Supplementary information

Supplementary information 1: ADT+ARPI patients' baseline characteristics

	enzalutamide n=49	abiraterone acetate n=25	p
Demographic data			
Age, years: mean (SD)	77.5 (5.65)	79.7 (6.75)	0.164
Married/cohabiting: n (%)	42 (86%)	17 (68%)	0.137
Education, years of schooling: mean (SD)	12.9 (3.76)	11.9 (3.05)	0.206
Clinical data			
ECOG performance status	[c]	[b]	0.213
0: n (%)	24 (52%)	7 (30%)	
1: n (%)	19 (41%)	13 (57%)	
2: n (%)	3 (7%)	3 (3%)	
Body mass index, kg/m²: mean (SD)	28.5 (3.51)[h]	26.4 (3.27)[d]	0.017
Charlson index: mean (SD)	1.41 (1.27)	0.76 (1.23)	0.040
Psychotropic drugs: n (%)	7 (14%)	2 (8%)	0.709
Analgesic drugs : n (%)	11 (22%)	5 (20%)	1.000
ADT duration, months: median (IQR)	13.10 (4.6-32.8)[a]	11.30 (2.4-20.6)[a]	0.559
Previous treatment			
Chemotherapy: n (%)	1 (2%)	2 (8%)	0.262
Radiotherapy: n (%)	41 (84%)	14 (56%)	0.022
Time since diagnosis, years: mean (SD)	13.7 (6.01)	16.2 (8.19)	0.180
Testosterone, abnormal: n (%)	44 (92%)[a]	20 (91%)[c]	1.000
TSH, abnormal: n (%)	6 (13%)[d]	1 (4%)	0.408
PSA, abnormal: n (%)	31 (78%)[9]	18 (86%)[d]	0.518
Gleason score	[a]	[f]	0.485
4-6: n (%)	10 (21%)	12 (18%)	
≥7: n (%)	38 (79%)	55 (82%)	
D'Amico risk classification	[e]	[f]	1.000
low: n (%)	0 (0%)	0 (0%)	
intermediate: n (%)	10 (23%)	4 (21%)	
high: n (%)	34 (77%)	15 (79%)	
Initially metastatic: n (%)	11 (22%)	6 (24%)	1.000
Geriatric data			
G8 screening tool: mean (SD)	14.8 (2.92)	14.3 (3.36)	0.543
IADL: mean (SD)	5.64 (0.896)	5.48 (1.19)	0.551
MNA: mean (SD)	26.4 (2.31)[g]	26.8 (1.38)[h]	0.415
Timed up and go: mean (SD)	3.67 (1.11)	3.84 (0.80)	0.462

Premorbid intellectual functioning and cognitive screening

fNART: mean (SD)	26.9 (6.97)[a]	27.0 (6.14)[b]	0.949
MoCA: mean (SD)	23.9 (3.35)	24.2 (3.90)	0.810

Other PROs

HADS – total, symptomatic: n (%)	16 (33%) [a]	8 (35%) [b]	1.000
depression: mean (SD)	4.05 (3.14)[a]	4.28 (3.36)[b]	
anxiety: mean (SD)	5.16 (3.11)[a]	5.19 (3.16)[b]	
ISI, symptomatic: n (%)	7 (15%)[a]	6 (26%)[b]	0.398
FACIT-F, symptomatic: n (%)	20 (42%)[a]	10 (43%)[b]	1.000
Visual analogue scale: mean (SD)	2.23 (2.35)[e]	2.60 (2.59)[f]	0.591

ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. ECOG: Eastern Cooperative Oncology Group. FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue. fNART: French National Adult Reading Test. HADS: Hospital Anxiety and Depression Scale. IADL: Instrumental Activities of Daily Life. IQR: interquartile range. ISI: Insomnia Severity Index. MoCA: Montréal Cognitive Assessment. MNA: Mini-Nutritional Assessment. PROs: Patient reported outcomes. PSA: prostatic specific antigen. SD: standard deviation. TSH: thyroid-stimulating hormone.

Missing data: [a]n=1 [b]n=2 [c]n=3 [d]n=4 [e]n=5 [f]n=6 [g]n=9 [h]n=10

Supplementary information 2A: Cognitive impairment (Z-scores) at baseline according to treatment group in ADT+ARPI patients (unadjusted)

	enzalutamide	abiraterone acetate
	impaired	impaired
Baseline	n=49	n=25
Overall objective impairment[1]	41% (19)	68% (17)
Subjective impairment[2]		
PCI	25% (12)	22% (5)
PCA	17% (8)	26% (6)

PCI: Perceived cognitive abilities. PCI: Perceived cognitive impairment.
[1] Proportion of participants impaired in at least two objective domains according to ICCTF guidelines[13].
[2] Proportion of participants with a FACT-Cog – PCI and PCA score of ≤10th percentile of norms[27].

Supplementary information 2B: Cognitive decline (RCI) during follow-up according to treatment group in ADT+ARPI patients (unadjusted)

	enzalutamide	abiraterone acetate
	declined	declined
3-month	n=49	n=25
Overall objective decline[1]	4% (2)	0% (0)
Subjective decline[2]		
PCI	27% (12)	19% (4)
PCA	27% (12)	23% (5)
6-month	n=36	n=18
Overall objective decline[1]	6% (2)	6% (1)
Subjective decline[2]		
PCI	34% (12)	33% (5)
PCA	37% (13)	67% (10)
12-month	n=27	n=15
Overall objective decline[1]	4% (1)	0% (0)
Subjective decline[2]		
PCI	42% (11)	38% (5)
PCA	46% (12)	31% (4)

PCI: Perceived cognitive abilities. PCI: Perceived cognitive impairment.
[1] Proportion of participants declining in at least two objective domains according to RCI
[2] Proportion of participants with a FACT-Cog – PCI and PCA score decreasing ≥10% from baseline

Supplementary information 3: Multivariable associations of baseline characteristics and PROs with variation in Z-scores during 12 months of treatment in ADT+ARPI patients

	baseline		3-month		6-month		12-month	
	β^1	p	β^2	p	β^2	p	β^2	p
fNART								
Processing speed/attention	0.080	0.001	0.001	0.965	0.062	0.021	0.042	0.082
Working memory	0.029	0.082	0.034	0.016	0.036	0.022	0.026	0.121
Verbal memory	0.039	0.200	-0.005	0.836	0.056	0.095	0.005	0.881
Visual memory	0.009	0.631	0.023	0.208	0.032	0.076	0.031	0.172
Visuospatial abilities	0.067	0.007	NA	NA	0.055	0.086	0.011	0.693
Executive functions	0.112	<0.001	-0.003	0.890	0.027	0.322	0.049	0.069
HADS - depression								
Working memory	-0.028	0.254	NA	NA	NA	NA	NA	NA
Visual memory	NA	NA	-0.014	0.623	NA	NA	NA	NA
Visuospatial abilities	NA	NA	NA	NA	NA	NA	-0.050	0.198
Executive functions	NA	NA	-0.080	0.014	-0.017	0.626	NA	NA
PCI	-0.883	0.024	0.072	0.808	-0.124	0.805	NA	NA
PCA	-0.345	0.135	-0.190	0.248	NA	NA	NA	NA
FACIT-F								
Visual memory	NA	NA	0.016	0.151	NA	NA	0.030	0.021
Visuospatial abilities	NA	NA	0.021	0.048	NA	NA	NA	NA
PCI	0.273	0.101	0.257	0.036	0.400	0.079	0.356	0.124
PCA	0.123	0.168	-0.021	0.764	0.009	0.915	0.215	0.014
G8 screening tool								
Processing speed/attention	0.112	0.007	0.024	0.546	NA	NA	NA	NA
Working memory	0.030	0.380	0.023	0.328	NA	NA	NA	NA
PCI	NA	NA	NA	NA	0.623	0.509	NA	NA
PCA	0.308	0.276	NA	NA	NA	NA	-0.695	0.086
IADL								
Processing speed/attention	NA	NA	0.011	0.923	NA	NA	NA	NA
PCI	NA	NA	NA	NA	1.867	0.522	NA	NA
PCA	NA	NA	NA	NA	NA	NA	1.172	0.343
HADS - anxiety								
PCI	NA	NA	NA	NA	-0.347	0.524	NA	NA
PCA	-0.335	0.168	NA	NA	NA	NA	NA	NA
ISI								
PCI	-0.385	0.138	-0.029	0.882	0.372	0.258	NA	NA
PCA	0.006	0.967	-0.131	0.220	NA	NA	-0.137	0.242
Pre-baseline ADT duration								
Verbal memory	NA	NA	NA	NA	0.001	0.958	0.001	0.900
Visuospatial abilities	NA	NA	NA	NA	-0.010	0.079	-0.007	0.147
Visual analogue scale								
PCI	NA	NA	NA	NA	-0.153	0.861	NA	NA
PCA	NA	NA	NA	NA	-0.350	0.268	NA	NA
Charlson index								
Executive functions	-0.133	0.226	NA	NA	NA	NA	NA	NA
Treated with abiraterone acetate								
PCA	NA	NA	NA	NA	-2.564	0.055	NA	NA
Treated with enzalutamide								
Visual memory	NA	NA	NA	NA	NA	NA	-0.013	0.953

ADT: androgen deprivation therapy. FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue. fNART: French National Adult Reading Test. HADS: Hospital Anxiety and Depression Scale. IADL: Instrumental Activities of Daily Life. ISI: Insomnia Severity Index. PCI: Perceived cognitive abilities. PCI: Perceived cognitive impairment.

NA Not applicable for factors that were not predictive in univariable models. Factors that were not predictive for any domain are not shown.
[1] Models adjusted on baseline age and education.
[2] Models adjusted on baseline age, education and cognition.

Supplementary information 4: Criteria for estimating frequency of cognitive impairment and decline

1. Frequency of overall objective cognitive impairment at baseline

For objective cognition, Z-scores were calculated for each cognitive measure using HC scores as a reference

$$z = \frac{X_p - \overline{X_{HC}}}{S_{HC}} \tag{1}$$

z: individual Z-score, where X_p is the score of the patient, $\overline{X_{HC}}$ and S_{HC} are the mean score and the standard deviation of HC, respectively.

The frequency of objective cognitive impairment was estimated as follows: (1) the proportion of participants with a Z-score ≤-2SD was calculated for each measure, (2) the proportion of participants with a Z-score ≤-1.5SD in at least two measures or ≤-2SD in at least one measure was calculated for each objective domain, and (3) the proportion of patients impaired in at least two domains was calculated to obtain an estimate of the frequency of overall objective cognitive impairment.

2. Frequency of overall objective cognitive decline during follow-up

The frequency of objective cognitive decline was estimated as follows: (1) individual Reliable change indexes (RCI) were calculated using the baseline measures as a reference and variations in HC measures as a correction for the practice effect, then the proportion of participants with a RCI ≤-1.645 was calculated for each measure, (2) the proportion of participants with a composite RCI (the mean RCI of the corresponding measures) ≤-1.645 was calculated for each objective domain, and (3) the proportion of patients impaired in at least two domains was calculated to obtain an estimate of overall objective decline.

$$SED = \sqrt{2(S1_p\sqrt{1-r})^2} \tag{2.1}$$

SED: standard error of the difference, where $S1_p$ is the standard deviation of patients at baseline, and r is the correlation between the baseline and follow-up scores.

$$RCI = (X2_p - X1_p) - \frac{(\overline{X2_{HC}} - \overline{X1_{HC}})}{SED} \tag{2.2}$$

RCI: individual reliable change index, where $X1_p$ and $X2_p$ are the scores of patient at baseline and during follow-up, respectively, and $\overline{X1_{HC}}$ and $\overline{X2_{HC}}$ are the mean scores of HC at baseline and during follow-up, respectively.

3. Frequency of subjective impairment at baseline and subjective decline during follow-up

Subjective cognition was assessed with the raw scores of the Perceived cognitive impairment (PCI) and Perceived cognitive abilities (PCA) subscales of the Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog).

The frequency of subjective impairment was estimated separately for PCI and PCA by calculating the proportion of participants scoring ≤10th percentile of published norms.

The frequency of subjective decline was estimated separately of PCI and PCA by calculating the proportion of participants with a score decreasing ≥10% from baseline.

Supplementary information 5A: Raw scores and Z-scores for cognitive impairment at baseline (unadjusted)

	All patients (ADT+/-ARPI) n=93			ADT+ARPI n=74			ADT n=19			HC n=30	
	mean (SD)	z	impaired	mean (SD)	z	impaired	mean (SD)	z	impaired	mean (SD)	impaired
Overall objective impairment[1]			46%			51%			26%		10%
Processing speed/attention		-0.977	24%		-1.171	28%		-0.221	5%		3%
Digit symbol-coding (WAIS-III): correct reproductions	45.1 (13.0)	-0.988	16%	42.9 (12.6)	-1.149	19%	53.5 (10.9)	-0.364	5%	58.4 (13.4)	0%
TMT: time A	54.6 (24.4)	-0.966	17%	57.8 (25.9)	-1.193	22%	42.1 (10.8)	0.079	0%	41.1 (13.9)	3%
Working memory		-0.530	8%		-0.487	4%		-0.700	21%		0%
Digit span (WAIS-III): score forward	7.6 (1.7)	-0.629	4%	7.7 (1.6)	-0.567	1%	7.2 (2.3)	-0.874	16%	8.8 (1.9)	0%
Digit span (WAIS-III): score backward	4.9 (1.7)	-0.431	0%	5.0 (1.7)	-0.407	0%	4.6 (1.7)	-0.526	0%	5.8 (2.1)	0%
Verbal memory		-0.880	34%		-1.055	42%		-0.216	5%		10%
Grober-Buschke test: sum of three free recalls	22.4 (7.0)	-0.676	11%	21.6 (7.2)	-0.819	14%	25.7 (4.9)	-0.134	0%	26.4 (5.8)	0%
Grober-Buschke test: sum of three total recalls	43.0 (5.0)	-0.771	12%	42.4 (5.4)	-0.953	15%	45.0 (2.3)	-0.079	0%	45.3 (3.1)	3%
Grober-Buschke test: free delayed recall	8.6 (3.2)	-0.848	18%	8.2 (3.4)	-0.999	22%	10.1 (1.8)	-0.273	0%	10.7 (2.5)	3%
Grober-Buschke test: total delayed recall	14.5 (1.9)	-1.224	23%	14.3 (2.0)	-1.448	28%	15.3 (0.8)	-0.376	5%	15.6 (0.8)	3%
Visual memory		0.015	9%		-0.053	11%		0.279	0%		7%
Doors test: test A	10.0 (1.6)	-0.135	5%	9.8 (1.7)	-0.239	7%	10.7 (0.9)	0.271	0%	10.2 (1.8)	7%
Doors test: test B	5.9 (2.0)	0.164	3%	5.9 (2.0)	0.133	4%	6.2 (2.0)	0.286	0%	5.5 (1.9)	0%
Visuospatial abilities		-0.408	29%		-0.412	30%		-0.396	26%		7%
Rey-Osterrieth complex figure: copy score	29.3 (5.5)	-0.153	10%	29.1 (5.5)	-0.180	10%	29.7 (5.7)	-0.052	11%	29.8 (4.3)	3%
Number location (VOSP): total score	8.6 (1.7)	-0.645	25%	8.6 (1.6)	-0.621	26%	8.5 (2.1)	-0.739	21%	9.1 (0.8)	7%
Executive functions		-0.901	59%		-1.004	60%		-0.518	58%		20%
TMT: time B/A	2.9 (1.1)	-0.542	15%	2.8 (1.1)	-0.475	15%	3.1 (1.0)	-0.769	16%	2.5 (0.7)	3%
TMT: errors B	1.0 (1.2)	-1.372	29%	1.0 (1.2)	-1.375	27%	1.0 (0.9)	-1.360	37%	0.3 (0.7)	0%
Stroop Victoria: time interference/colors	2.7 (1.2)	-0.702	15%	2.8 (1.3)	-0.826	16%	2.4 (0.6)	-0.247	11%	2.3 (0.6)	7%
Stroop Victoria: total errors interference	1.8 (2.7)	-1.072	27%	2.1 (2.9)	-1.292	30%	0.9 (1.4)	-0.248	16%	0.7 (1.0)	10%
Verbal fluencies: letter fluency	18.2 (7.4)	-0.814	15%	17.8 (7.2)	-0.876	17%	19.7 (8.1)	-0.583	11%	23.4 (6.4)	0%
Verbal fluencies: category fluency	23.6 (8.3)	-0.749	22%	22.4 (7.8)	-0.973	25%	28.4 (8.6)	0.101	11%	27.8 (5.7)	3%
Subjective impairment[2]											
FACT-Cog: PCI	57.8 (12.1)		24%	57.4 (11.6)		24%	59.7 (14)		22%	63.1 (5.6)	7%
FACT-Cog: PCA	18.9 (5.8)		18%	18.3 (6.0)		20%	21.0 (4.2)		11%	19.6 (4.0)	7%

ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. FACT-Cog: Functional Assessment of Cancer Therapy - Cognitive Function. HC: healthy controls without cancer. PCA: Perceived cognitive abilities. PCI: Perceived cognitive impairment. SD: standard deviation. TMT: Trail-Making Test. VOSP: Visual Object and Space Perception Battery. WAIS-III: Wechsler Adult Intelligent Scale, third edition.

[1] Proportion of participants impaired in at least two objective domains.

[2] Proportion of participants with a FACT-Cog – PCI and PCA score ≤10th percentile of norms[27].

Supplementary information 5B: Raw scores and RCI for cognitive decline at 3 months (unadjusted)

	All patients (ADT+/-ARPI) n=93			ADT+ARPI n=74			ADT n=19			HC n=30	
	mean (SD)	RCI	declined	mean (SD)	RCI	declined	mean (SD)	RCI	declined	mean (SD)	declined
Overall objective decline[1]			3%			3%			5%		0%
Processing speed/attention		-0.209	5%		-0.281	7%		0.063	0%		3%
Digit symbol-coding (WAIS-III): correct reproductions	43.6 (14.2)	-0.382	10%	41.1 (13.6)	-0.452	12%	53.3 (12.3)	-0.115	0%	58.3 (15.1)	7%
TMT: time A	55.3 (22.3)	-0.009	11%	57.9 (23.5)	-0.074	14%	45.4 (13.9)	0.241	0%	42.0 (14.0)	7%
Working memory		-0.304	2%		-0.411	3%		0.105	0%		0%
Digit span (WAIS-III): score forward	7.7 (1.8)	-0.338	20%	7.7 (1.9)	-0.440	21%	7.8 (1.5)	0.054	16%	9.4 (2.28)	13%
Digit span (WAIS-III): score backward	4.7 (2.0)	-0.270	8%	4.6 (1.9)	-0.381	10%	5.3 (2.1)	0.156	0%	6.1 (2.1)	3%
Verbal memory		0.025	5%		0.117	3%		-0.323	11%		3%
Grober-Buschke test: sum of three free recalls	22.5 (8.1)	-0.095	9%	21.7 (8.5)	-0.089	10%	25.6 (5.2)	-0.118	6%	26.8 (5.6)	10%
Grober-Buschke test: sum of three total recalls	42.2 (5.8)	-0.013	12%	41.9 (6.0)	0.049	13%	43.2 (5.1)	-0.253	11%	44.5 (3.4)	7%
Grober-Buschke test: free delayed recall	8.8 (3.3)	-0.005	7%	8.6 (3.4)	0.094	4%	9.3 (2.8)	-0.382	17%	10.7 (2.2)	3%
Grober-Buschke test: total delayed recall	14.6 (2.1)	0.138	10%	14.6 (2.1)	0.317	9%	14.7 (2.1)	-0.539	17%	15.5 (0.8)	3%
Visual memory		-0.620	19%		-0.670	21%		-0.430	11%		0%
Doors test: test A	9.8 (1.9)	-0.503	22%	9.6 (1.9)	-0.491	23%	10.5 (1.5)	-0.551	16%	10.6 (1.5)	3%
Doors test: test B	5.6 (2.2)	-0.744	31%	5.3 (2.2)	-0.860	35%	6.5 (2.0)	-0.308	16%	6.4 (2.1)	17%
Visuospatial abilities		0.077	1%		0.044	1%		0.196	0%		0%
Rey-Osterrieth complex figure: copy score	29.8 (4.2)	-0.106	6%	29.5 (4.3)	-0.196	7%	31.3 (3.3)	0.234	0%	30.5 (3.6)	3%
Number location (VOSP): total score	8.8 (1.4)	0.245	9%	8.8 (1.4)	0.268	8%	8.6 (1.7)	0.158	11%	9.1 (1.1)	10%
Executive functions		0.132	0%		0.209	0%		-0.148	0%		0%
TMT: time B/A	2.9 (1.2)	0.124	13%	2.9 (1.3)	0.338	7%	2.6 (0.9)	-0.587	33%	2.4 (0.6)	3%
TMT: errors B	1.1 (1.5)	0.162	6%	1.3 (1.6)	0.357	5%	0.6 (0.9)	-0.489	11%	0.4 (0.7)	0%
Stroop Victoria: time interference/colors	2.7 (1.2)	0.098	14%	2.8 (1.3)	0.144	15%	2.3 (0.5)	-0.066	11%	2.2 (0.5)	3%
Stroop Victoria: total errors interference	2.1 (3.1)	0.358	16%	2.3 (3.3)	0.392	16%	1.1 (1.6)	0.237	16%	0.6 (1.0)	10%
Verbal fluencies: letter fluency	17.7 (6.6)	-0.150	7%	17.7 (6.8)	-0.080	6%	17.7 (6.2)	-0.409	11%	23.6 (5.5)	7%
Verbal fluencies: category fluency	23.9 (7.9)	0.216	6%	22.5 (7.2)	0.190	6%	29.0 (8.6)	0.310	5%	26.8 (6.2)	10%
Subjective decline[2]											
FACT-Cog: PCI	56.2 (12.9)		37%	54.8 (13.0)		42%	61.0 (11.8)		17%	62.1 (6.8)	17%
FACT-Cog: PCA	18.6 (5.1)		41%	18.2 (5.1)		48%	20.1 (4.6)		17%	19.5 (4.8)	33%

ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. FACT-Cog: Functional Assessment of Cancer Therapy - Cognitive Function. HC: healthy controls without cancer. PCA: Perceived cognitive abilities. PCI: Perceived cognitive impairment. RCI: reliable change index. SD: standard deviation. TMT: Trail-Making Test. VOSP: Visual Object and Space Perception Battery. WAIS-III: Wechsler Adult Intelligent Scale, third edition.

[1] Proportion of participants declining in at least two objective domains.

[2] Proportion of participants with a FACT-Cog – PCI and PCA score decreasing ≥10% from baseline.

Supplementary information 5C: Raw scores and RCI for cognitive decline at 6 months (unadjusted)

	All patients (ADT+/-ARPI) n=71			ADT+ARPI n=54			ADT n=17			HC n=28	
	mean (SD)	RCI	declined	mean (SD)	RCI	declined	mean (SD)	RCI	declined	mean (SD)	declined
Overall objective decline[1]			4%			6%			0%		0%
Processing speed/attention		-0.055	3%		-0.037	4%		-0.117	0%		0%
Digit symbol-coding (WAIS-III): correct reproductions	46.4 (14.5)	-0.542	14%	43.1 (13.2)	-0.654	17%	57.4 (13.3)	-0.172	6%	60.9 (14.5)	4%
TMT: time A	58.6 (33.5)	0.618	10%	64.1 (35.9)	0.820	9%	40.3 (12.5)	-0.061	12%	41.8 (10.8)	4%
Working memory		-0.174	3%		-0.236	4%		0.033	0%		0%
Digit span (WAIS-III): score forward	7.9 (2.0)	-0.037	3%	7.9 (1.9)	-0.083	2%	7.9 (2.4)	0.121	6%	9.0 (2.0)	7%
Digit span (WAIS-III): score backward	5.1 (1.9)	-0.312	3%	5.0 (1.9)	-0.388	2%	5.5 (1.3)	-0.055	6%	6.4 (2.3)	0%
Verbal memory		0.046	2%		0.048	2%		0.040	0%		4%
Grober-Buschke test: sum of three free recalls	24.2 (7.2)	0.094	5%	23.2 (7.4)	0.066	6%	27.4 (5.6)	0.185	0%	26.8 (6.7)	4%
Grober-Buschke test: sum of three total recalls	41.5 (5.7)	-0.086	17%	40.9 (6.2)	-0.116	21%	43.5 (3.4)	0.012	7%	43.5 (4.2)	11%
Grober-Buschke test: free delayed recall	10.0 (2.9)	0.084	5%	9.5 (3.1)	0.076	7%	11.4 (1.9)	0.108	0%	11.3 (2.3)	7%
Grober-Buschke test: total delayed recall	14.6 (1.8)	0.026	8%	14.5 (1.9)	0.082	9%	15.1 (1.0)	-0.145	7%	15.4 (1.1)	7%
Visual memory		-0.423	3%		-0.440	4%		-0.370	0%		4%
Doors test: test A	10.3 (1.6)	-0.165	4%	10.0 (1.7)	-0.173	6%	11.1 (1.0)	-0.142	0%	10.7 (1.3)	4%
Doors test: test B	5.8 (1.9)	-0.689	14%	5.6 (1.9)	-0.717	15%	6.4 (1.9)	-0.598	12%	6.9 (2.0)	7%
Visuospatial abilities		-0.274	8%		-0.377	10%		0.045	0%		0%
Rey-Osterrieth complex figure: copy score	30.5 (4.6)	-0.149	9%	30.0 (4.9)	-0.248	10%	32.1 (2.8)	0.161	6%	30.9 (3.3)	7%
Number location (VOSP): total score	8.8 (1.5)	-0.402	27%	8.6 (1.7)	-0.505	25%	9.3 (0.9)	-0.072	31%	9.5 (0.9)	7%
Executive functions		0.152	0%		0.207	0%		-0.017	0%		0%
TMT: time B/A	2.7 (0.8)	0.080	3%	2.6 (0.8)	0.053	0%	2.9 (0.9)	0.166	13%	2.4 (0.7)	4%
TMT: errors B	0.8 (1.0)	-0.088	5%	0.8 (1.1)	-0.026	6%	0.7 (0.9)	-0.280	0%	0.5 (0.9)	0%
Stroop Victoria: time interference/colors	2.4 (1.0)	0.485	3%	2.5 (1.1)	0.621	2%	2.2 (0.5)	0.077	6%	2.1 (0.5)	7%
Stroop Victoria: total errors interference	1.0 (2.0)	0.161	15%	1.2 (2.3)	0.138	18%	0.5 (0.9)	0.234	6%	0.4 (0.7)	11%
Verbal fluencies: letter fluency	18.9 (6.8)	-0.237	8%	18.2 (7.1)	-0.209	4%	21.1 (5.5)	-0.323	19%	23.9 (6.3)	4%
Verbal fluencies: category fluency	26.4 (8.5)	0.224	2%	25.0 (8.1)	0.290	0%	30.9 (8.2)	0.019	6%	28.3 (6.7)	0%
Subjective decline[2]											
FACT-Cog: PCI	53.9 (15.0)		50%	51.7 (15.1)		57%	60.4 (12.8)		29%	60.6 (9.3)	30%
FACT-Cog: PCA	17.6 (5.5)		42%	16.8 (5.4)		47%	20.2 (5.2)		29%	19.6 (4.0)	37%

ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. FACT-Cog: Functional Assessment of Cancer Therapy - Cognitive Function. HC: healthy controls without cancer. PCA: Perceived cognitive abilities. PCI: Perceived cognitive impairment. RCI: reliable change index. SD: standard deviation. TMT: Trail-Making Test. VOSP: Visual Object and Space Perception Battery. WAIS-III: Wechsler Adult Intelligent Scale, third edition.

[1] Proportion of participants declining in at least two objective domains.

[2] Proportion of participants with a FACT-Cog – PCI and PCA score decreasing ≥10% from baseline.

Supplementary information 5D: Raw scores and RCI for cognitive decline at 12 months (unadjusted)

	All patients (ADT+/-ARPI) n=55			ADT+ARPI n=42			ADT n=13			HC n=29	
	mean (SD)	RCI	declined	mean (SD)	RCI	declined	mean (SD)	RCI	declined	mean (SD)	declined
Overall objective decline[1]			4%			2%			8%		0%
Processing speed/attention		-0.202	5%		-0.256	5%		-0.027	8%		0%
Digit symbol-coding (WAIS-III): correct reproductions	44.9 (13.1)	-0.700	16%	41.5 (11.8)	-0.877	19%	56.0 (10.6)	-0.125	8%	59.1 (14.9)	7%
TMT: time A	55.9 (18.5)	0.296	9%	59.5 (18.3)	0.365	12%	44.5 (14.3)	0.072	0%	43.1 (12.1)	7%
Working memory		-0.184	0%		-0.297	0%		0.182	0%		0%
Digit span (WAIS-III): score forward	8.1 (1.8)	-0.100	16%	8.3 (1.8)	-0.161	17%	7.7 (1.7)	0.096	15%	9.2 (2.2)	10%
Digit span (WAIS-III): score backward	5.0 (1.9)	-0.267	2%	4.8 (1.7)	-0.432	2%	5.8 (2.1)	0.268	0%	6.1 (2.0)	0%
Verbal memory		-0.218	10%		-0.227	8%		-0.191	15%		0%
Grober-Buschke test: sum of three free recalls	24.9 (7.9)	-0.545	17%	23.7 (7.5)	-0.693	20%	28.6 (8.5)	-0.089	8%	30.3 (6.3)	3%
Grober-Buschke test: sum of three total recalls	43.4 (5.3)	-0.259	8%	42.7 (5.8)	-0.402	10%	45.4 (2.5)	0.182	0%	45.9 (2.5)	3%
Grober-Buschke test: free delayed recall	10.6 (3.1)	-0.109	8%	10.4 (3.2)	-0.080	8%	11.3 (2.5)	-0.194	8%	12.1 (1.9)	0%
Grober-Buschke test: total delayed recall	15.1 (1.5)	-0.058	16%	15.1 (1.6)	0.149	13%	15.2 (1.4)	-0.664	23%	15.9 (0.3)	3%
Visual memory		-0.346	7%		-0.385	7%		-0.220	8%		0%
Doors test: test A	10.4 (1.4)	-0.240	7%	10.3 (1.5)	-0.148	5%	10.8 (1.4)	-0.533	15%	10.9 (1.1)	0%
Doors test: test B	6.5 (2.3)	-0.451	11%	6.1 (2.1)	-0.623	12%	7.9 (2.5)	0.093	8%	6.8 (2.2)	3%
Visuospatial abilities		-0.112	2%		-0.157	2%		0.027	0%		3%
Rey-Osterrieth complex figure: copy score	31.3 (2.9)	-0.132	4%	31.1 (3.2)	-0.108	2%	32.1 (2.1)	-0.208	8%	31.1 (3.4)	3%
Number location (VOSP): total score	8.9 (1.5)	-0.013	13%	8.7 (1.5)	-0.100	15%	9.4 (1.7)	0.262	8%	9.2 (1.1)	7%
Executive functions		-0.110	2%		0.016	2%		-0.496	0%		0%
TMT: time B/A	2.3 (0.7)	-0.116	18%	2.4 (0.6)	0.026	15%	2.3 (0.9)	-0.581	25%	2.2 (0.5)	4%
TMT: errors B	0.6 (0.9)	-0.223	37%	0.7 (0.9)	0.038	31%	0.3 (0.7)	-1.072	58%	0.3 (0.5)	18%
Stroop Victoria: time interference/colors	2.4 (0.7)	0.453	6%	2.4 (0.8)	0.567	5%	2.24 (0.6)	0.114	8%	2.1 (0.4)	3%
Stroop Victoria: total errors interference	0.9 (1.4)	-0.116	11%	1.0 (1.6)	-0.198	12%	0.8 (0.7)	0.138	8%	0.5 (0.9)	7%
Verbal fluencies: letter fluency	18.0 (6.5)	-0.519	12%	17.6 (6.5)	-0.461	10%	19.5 (6.7)	-0.695	15%	24.6 (6.1)	7%
Verbal fluencies: category fluency	25.8 (7.6)	-0.303	19%	25.1 (7.5)	-0.108	15%	28.1 (7.7)	-0.889	31%	29.3 (7.0)	0%
Subjective decline[2]											
FACT-Cog: PCI	54.9 (14.3)		40%	53.5 (14.4)		46%	59.4 (13.6)		23%	61.0 (7.7)	14%
FACT-Cog: PCA	17.6 (5.6)		42%	17.0 (5.9)		46%	19.4 (4.2)		31%	19.8 (3.9)	28%

ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. FACT-Cog: Functional Assessment of Cancer Therapy - Cognitive Function. HC: healthy controls without cancer. PCA: Perceived cognitive abilities. PCI: Perceived cognitive impairment. RCI: reliable change index. SD: standard deviation. TMT: Trail-Making Test. VOSP: Visual Object and Space Perception Battery. WAIS-III: Wechsler Adult Intelligent Scale, third edition.

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