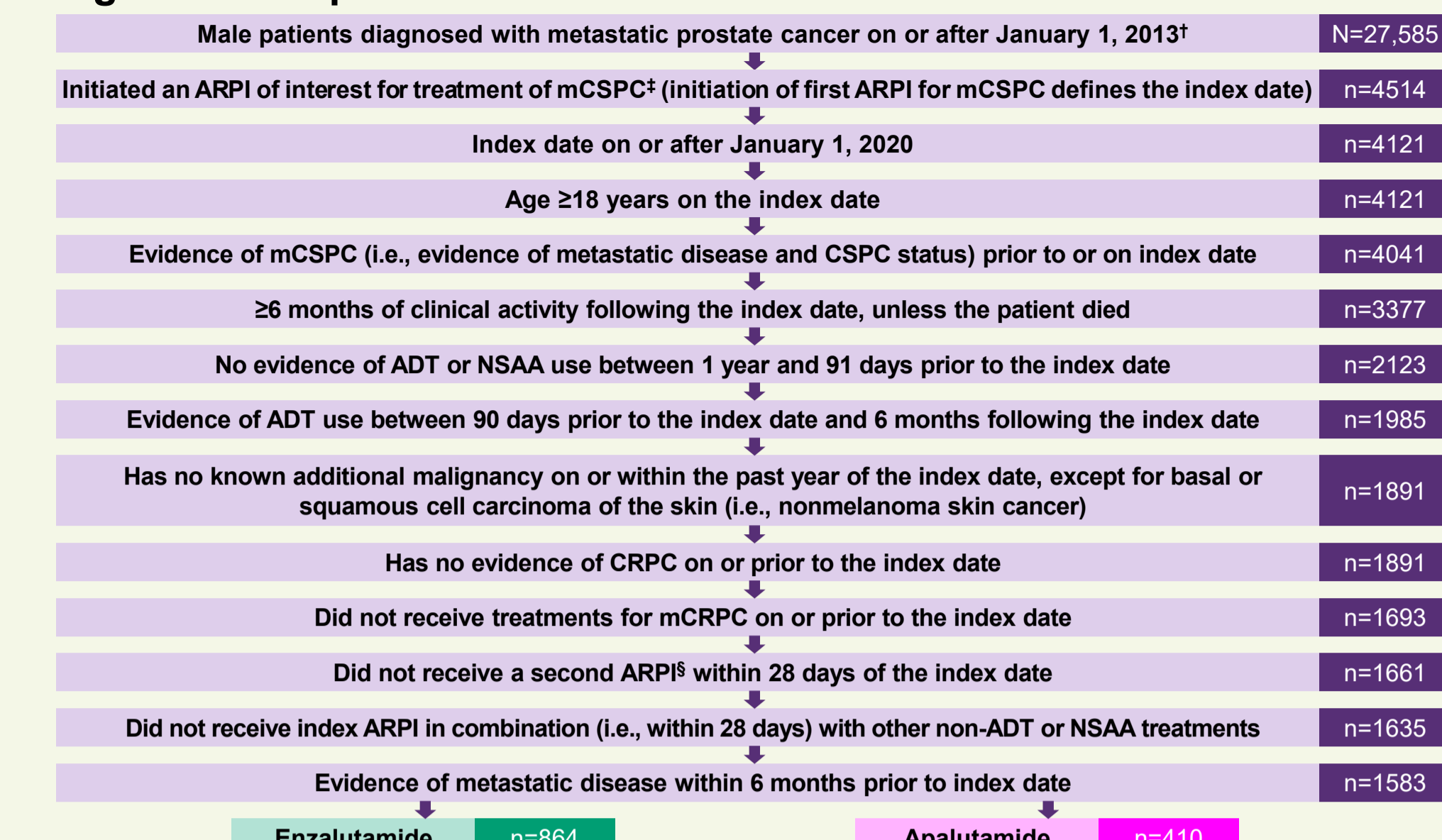
- Clinical trial data demonstrate the efficacy of adding androgen receptor pathway inhibitors (ARPIs) to androgen deprivation therapy for the treatment of mCSPC.^{1,2} – Enzalutamide and apalutamide (along with darolutamide and abiraterone) are the approved ARPIs for mCSPC treatment.^{3,4}
- Real-world studies that compare 1L enzalutamide and apalutamide in the mCSPC setting are limited.^{5,6} Misclassification of disease state and confounding by indication can further complicate the interpretation of real-world data as enzalutamide is approved for both mCSPC and mCRPC, while apalutamide is indicated only for mCSPC.^{7,8}
- This retrospective analysis of the US Flatiron EHR database (January 2013 to May 2025) compared outcomes of 1L enzalutamide vs apalutamide among patients with mCSPC.

Methods

- Eligible patients (**Figure 1**) were males aged ≥18 years in the US with chart-abstracted evidence of mCSPC who:
 - initiated index treatment (1L enzalutamide or apalutamide; index date) on or after January 1, 2020, and
 - had no evidence of mCRPC prior to or within 3 months after 1L treatment initiation.

- Additional criteria (e.g., exclusion of documented prior mCRPC treatment) were applied to minimize misclassification.
- In the main analysis, outcomes included:
 - duration of treatment, defined as the time from the index date to the discontinuation of index ARPI for any reason;
 - time to next treatment (time from the index date to the initiation of subsequent treatment); and
 - time to mCRPC (time from the index date to mCRPC date).
- A sensitivity analysis was limited to patients whose entire index treatment was within the mCSPC setting (a more restrictive mCSPC definition).
 - Patients who initiated 1L ARPI in the mCSPC setting but progressed to mCRPC while on treatment were excluded.
 - Outcomes included duration of treatment and time to next treatment.
- In the main and sensitivity analyses, inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazards models compared outcomes between enzalutamide and apalutamide, controlling for baseline characteristics.
 - Time-to-event outcomes were evaluated using the Kaplan–Meier method.

Figure 1. Sample selection



¹Prostate cancer diagnosis code (ICD-9-CM 185.x or ICD-10-CM C61.x) and ≥2 documented clinical visits on different days between 01/01/2013 and 5/31/2025. ²ARPI of interest included apalutamide, enzalutamide, darolutamide, and darolutamide in combination with docetaxel. ³ARPI in this step included apalutamide, enzalutamide, darolutamide, and abiraterone. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitors; CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer; ICD-X-CM, International Classification of Diseases, Xth Revision, Clinical Modification; mCRPC, metastatic CRPC; mCSPC, metastatic CSPC; NSAA, nonsteroidal antiandrogens.

Results

- Overall, 864 patients initiated enzalutamide and 410 initiated apalutamide as 1L mCSPC treatment.
- The median follow-up was 23 months for enzalutamide and 24 months for apalutamide.
- In the unadjusted analysis, index year and Gleason score at initial prostate cancer diagnosis were different between the groups. After IPTW adjustment, clinical characteristics were balanced across the treatment groups for all variables measured (**Table 1**).

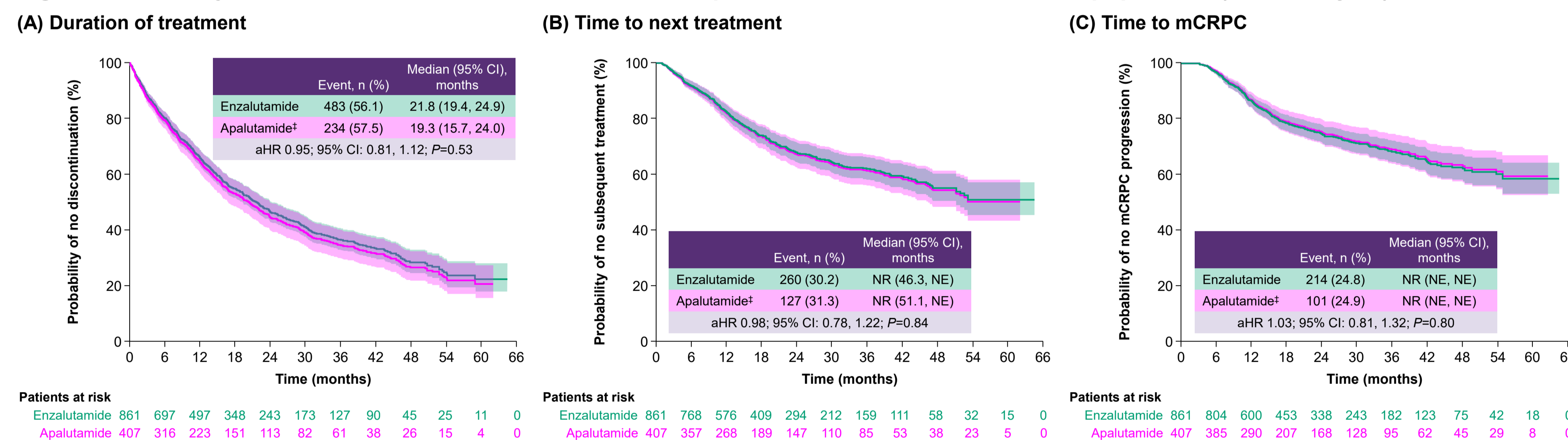
Table 1. Baseline demographic and clinical characteristics

Baseline characteristics	Unadjusted			IPTW-adjusted [†]		
	Enzalutamide (n=864)	Apalutamide (n=410)	Standardized difference [‡]	Enzalutamide (n=862)	Apalutamide (n=407)	Standardized difference [‡]
Age at index date, years						
Mean ± SD	72.9 ± 8.0	72.3 ± 8.3	8.3	72.7 ± 8.1	72.8 ± 8.1	0.7
Median (IQR)	74.0 (67.0–80.0)	73.0 (66.0–79.0)		73.0 (67.0–80.0)	74.0 (67.0–80.0)	
Race, n (%)						
White	496 (57.4)	237 (57.8)	0.8	496 (57.6)	234 (57.5)	0.2
Non-White [§]	368 (42.6)	173 (42.2)	0.8	365 (42.4)	173 (42.5)	0.2
Practice setting, n (%)						
Community	698 (80.8)	320 (78.0)	6.8	687 (79.8)	323 (79.5)	0.8
Academic or both	166 (19.2)	90 (22.0)	6.8	174 (20.2)	84 (20.5)	0.8
Index year, n (%)						
2020	161 (18.6)	57 (13.9)	12.8	147 (17.0)	68 (16.7)	0.9
2021	195 (22.6)	84 (20.5)	5.1	190 (22.0)	89 (21.9)	0.2
2022	173 (20.0)	98 (23.9)	9.4	181 (21.0)	85 (20.9)	0.3
2023	182 (21.1)	99 (24.1)	7.4	192 (22.2)	91 (22.5)	0.5
2024	153 (17.7)	72 (17.6)	0.4	153 (17.7)	74 (18.1)	0.9
Time from metastatic diagnosis to index date, months						
Mean ± SD	1.7 ± 1.1	1.6 ± 1.0	7.7	1.7 ± 1.1	1.7 ± 1.1	1.2
Median (IQR)	1.5 (0.9–2.4)	1.5 (0.9–2.2)		1.5 (0.8–2.3)	1.5 (0.9–2.3)	
De novo metastatic diagnosis, n (%)	590 (68.3)	272 (66.3)	4.1	586 (68.0)	279 (68.6)	1.3
Gleason score at initial PC diagnosis, n (%)						
≤6	34 (3.9)	16 (3.9)	0.2	33 (3.9)	14 (3.5)	1.9
7	112 (13.0)	76 (18.5)	15.3	124 (14.4)	60 (14.7)	0.9
8	131 (15.2)	60 (14.6)	1.5	129 (15.0)	60 (14.9)	0.3
9	285 (33.0)	114 (27.8)	11.3	272 (31.6)	128 (31.5)	0.2
10	53 (6.1)	27 (6.6)	1.8	55 (6.4)	27 (6.7)	1.3
Unknown	249 (28.8)	117 (28.5)	0.6	249 (28.9)	117 (28.8)	0.2
PSA level at metastatic PC diagnosis (ng/mL), n (%)						
≤15.0	190 (22.0)	93 (22.7)	1.7	192 (22.3)	91 (22.5)	0.5
>15.0–69.3	193 (22.3)	88 (21.5)	2.1	190 (22.0)	88 (21.7)	0.8
>69.3–307.8	188 (21.8)	94 (22.9)	2.8	190 (22.1)	92 (22.5)	0.9
>307.8	186 (21.5)	96 (23.4)	4.5	190 (22.0)	89 (21.9)	0.3
Missing	107 (12.4)	39 (9.5)	9.2	100 (11.6)	46 (11.4)	0.5

[†]Stabilized IPTW based on age at index date, race, geographic region, insurance type, practice setting, index year, body mass index, time from PC diagnosis to metastatic diagnosis, time from metastatic diagnosis to index date, clinical stage at initial PC, de novo metastatic diagnosis, Gleason score at initial PC diagnosis, PSA level at initial PC diagnosis, PSA level at metastatic diagnosis, Eastern Cooperative Oncology Group performance status, prior radical prostatectomy, prior radiation therapy, nonsteroidal antiandrogen use, prior ADT use, and duration of ADT. [‡]Enzalutamide vs apalutamide; a standardized difference of >10% indicates meaningful imbalance. [§]Includes Black, Asian, other, and missing. ADT, androgen deprivation therapy; IPTW, inverse probability of treatment weighting; IQR, interquartile range; PC, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation.

- In the IPTW-adjusted main analysis, patients in the enzalutamide and apalutamide groups had comparable outcomes; just over half discontinued treatment, approximately one-third received a subsequent treatment, and one quarter progressed to mCRPC (**Figure 2A–C**).

Figure 2. IPTW-adjusted[†] outcomes for 1L enzalutamide and apalutamide in the overall mCSPC population (main analysis)



[†]Please refer to the [†] footnote in Table 1. [‡]Reference group. 1L, first-line; aHR, adjusted hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NE, not evaluable; NR, not reached.

- The sensitivity analysis among patients in the mCSPC setting only was consistent with the main analysis for duration of treatment and time to next treatment (**Table 2**).

Table 2. IPTW-adjusted[†] outcomes for 1L enzalutamide and apalutamide in the mCSPC-only setting (sensitivity analysis)

Outcome	Enzalutamide (n=738)	Apalutamide [‡] (n=355)
Duration of treatment		
Event, n (%)	380 (51.4)	194 (54.7)
Median (95% CI), months	25.3 (21.9, 29.4)	22.1 (16.7, 29.7)
aHR (95% CI)	0.90 (0.75, 1.08)	
<i>P</i> -value	0.26	
Time to next treatment		
Event, n (%)	183 (24.8)	95 (26.8)
Median (95% CI), months	NR (NE, NE)	NR (53.1, NE)
aHR (95% CI)	0.93 (0.72, 1.21)	
<i>P</i> -value	0.60	

[†]Please refer to the [†] footnote in Table 1. [‡]Reference group. 1L, first-line; aHR, adjusted hazard ratio; CI, confidence interval; mCSPC, metastatic castration-sensitive prostate cancer; NE, not evaluable; NR, not reached.

Conclusion

- In this real-world study of Flatiron EHR data, duration of treatment, time to next treatment, and time to mCRPC progression were comparable for patients with mCSPC (defined stringently to minimize misclassification bias) who initiated 1L enzalutamide vs apalutamide in US oncology practices.
- These findings support similar effectiveness of enzalutamide and apalutamide in the mCSPC setting.