Supplementary Material

Real-World Treatment Patterns in Patients with Metastatic Castration-Sensitive Prostate Cancer in Japan: A Retrospective Health Administrative Data Analysis

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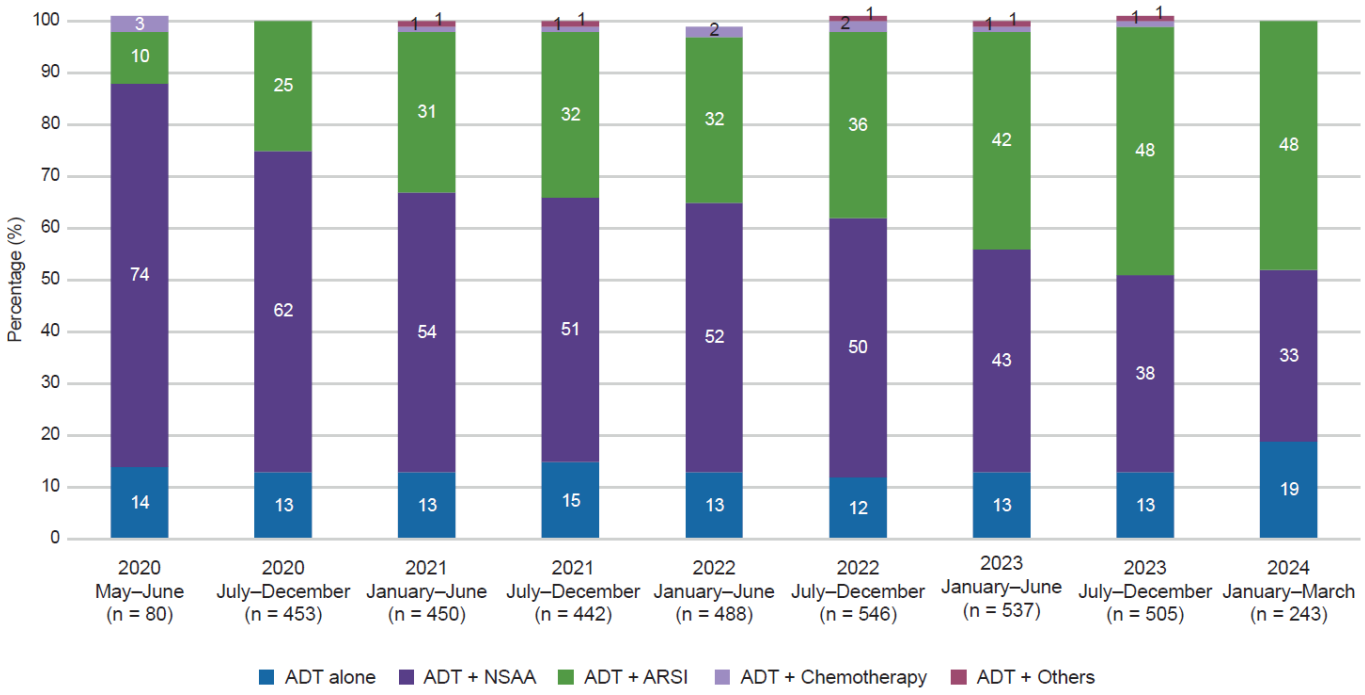
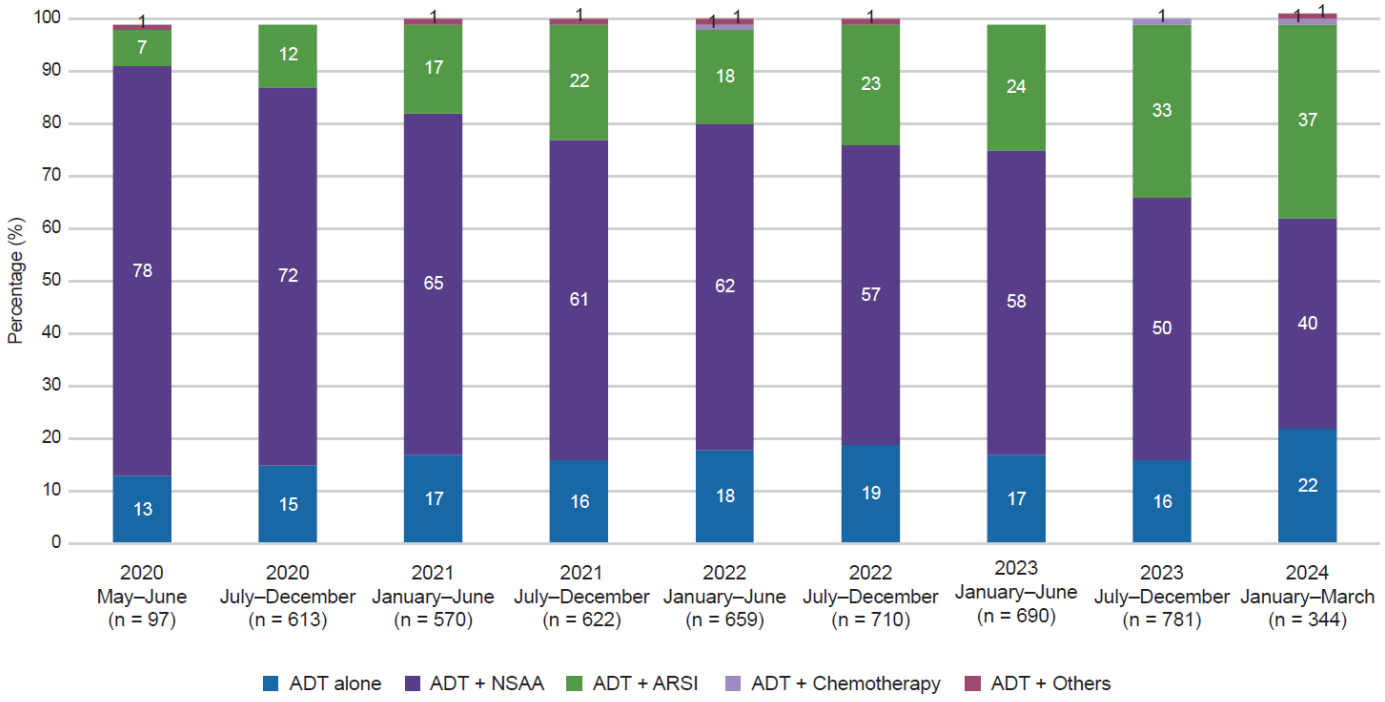
Fig. S1 Trends in the distribution of first-line treatments for **(a)** patients aged < 75 years, and **(b)** patients aged ≥ 75 years

a)



b)

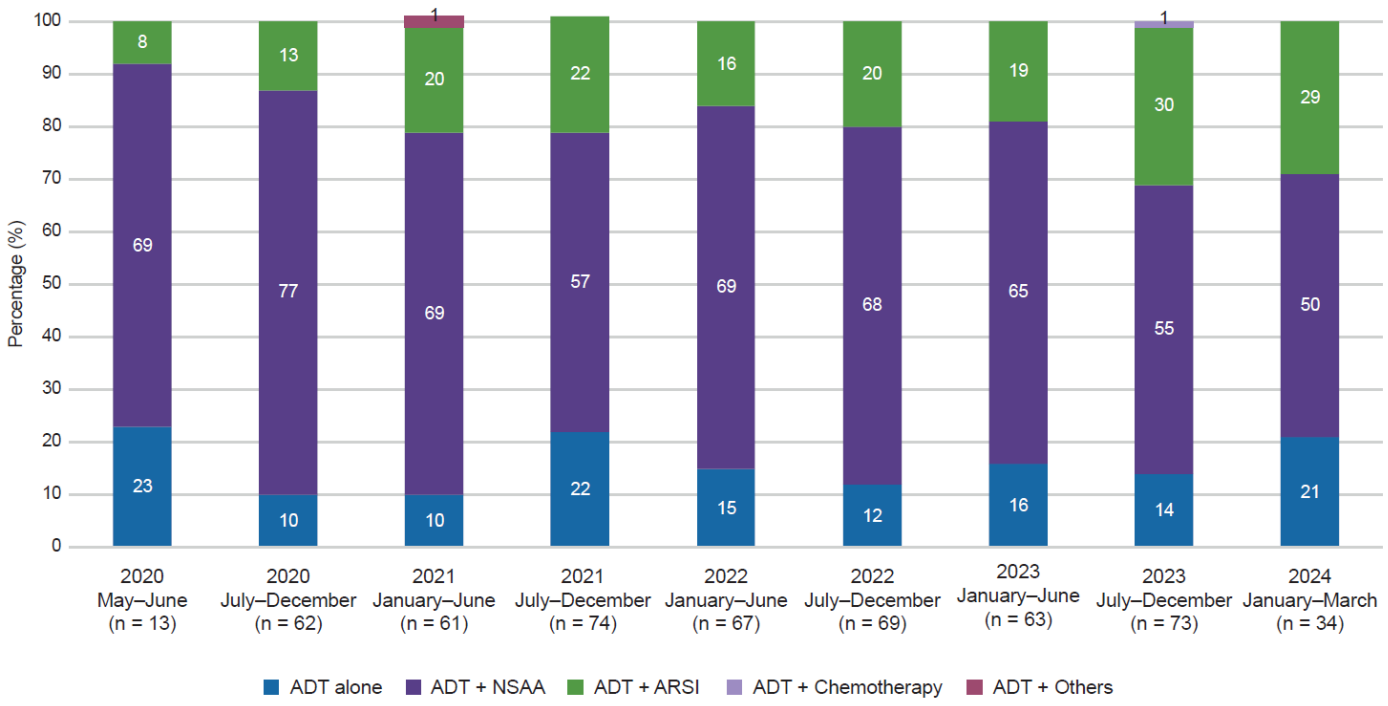


Values may not sum to 100% due to rounding

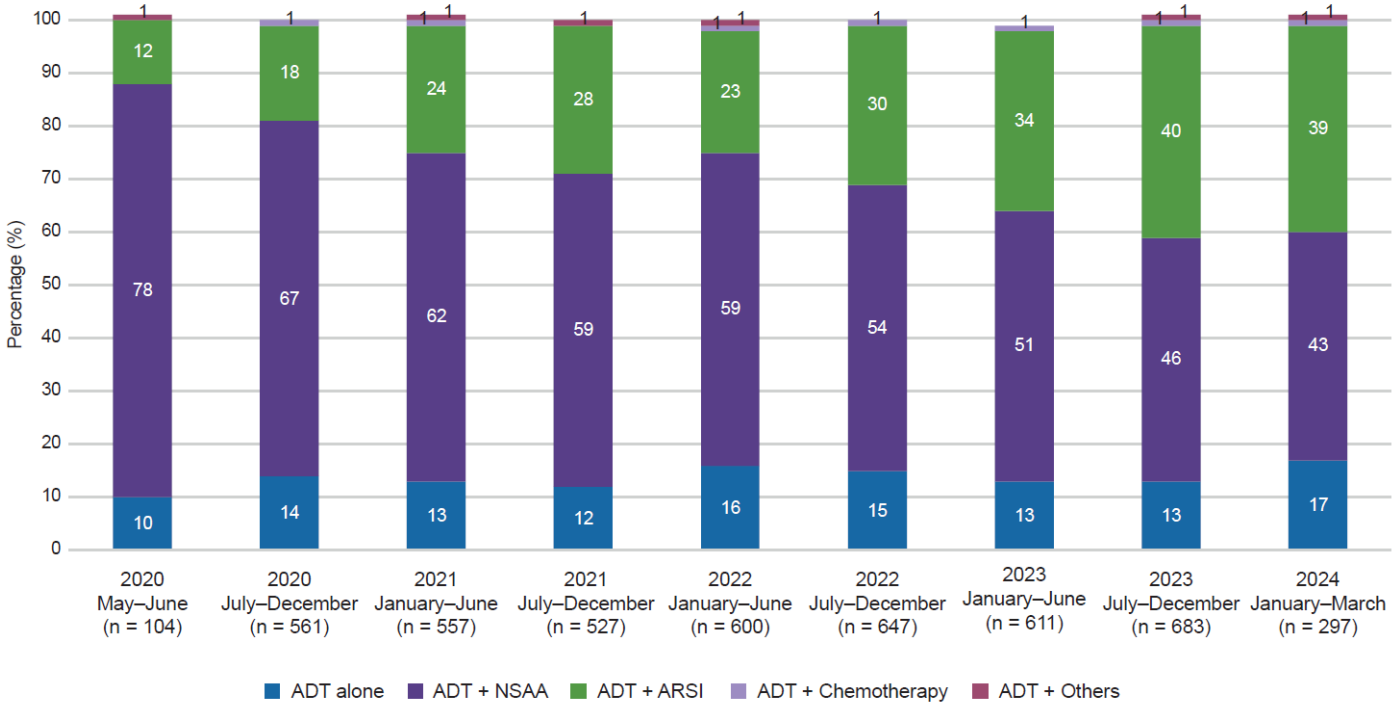
ADT androgen-deprivation therapy, *ARSI* androgen receptor pathway inhibitor, *NSAA* nonsteroidal antiandrogen

Fig. S2 Trends in the distribution of first-line treatments for **(a)** hospital size < 200 beds, **(b)** hospital size 200–499 beds, and **(c)** hospital size ≥ 500 beds

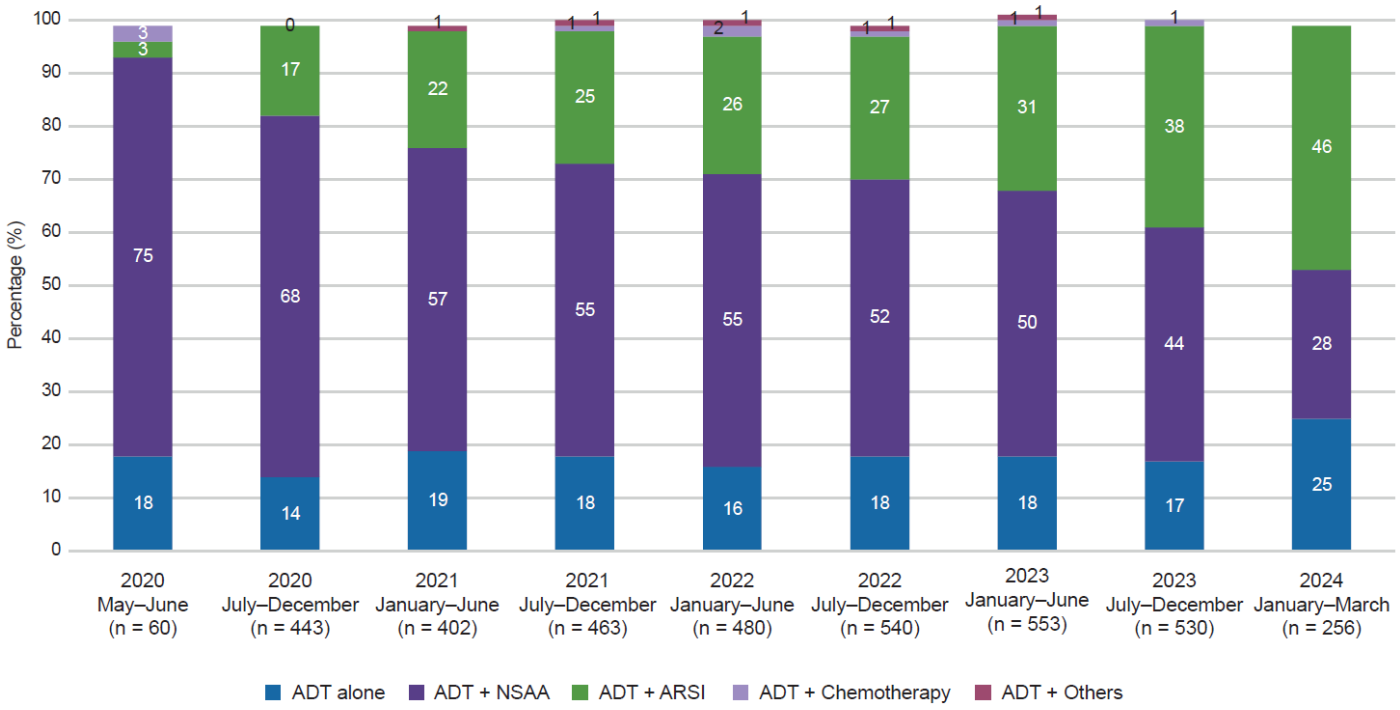
a)



b)


Percentage (%)
100
90
80
70
60
50
40
30
20
10
0
2020 May–June (n = 104)
2020 July–December (n = 561)
2021 January–June (n = 557)
2021 July–December (n = 527)
2022 January–June (n = 600)
2022 July–December (n = 647)
2023 January–June (n = 611)
2023 July–December (n = 683)
2024 January–March (n = 297)
10
78
12
1
14
67
18
1
13
62
24
1
12
59
28
1
16
59
23
1
15
54
30
1
13
51
34
1
13
46
40
1
17
43
39
1
ADT alone
ADT + NSAA
ADT + ARSI
ADT + Chemotherapy
ADT + Others

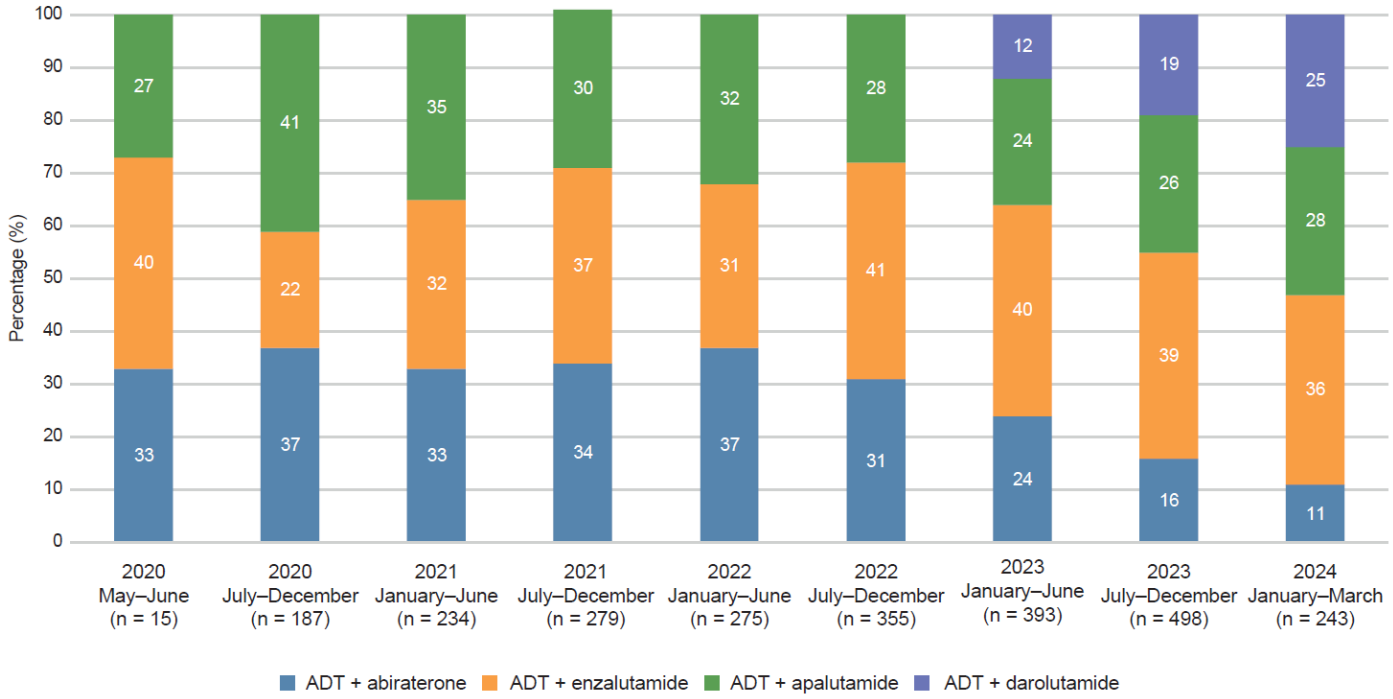
c)



Values may not sum to 100% due to rounding

ADT androgen-deprivation therapy, *ARSI* androgen receptor pathway inhibitor, *NSAA* nonsteroidal antiandrogen

Fig. S3 Trends in the distribution of first-line treatments



ADT androgen-deprivation therapy

Table S1 Demographic by first-line drug class (adjusted by IPTW)

Parameter	ADT alone (*n* = 8,580)	ADT + NSAA (*n* = 8,750)	ADT + ARSI (*n* = 8,462)	Standardized mean difference		
				ADT alone vs ADT + NSAA	ADT alone vs ADT + ARSI	ADT + NSAA vs ADT + ARSI
Age at index date (years)						
n (%)	8,580 (100.0%)	8,750 (100.0%)	8,462 (100.0%)	-	-	-
Median (IQR)	76.0 (71.0–83.0)	76.0 (71.0–82.0)	76.0 (71.0–81.0)	-	-	-
CCI score[a]						
n (%)	8,580 (100.0%)	8,750 (100.0%)	8,462 (100.0%)	-	-	-
Mean (SD)	1.4 (1.9)	1.4 (2.0)	1.4 (1.9)	0.0122	0.0135	0.0011
Median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	-	-	-
CCI score group[a]						
≤1	5,456 (63.6%)	5,758 (65.8%)	5,567 (65.8%)	-	-	-
>1	3,124 (36.4%)	2,993 (34.2%)	2,894 (34.2%)	-	-	-
Hypertension	2,350 (27.4%)	2,372 (27.1%)	2,322 (27.4%)	0.0063	0.0011	0.0074
Hyperlipidemia	1,169 (13.6%)	1,192 (13.6%)	1,145 (13.5%)	0.0001	0.0028	0.0028
Metastasis site						
Bone	5,870 (68.4%)	6,007 (68.6%)	5,913 (69.9%)	0.0050	0.0318	0.0268
Lymph	1,883 (21.9%)	2,029 (23.2%)	1,988 (23.5%)	0.0297	0.0369	0.0072
Lung	761 (8.9%)	799 (9.1%)	781 (9.2%)	0.0093	0.0127	0.0034
Liver	146 (1.7%)	157 (1.8%)	167 (2.0%)	0.0066	0.0196	0.0131
Others	276 (3.2%)	336 (3.8%)	299 (3.5%)	-	-	-
Previous treatment						
Prostatectomy (radical)	74 (0.9%)	71 (0.8%)	53 (0.6%)			
EBRT or SBRT	292 (3.4%)	306 (3.5%)	292 (3.4%)			
Laboratory data						
PSA levels (ng/mL)						
n (%)	1,346 (15.7%)	1,128 (12.9%)	911 (10.8%)	-	-	-
Median (IQR)	98.85 (16.43–709.00)	157.00 (22.34–701.77)	112.00 (21.46–443.29)			

Parameter	ADT alone (*n* = 8,580)	ADT + NSAA (*n* = 8,750)	ADT + ARSI (*n* = 8,462)	Standardized mean difference		
				ADT alone vs ADT + NSAA	ADT alone vs ADT + ARSI	ADT + NSAA vs ADT + ARSI
ALP levels (U/L)						
n (%)	1,529 (17.8%)	1,275 (14.6%)	1,016 (12.0%)	-	-	-
Median (IQR)	295.00 (207.00–594.00)	332.00 (227.00–801.00)	344.00 (239.00–730.00)			
Hb levels (g/dL)						
n (%)	1,561 (18.2%)	1,350 (15.4%)	1,028 (12.2%)	-	-	-
Median (IQR)	13.10 (11.10–14.50)	12.60 (11.00–14.10)	12.80 (11.40–14.00)			
LDH levels (U/L)						
n (%)	161 (1.9%)	114 (1.3%)	68 (0.8%)	-	-	-
Median (IQR)	184.00 (153.00–214.00)	211.00 (187.00–252.00)	187.00 (173.00–200.00)			
BMI (kg/m^2)						
n (%)	5,325 (62.1%)	6,165 (70.5%)	6,557 (77.5%)	-	-	-
Median (IQR)	22.39 (20.20–24.80)	22.59 (20.43–24.86)	22.76 (20.55–24.84)			
Inpatient	3,010 (35.1%)	2,508 (28.7%)	834 (9.9%)	-	-	-
Outpatient	5,570 (64.9%)	6,242 (71.3%)	7,628 (90.1%)			
Size of hospital (number of beds)						
≤199	543 (6.3%)	512 (5.8%)	484 (5.7%)	0.0201	0.0254	0.0054
200–499	4,373 (51.0%)	4,582 (52.4%)	4,420 (52.2%)	0.0279	0.0253	0.0026
≥500	3,664 (42.7%)	3,657 (41.8%)	3,557 (42.0%)	0.0185	0.0134	0.0051
Year of index date						
2020	1,245 (14.5%)	1,239 (14.2%)	1,151 (13.6%)	0.0102	0.0263	0.0161
2021	2,001 (23.3%)	2,066 (23.6%)	2,011 (23.8%)	0.0068	0.0106	0.0039
2022	2,314 (27.0%)	2,368 (27.1%)	2,301 (27.2%)	0.0022	0.0051	0.0028
2023	2,424 (28.3%)	2,477 (28.3%)	2,402 (28.4%)	0.0011	0.0028	0.0017
2024	595 (6.9%)	601 (6.9%)	597 (7.1%)	0.0030	0.0044	0.0074

[a] Diagnosis of prostate cancer and metastases (which were analyzed in this study) is excluded from the calculation of the CCI score

ADT androgen-deprivation therapy, *ALP* alkaline phosphatase, *ARSI* androgen receptor signaling inhibitor, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *EBRT* external beam radiation therapy, *Hb* hemoglobin, *IPTW* inverse probability of treatment weighting, *IQR* interquartile range, *LDH*

lactate dehydrogenase, *n* sample size, *NSAA* nonsteroidal antiandrogen, *PSA* prostate-specific antigen, *SBRT* stereotactic body radiation therapy, *SD* standard deviation

Table S2 Patient characteristics by ARSI (unadjusted)

Parameter	Category/statistic	ADT + abiraterone (*n* = 657)	ADT + enzalutamide (*n* = 894)	ADT + apalutamide (*n* = 724)	ADT + darolutamide (*n* = 204)
Age at index date (years)	*n* (%)	657 (100.0%)	894 (100.0%)	724 (100.0%)	204 (100.0%)
	Median (IQR)	74.0 (69.0–79.0)	74.0 (70.0–80.0)	74.0 (69.0–79.0)	70.0 (65.5–74.0)
CCI score[a]	*n* (%)	657 (100.0%)	894 (100.0%)	724 (100.0%)	204 (100.0%)
	Mean (SD)	1.1 (1.7)	1.2 (1.8)	1.3 (1.8)	1.2 (1.8)
	Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	1.0 (0.0–2.0)	0.0 (0.0–2.0)
Comorbidities					
CCI score group[a]	≤1	483 (73.5%)	618 (69.1%)	496 (68.5%)	147 (72.1%)
	>1	174 (26.5%)	276 (30.9%)	228 (31.5%)	57 (27.9%)
Hypertension	Yes	155 (23.6%)	211 (23.6%)	187 (25.8%)	51 (25.0%)
Hyperlipidemia	Yes	72 (11.0%)	126 (14.1%)	93 (12.8%)	24 (11.8%)
Metastasis site					
Bone	Yes	527 (80.2%)	665 (74.4%)	549 (75.8%)	166 (81.4%)
Lymph	Yes	138 (21.0%)	227 (25.4%)	203 (28.0%)	50 (24.5%)
Lung	Yes	76 (11.6%)	94 (10.5%)	71 (9.8%)	31 (15.2%)
Liver	Yes	13 (2.0%)	9 (1.0%)	8 (1.1%)	9 (4.4%)
Others	Yes	40 (6.1%)	62 (6.9%)	33 (4.6%)	27 (13.2%)
Laboratory data					
PSA levels (ng/mL)	*n* (%)	73 (11.1%)	116 (13.0%)	90 (12.4%)	23 (11.3%)
	Median (IQR)	182.42 (51.20–531.00)	104.45 (14.49–456.40)	60.90 (13.30–253.57)	226.00 (14.21–1,368.00)
ALP levels (U/L)	*n* (%)	76 (11.6%)	138 (15.4%)	96 (13.3%)	25 (12.3%)

Parameter	Category/statistic	ADT + abiraterone (*n* = 657)	ADT + enzalutamide (*n* = 894)	ADT + apalutamide (*n* = 724)	ADT + darolutamide (*n* = 204)
	Median (IQR)	370.00 (258.50–804.00)	311.00 (216.00–807.00)	347.50 (237.50–717.50)	474.00 (287.00–1,020.00)
Hb levels (g/dL)	*n* (%)	83 (12.6%)	132 (14.8%)	96 (13.3%)	25 (12.3%)
	Median (IQR)	12.80 (11.30–13.90)	13.05 (11.90–14.30)	13.10 (11.85–14.25)	11.90 (10.40–13.60)
LDH levels (U/L)	*n* (%)	4 (0.6%)	2 (0.2%)	9 (1.2%)	0 (0.0%)
	Median (IQR)	191.50 (184.00–215.00)	174.00 (173.00–175.00)	199.00 (169.00–212.00)	-
BMI (kg/m^2)	*n* (%)	505 (76.9%)	661 (73.9%)	592 (81.8%)	168 (82.4%)
	Median (IQR)	22.61 (20.27–24.61)	22.78 (20.64–25.09)	22.91 (20.89–24.92)	23.04 (20.98–25.28)
Inpatient/outpatient	Inpatient	70 (10.7%)	80 (8.9%)	42 (5.8%)	35 (17.2%)
	Outpatient	587 (89.3%)	814 (91.1%)	682 (94.2%)	169 (82.8%)
Size of hospital (number of beds)	≤ 199	34 (5.2%)	37 (4.1%)	25 (3.5%)	10 (4.9%)
	200–499	347 (52.8%)	489 (54.7%)	399 (55.1%)	93 (45.6%)
	≥ 500	276 (42.0%)	368 (41.2%)	300 (41.4%)	101 (49.5%)
Year of index date	2020	74 (11.3%)	47 (5.3%)	81 (11.2%)	0 (0.0%)
	2021	171 (26.0%)	176 (19.7%)	166 (22.9%)	0 (0.0%)
	2022	210 (32.0%)	232 (26.0%)	188 (26.0%)	0 (0.0%)
	2023	175 (26.6%)	352 (39.4%)	221 (30.5%)	143 (70.1%)
	2024	27 (4.1%)	87 (9.7%)	68 (9.4%)	61 (29.9%)
Duration of follow-up, days, median (IQR)		463.0 (225.0–759.0)	343.5 (127.0–610.0)	432.5 (162.0–789.5)	147.0 (62.5–238.5)

[a] Diagnosis of prostate cancer and metastases (which were analyzed in this study) is excluded from the calculation of the CCI score

ADT androgen-deprivation therapy, *ALP* alkaline phosphatase, *ARSI* androgen receptor signaling inhibitor, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *Hb* hemoglobin, *IQR* interquartile range, *LDH* lactate dehydrogenase, *n* sample size, *NSAA* nonsteroidal antiandrogen, *PSA* prostate-specific antigen, *SD* standard deviation

Supplementary Results

Sensitivity analyses of treatment class

Sensitivity Analysis 1. Patients >12 weeks' follow-up

Among patients with > 12 weeks' follow-up, time to treatment discontinuation (TTD) findings were similar to those observed in the overall population. The median (95% confidence interval [CI]) TTD was longest for the androgen-deprivation therapy (ADT) plus androgen receptor signaling inhibitor (ARSI) group (753.0 [672.0–966.0] days) compared with ADT alone (343.0 [307.0–414.0] days) and ADT plus nonsteroidal antiandrogen (NSAA; 286.0 [273.0–301.0] days). Compared with ADT alone, the risk of discontinuation was significantly higher for ADT plus NSAA (adjusted hazard ratio [aHR], 1.238 [95% CI: 1.184–1.294]; *P*<0.0001) and significantly lower for ADT plus ARSI (aHR, 0.629 [95% CI: 0.598–0.661]; *P*<0.001). Compared with ADT plus NSAA, the risk of discontinuation was also significantly lower for ADT plus ARSI (aHR, 0.508 [95% CI: 0.485–0.532]; *P*<0.0001).

Sensitivity Analysis 2. Excluding patients who discontinued first-line treatment within 30 days

After excluding patients who discontinued treatment within 30 days, the TTD for both ADT alone and ADT plus NSAA was similar over the long term. ADT plus ARSI consistently displayed the longest TTD over the study period. Median (95% CI) TTD was longest for the ADT plus ARSI group (904.0 [735.0–1151.0] days) compared with ADT alone (377.0 [329.0–465.0] days) and ADT plus NSAA (365.0 [343.0–382.0] days). Compared with ADT alone, the risk of discontinuation was significantly higher for ADT plus NSAA (aHR, 1.080 [95% CI: 1.030–1.133]; *P*=0.0015), although this was attenuated compared with the overall and sensitivity analyses. The risk remained significantly lower for ADT plus ARSI (aHR, 0.591 [95% CI: 0.561–0.623]; *P*<0.001), consistent with the findings from both the overall and sensitivity analyses. Likewise, compared with ADT plus NSAA, the risk of discontinuation was also significantly lower for ADT plus ARSI (aHR, 0.539 [95% CI: 0.512–0.567]; *P*<0.0001).

Sensitivity Analysis 3. Excluding patients who discontinued first-line treatment within 60 days

After excluding patients who discontinued treatment within 60 days, this analysis also indicated that patients on ADT plus ARSI had longer TTD compared with those on ADT alone and ADT plus NSAA. The median (95% CI) TTD was longest for the ADT plus ARSI group (1,071.0 [899.0–1294.0] days) compared with the ADT alone (404.0 [343.0–485.0] days) and ADT plus NSAA (414.0 [395.0–447.0] days) groups. In contrast to the overall and sensitivity analyses, the TTD was slightly shorter for ADT alone than for ADT plus NSAA. Compared with ADT plus NSAA, the risk of discontinuation remained significantly lower for ADT plus ARSI (aHR, 0.549 [95% CI: 0.520–0.580]; *P*<0.0001).

Sensitivity Analysis 4. Post hoc analysis of TTD

In the post hoc analysis of TTD across drug classes when the grace period for ADT alone was set to 60 days, patients on ADT plus ARSI had relatively longer TTD compared with those on ADT alone and ADT plus NSAA (55.6%). The median (95% CI) TTD was longest for the ADT plus ARSI group (750.0 [665.0–966.0] days) compared with the ADT alone (259.0 [212.0–321.0] days) and ADT plus NSAA (281.0 [269.0–294.0] days) groups. Compared with ADT alone, the risk of discontinuation was slightly higher for ADT plus NSAA (aHR, 1.085 [95% CI: 1.040–1.132]; *P*=0.0001) and remained significantly lower for ADT plus ARSI (aHR, 0.548 [95% CI: 0.522–0.575]; *P*<0.001). Compared with ADT plus NSAA, the risk of discontinuation also remained significantly and consistently lower for ADT plus ARSI (aHR, 0.500 [95% CI: 0.477–0.523]; *P*<0.0001).

Sensitivity analyses of ARSIs

Sensitivity Analysis 1. Patients >12 weeks' follow-up

Among patients with > 12 weeks' follow-up, the TTD for abiraterone and enzalutamide were initially similar; however, over time, enzalutamide consistently demonstrated a slower discontinuation rate compared to other first-line ARSIs. Enzalutamide had the lowest discontinuation rate (31.8%, 234/735 events), followed by abiraterone (39.4%, 233/591 events), and apalutamide 46.4%, 285/614 events). The low discontinuation rate (17.9%, 24/134 events) for darolutamide was attributed to the short follow-up time.

The median (95% CI) TTD was longest for the enzalutamide group (1,151.0 [876.0–not reached [NR] days) compared with the abiraterone (874.0 [728.0–1,071.0] days), apalutamide (595.0 [444.0–803.0] days), and darolutamide (369.0 [316.0–NR] days) groups. The 25th percentiles for early discontinuation were 278.0 days (95% CI: 224.0–323.0) for abiraterone, 288.0 days (95% CI: 224.0–345.0) for enzalutamide, 126.0 days (95% CI: 112.0–151.0) for apalutamide, and 316.0 days (95% CI: 154.0–NR) for darolutamide. The 75th percentiles for later discontinuation were not applicable for any of the ARSIs.

Sensitivity Analysis 2. Excluding patients who discontinued first-line treatment within 30 days

After excluding patients who discontinued first-line treatment within 30 days, the TTD for the different ARSIs were similar to those observed in the overall population. Enzalutamide had the lowest discontinuation rate (23.4%, 199/850 events), followed by abiraterone (32.9%, 205/623 events), and apalutamide (37.0%, 254/687 events). The low discontinuation rate (8.7%, 17/195 events) observed for darolutamide was influenced by its shorter follow-up period.

The median (95% CI) TTD was longest for the enzalutamide group (median NR [1,042.0–NR] days) compared to the abiraterone (932.0 [755.0–1,292.0] days), apalutamide (665.0 [507.0–1,071.0] days) and darolutamide (369.0 [316.0–NR] days) groups. The 25th percentiles for early discontinuation were 323.0 days (95% CI: 278.0–392.0) for abiraterone, 351.0 days (95% CI: 296.0–415.0) for enzalutamide, 158.0 days (95% CI: 128.0–196.0) for apalutamide, and 316.0 days (95% CI: 316.0–NR) for darolutamide. The 75th percentiles for later discontinuation were not applicable for any of the ARSIs.

Sensitivity Analysis 3. Excluding patients who discontinued first-line treatment within 60 days

After excluding patients who discontinued first-line treatment within 60 days, this analysis also demonstrated similar findings to the main analysis. Enzalutamide exhibited the lowest discontinuation rate (20.2%, 165/816 events), followed by abiraterone (29.4%, 174/592 events), and apalutamide (34.4%, 227/660 events). The low discontinuation rate (6.8%, 13/191 events) observed for darolutamide was influenced by its shorter follow-up period.

The median (95% CI) TTD was noncalculable for enzalutamide and longer for abiraterone (1,064 [874.0–1,294.0] days) compared to the apalutamide (803.0 [595.0–NR] days) and darolutamide (369.0 [316.0–NR] days) groups. The 25th percentiles for early discontinuation were 413.0 days (95% CI: 350.0–557.0) for enzalutamide, 401.0 days (95% CI: 328.0–468.0) for abiraterone, 316.0 days (95% CI: 316.0–NR) for darolutamide, and 189.0 days (95% CI: 157.0–240.0) for apalutamide. The 75th percentiles for later discontinuation were noncalculable for any of the ARSIs.