Title: A European, prospective, observational study of enzalutamide in patients with metastatic castration-resistant prostate cancer: PREMISE

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Supporting Information

Sample size estimation was based on the precision desired for the 95% confidence intervals of the primary endpoint, time to treatment failure, and expected patient dropout rate of 20%. Based on the previous criteria, a minimum number of 1930 patients were expected to be enrolled in the following cohorts based on treatment history: 532 chemotherapy-naïve and abiraterone-naïve patients in cohort 1; 397 post-chemotherapy and abiraterone-naïve patients in cohort 2; 601 chemotherapy-naïve and post-abiraterone patients in cohort 3; and 400 post-chemotherapy and post-abiraterone patients (ie, patients who received prior chemotherapy and then abiraterone consecutively) in cohort 4. However, final cohort sample sizes could differ as study enrollment was not controlled for sample size by treatment history groups.

TABLE S1 Endpoint definitions

Endpoint variable	Definition
TTF	Time from initiation of enzalutamide to the date of permanent treatment discontinuation for any reason, including disease progression (radiographic progression, PSA progression or clinical progression according to the investigator's assessment), skeletal-related events, treatment toxicity, patient preference, or death, whichever occurred first
Time to PSA progression	Time from initiation of enzalutamide to the date of PSA progression according to the investigator's assessment; PSA progression was defined as a PSA rise of ≥25% and an absolute increase of ≥2 ng/ml above nadir (ie, the lowest value reported at baseline or later)
PSA response	A 30, 50, or 90 percentage point reduction from the baseline PSA level
Time to disease progression	Time from initiation of enzalutamide to the date of radiographic progression, PSA progression, or clinical progression, whichever occurred first
EQ-5D-5L	An international, standardized, generic questionnaire to assess HRQoL. The population-preference-based health state utility score (EQ-5D index; range 0.59–1.0) and patient's overall health state on a visual analog scale (EQ-5D VAS; range 0–100) are reliable and valid for assessing HRQoL in cancer patients.[1] Higher scores represent better HRQoL. The index score range is based on the crosswalk algorithm used, where 1.0 represents full health, 0 represents dead, and negative values relate to states worse than dead
FACT-P	A multidimensional, self-reported, quality-of-life questionnaire used with prostate cancer patients consisting of 27 core items (FACT-G subscale) to assess patient function in four domains (physical, social/family, emotional, and functional well-being) and is supplemented by 12 specific items to assess for prostate-related symptoms (FACT-PCS scale). Each individual item is rated on a 0 to 4 Likert-type scale. Combined, the FACT-G (range 0–108) and FACT-PCS (range 0–48) subscale scores equal the FACT-P total score (range 0–156). Higher scores represent better HRQoL[2]

BPI-SF	A validated questionnaire that includes the four-item pain severity subscale and seven-item pain interference subscale. Individual items are measured on a scale of 0 to 10. Separate scores are presented for pain severity (the mean of items 3–6) and pain interference (the mean of item 9A–9G). Lower mean scores (range 0–10) represent lower levels of pain intensity or less interference of pain with activities of daily living (eg, sleep, mood, and activity)[3]
Safety	Assessed via TEAEs, modification of treatment with enzalutamide due to TEAEs (ie, dose changes or dose interruptions) and deaths. TEAEs were defined as an AE that started or worsened on or after the date of the first dose of enzalutamide, assessed up to 30 days following the end of enzalutamide treatment. Treatment-related TEAEs were considered related to enzalutamide treatment based on investigator's assessment. Deaths reported as a safety event included all deaths from any cause in the reporting period from the time of consent to the end of the study (including 30-day follow-up period)

Abbreviations: AE, adverse event; BPI-SF, Brief Pain Inventory–Short Form; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FACT-PCS, Functional Assessment of Cancer Therapy–Prostate Cancer Subscale; HRQoL, health-related quality of life; PSA, prostate-specific antigen; TEAE, treatment-emergent AE; TTF, time to treatment failure.

TABLE S2 MID thresholds for PRO instruments

PRO instruments	MID thresholds
EQ index	0.12[a]
EQ VAS	7[b]
FACT-P	6[b]
FACT-G	3[b]
FACT-PCS	2[b]
BPI–SF severity	2[b]
BPI–SF interference	1.25[c]

Abbreviations: BPI-SF, Brief Pain Inventory–Short Form; EQ, EuroQol; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FACT-PCS, Functional Assessment of Cancer Therapy–Prostate Cancer Subscale; MID, minimally important difference; PRO, patient-reported outcome; VAS, visual analog scale.

[a]The MID threshold for EQ index was based on 0.5 of the standard deviation for the current full study population at baseline.

[b]MID thresholds for EQ VAS, FACT-P, FACT-G, FACT-PCS, and BPI-SF severity were based on earlier estimates.[4-9]

[c]The MID threshold for BPI-SF interference was based on 0.5 of the standard deviation of the overall population's baseline score.

TABLE S3 Baseline demographics and disease history of enzalutamide-treated cohorts

	Enzalutamide cohort 1: chemotherapy naive + abiraterone naïve (n = 1175)	**Enzalutamide cohort 2: post-chemotherapy + abiraterone naïve (n = 418)**	**Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone (n = 42)**	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 97)**
Age, years, median (range)	77.0 (48–95)	71.0 (44–89)	79.0 (65–92)	73.0 (53–86)
Race, n (%)				
White	801 (68.2)	319 (76.3)	41 (97.6)	96 (99.0)
Black	6 (0.5)	4 (1.0)	0	0
Asian	5 (0.4)	1 (0.2)	0	0
Other	5 (0.4)	2 (0.5)	0	0
Missing	358 (30.5)	92 (22.0)	1 (2.4)	1 (1.0)
Country, n (%)				
France	337 (28.7)	82 (19.6)	0	0
UK	302 (25.7)	66 (15.8)	3 (7.1)	3 (3.1)
Italy	104 (8.9)	62 (14.8)	11 (26.2)	38 (39.2)
Netherlands	77 (6.6)	57 (13.6)	1 (2.4)	5 (5.2)
Denmark	72 (6.1)	21 (5.0)	2 (4.8)	13 (13.4)

Other[a]	283 (24.1)	130 (31.1)	25 (59.5)	38 (39.2)
Time since diagnosis of prostate cancer, years, median (range)	4.9 (0–36)	4.0 (0–27)	6.2 (1–22)	7.9 (1–19)
Time since diagnosis of metastasis, years, median (range)	1.0 (0–19)	1.6 (0–14)	2.3 (0–13)	3.5 (0–18)
Prior prostatectomy, n (%)	220 (18.7)	96 (23.0)	13 (31.0)	35 (36.1)
PSA, ng/mL, median (range)	27.7 (0.1–4384.0)	44.4 (0–5162.0)	17.7 (0.2–7651.1)	81.3 (0.8–3793.0)
Gleason score at diagnosis, n (%)				
<8	476 (40.5)	132 (31.6)	21 (50.0)	29 (29.8)
≥8	542 (46.1)	246 (58.8)	15 (35.7)	54 (55.7)
Unknown	156 (13.3)	40 (9.6)	6 (14.3)	14 (14.4)
Missing	1 (0.1)	0	0	0
Type of metastases, n (%)[b]				
Bone	928 (79.0)	359 (85.9)	33 (78.6)	83 (85.6)
Visceral	128 (10.9)	87 (20.8)	4 (9.5)	15 (15.5)

Both bone and visceral	86 (7.3)	69 (16.5)	1 (2.4)	11 (11.3)
Lymph nodes	395 (33.6)	148 (35.4)	17 (40.5)	40 (41.2)
ECOG score, n (%)[c]				
0	436 (46.0)	150 (44.5)	13 (35.1)	37 (42.1)
1	404 (42.6)	161 (47.8)	18 (48.7)	45 (51.1)
≥2	108 (11.4)	26 (7.7)	6 (16.2)	6 (6.8)

Note: Data presented as n (%) unless otherwise stated. Data from SAF (n = 1732).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; SAF, safety analysis set.

[a]Austria, Belgium, Bulgaria, Czech Republic, Germany, Greece, Hungary, Ireland, Portugal, Slovenia, and Spain.

[b]Categories are not mutually exclusive.

[c]322 patients missing; percentages calculated using denominators of 948 (cohort 1), 337 (cohort 2), 37 (cohort 3), and 88 (cohort 4).

TABLE S4 Primary endpoint: TTF for cohorts 3 and 4

	Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone (n = 42)	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 96)**
TTF, months, median (95% CI)[a]	7.1 (4.6–8.9)	4.6 (3.6–5.6)
Patients with treatment failure	30 (71.4)	83 (86.5)
Primary reason for treatment failure[b]		
PSA progression[c]	5 (11.9)	23 (24.0)
Radiographic progression	9 (21.4)	15 (15.6)
Clinical progression	6 (14.3)	15 (15.6)
Lack of efficacy	0	0
TEAEs	7 (16.7)	22 (22.9)
Withdrawal of consent by patient	3 (7.1)	1 (1.0)
Deaths[d]	0	4 (4.2)
Other	0	3 (3.1)

Note: Data presented as n (%) unless otherwise stated. Data from FAS (n = 1727).

Abbreviations: CI, confidence interval; FAS, full analysis set; PSA, prostate-specific antigen; TEAE, treatment-emergent adverse event; TTF, time to treatment failure.

[a]Defined as the time from initiation of enzalutamide to the date of treatment discontinuation for any reason, including disease progression, skeletal-related events, treatment toxicity, patient preference, or death.

[b]No skeletal-related events leading to treatment failure were observed across all cohorts.

[c]Defined as a PSA rise of ≥25% and an absolute increase of ≥2 ng/mL above nadir.

[d]Deaths that were the primary cause of treatment failure were those that occurred during the 18-month study period.

TABLE S5 Primary endpoint: TTF in subgroups defined by age

	Enzalutamide cohort 1: chemotherapy naïve + abiraterone naïve (n = 1171)	**Enzalutamide cohort 2: post-chemotherapy + abiraterone naïve (n = 418)**	**Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone (n = 42)**	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 96)**
Median age ≤ 75, n	509	294	13	58
TTF, months, median (95% CI)[a]	15.1 (13.7–17.0)	8.1 (6.8–9.8)	8.0 (5.8–NC)	4.0 (2.8–5.6)
Patients with treatment failure	272 (53.4)	216 (73.5)	8 (61.5)	50 (86.2)
Primary reason for treatment failure				
PSA progression[b]	86 (16.9)	58 (19.7)	1 (7.7)	14 (24.1)
Radiographic progression	74 (14.5)	77 (26.2)	4 (30.8)	10 (17.2)
Clinical progression	23 (4.5)	29 (9.9)	1 (7.7)	6 (10.3)
Lack of efficacy	7 (1.4)	3 (1.0)	0	0
TEAEs	50 (9.8)	40 (13.6)	2 (15.4)	14 (24.1)

Withdrawal of consent by patient	11 (2.2)	2 (0.7)	0	1 (1.7)
Deaths[c]	11 (2.2)	5 (1.7)	0	3 (5.2)
Other	10 (2.0)	2 (0.7)	0	2 (3.4)
Median age > 75, n	662	124	29	38
TTF, months, median (95% CI)[a]	11.2 (10.2–12.6)	9.0 (6.2–11.2)	5.7 (2.5–8.9)	5.0 (3.9–7.5)
Patients with treatment failure	418 (63.1)	95 (76.6)	22 (75.9)	33 (86.8)
Primary reason for treatment failure				
PSA progression[b]	102 (15.4)	35 (28.2)	4 (13.8)	9 (23.7)
Radiographic progression	70 (10.6)	23 (18.5)	5 (17.2)	5 (13.2)
Clinical progression	49 (7.4)	11 (8.9)	5 (17.2)	9 (23.7)
Lack of efficacy	3 (0.5)	1 (0.8)	0	0
TEAEs	136 (20.5)	13 (10.5)	5 (17.2)	8 (21.1)
Withdrawal of consent by patient	13 (2.0)	3 (2.4)	3 (10.3)	0
Deaths	27 (4.1)	4 (3.2)	0	1 (2.6)

Other	18 (2.7)	5 (4.0)	0	1 (2.6)

Note: Data presented as n (%) unless otherwise stated. Data from FAS (n = 1727).

Abbreviations: CI, confidence interval; FAS, full analysis set; NC, not calculable; PSA, prostate-specific antigen; TEAE, treatment-emergent adverse event; TTF, time to treatment failure.

[a]Defined as the time from initiation of enzalutamide to the date of treatment discontinuation for any reason, including disease progression, skeletal-related events, treatment toxicity, patient preference, or death.

[b]Defined as a PSA rise of ≥25% and an absolute increase of ≥2 ng/mL above nadir.

[c]Deaths that were the primary cause of treatment failure were those that occurred during the 18-month study period.

TABLE S6 Secondary endpoint: efficacy for cohorts 3 and 4

	Enzalutamide cohort 3: chemotherapy naïve + post abiraterone (n = 42)	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 96)**
PSA progression[a]		
Time to PSA progression, months, median (95% CI)	14.5 (8.0−NC)[b]	5.8 (3.4−6.5)
Patients with PSA progression	18 (42.9)	60 (62.5)
PSA response rate[c]		
30% (95% CI)	64.5 (47.7−81.4)	42.5 (31.7−53.3)
50% (95% CI)	48.4 (30.8−66.0)	31.3 (21.1−41.4)
90% (95% CI)	25.8 (10.4−41.2)	13.8 (6.2−21.3)
Disease progression		
Time to disease progression, months, median (95% CI)	8.0 (6.6−14.5)	3.4 (2.9−4.8)
Patients with disease progression[d]	26 (61.9)	77 (80.2)
PSA progression	18 (42.9)	59 (61.5)
Radiographic progression	13 (31.0)	34 (35.4)

Clinical progression	7 (16.7)	31 (32.3)

Note: Data presented as n (%) unless otherwise stated. Data from FAS (n = 1727).

Abbreviations: CI, confidence interval; FAS, full analysis set; NC, not calculable; PSA, prostate-specific antigen.

[a]PSA progression was defined as a PSA rise of ≥25% and an absolute increase of ≥2 ng/mL above nadir.

[b]NC is used to indicate those result values that are not calculated because the number of events was too small for the variable to be estimated.

[c]Defined as best percentage change in PSA levels from baseline.

[d]The percentage of patients with any type of disease progression calculated within the overall cohort; a patient can belong to more than one subcategory of disease progression.

TABLE S7 EQ-5D-5L scores at baseline and at 3-, 6-, and 9-month visits

	Enzalutamide cohort 1: Chemotherapy naïve + abiraterone naïve	**Enzalutamide cohort 2: post-chemotherapy + abiraterone naïve**	**Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone**	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone**
EQ index				
Baseline	n = 1109 0.71 (0.24)	n = 398 0.68 (0.24)	n = 42 0.67 (0.27)	n = 94 0.63 (0.24)
3 months	n = 925 0.72 (0.23)	n = 355 0.68 (0.24)	n = 31 0.68 (0.23)	n = 67 0.63 (0.24)
6 months	n = 693 0.73 (0.23)	n = 231 0.74 (0.20)	n = 21 0.73 (0.19)	n = 36 0.69 (0.27)
9 months	n = 558 0.76 (0.2)	n = 166 0.73 (0.23)	n = 13 0.83 (0.13)	n = 21 0.65 (0.32)
EQ VAS				
Baseline	n = 1105 68.0 (19.0)	n = 398 66.2 (20.4)	n = 42 63.6 (20.8)	n = 93 62.7 (20.1)

3 months	n = 925 58.8 (19.4)	n = 353 68.1 (20.3)	n = 31 63.2 (19.8)	n = 67 59.9 (22.8)
6 months	n = 697 70.4 (18.5)	n = 232 72.6 (17.8)	n = 21 67.1 (15.7)	n = 36 64.3 (21.0)
9 months	n = 558 71.9 (17.5)	n = 165 71.8 (19.5)	n = 13 65.0 (18.6)	n = 21 61.0 (25.0)

Note: Data presented as mean (SD) unless otherwise stated.

Abbreviations: EQ, EuroQol; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; SD, standard deviation; VAS, visual analog scale.

TABLE S8 FACT-P scores at baseline and 3-, 6-, and 9-month visits

	Enzalutamide cohort 1: chemotherapy naïve + abiraterone naïve	**Enzalutamide cohort 2: post-chemotherapy + abiraterone naïve**	**Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone**	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone**
FACT-P				
Baseline	n = 1086 109.5 (21.0)	n = 391 107.0 (22.3)	n = 42 106.7 (23.5)	n = 90 101.5 (22.5)
3 months	n = 908 109.5 (21.4)	n=356 105.8 (23.6)	n = 33 105.6 (23.6)	n = 67 101.2 (24.3)
6 months	n = 688 111.8 (20.6)	n = 229 112.8 (19.4)	n = 21 111.8 (20.3)	n = 37 108.3 (26.1)
9 months	n = 543 113.9 (18.9)	n = 164 111.6 (21.1)	n = 12 116.3 (14.6)	n = 20 104.0 (28.3)
FACT-G				
Baseline	n = 1090 78.7 (15.3)	n = 391 76.2 (16.2)	n = 42 76.2 (17.5)	n = 90 73.2 (17.0)
3 months	n = 916 77.8 (15.9)	n = 357 75.0 (17.1)	n = 33 75.1 (17.9)	n = 67 72.0 (18.1)
6 months	n = 694 79.5 (15.5)	n = 229 79.9 (14.3)	n = 21 79.8 (14.4)	n = 37 76.5 (19.0)

9 months	n = 550 81.0 (14.1)	n = 164 79.3 (15.7)	n = 12 80.8 (10.2)	n = 20 73.8 (19.6)
FACT-PCS				
Baseline	n = 1103 30.9 (7.5)	n = 397 30.8 (7.6)	n = 42 30.4 (7.5)	n = 90 28.3 (7.4)
3 months	n = 928 31.6 (7.3)	n = 358 30.8 (7.8)	n = 33 30.5 (7.5)	n = 67 29.2 (8.4)
6 months	n = 698 32.2 (6.8)	n = 235 33.0 (6.7)	n = 21 32.0 (7.1)	n = 37 31.8 (8.3)
9 months	n = 558 32.9 (6.5)	n = 165 32.4 (6.8)	n = 13 34.7 (6.4)	n = 21 30.4 (10.1)

Note: Data presented as mean (SD) unless otherwise stated.

Abbreviations: FACT-G, Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FACT-PCS, Functional Assessment of Cancer Therapy–Prostate Cancer Subscale; SD, standard deviation

TABLE S9 BPI-SF scores at baseline and 3-, 6-, 9-month visits

	Enzalutamide cohort 1: chemotherapy naïve + abiraterone naïve	**Enzalutamide cohort 2: post-chemotherapy + abiraterone naïve**	**Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone**	**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone**
Severity				
Baseline	n = 1075 2.01 (2.13)	n = 390 2.22 (2.07)	n = 38 2.37 (2.00)	n = 88 3.02 (2.48)
3 months	n = 883 1.80 (2.01)	n = 342 2.42 (2.24)	n = 33 1.87 (2.07)	n = 67 2.77 (2.35)
6 months	n = 666 1.74 (1.98)	n = 227 1.82 (1.98)	n = 21 1.88 (1.94)	n = 37 2.47 (2.22)
9 months	n = 532 1.55 (1.85)	n = 147 1.89 (2.01)	n = 13 0.56 (1.38)	n = 20 2.35 (2.80)
Interference				
Baseline	n = 1065 2.00 (2.41)	n = 380 2.56 (2.64)	n = 40 2.54 (2.68)	n = 89 3.49 (2.89)
3 months	n = 869 1.91 (2.27)	n = 343 2.62 (2.64)	n = 33	n = 65
6 months	n = 644 1.90 (2.29)	n = 226 1.88 (2.22)	n = 21 1.88 (2.05)	n = 37 2.70 (2.50)
9 months	n = 519 1.57 (2.01)	n = 149 2.01 (2.29)	n = 13 0.87 (1.99)	n = 20 2.51 (2.86)

Note: Data presented as mean (SD) unless otherwise stated.

Abbreviations: BPI-SF, Brief Pain Inventory–Short Form; SD, standard deviation.

TABLE S10 Secondary endpoint: treatment response at selected study visits based on MIDs for FACT-G and FACT-PCS

	Enzalutamide cohort 1: chemotherapy naïve + abiraterone naïve (n = 1171)			**Enzalutamide cohort 2: post-chemotherapy + abiraterone naïve (n = 418)**			**Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone (n = 42)**			**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 96)**		
	Improve	**No change**	**Worsen**	**Improve**	**No change**	**Worsen**	**Improve**	**No change**	**Worsen**	**Improve**	**No change**	**Worsen**
FACT-G (MID, 3)												
3 months	297 (34.4)	230 (26.7)	336 (38.9)	126 (37.2)	70 (20.7)	143 (42.2)	9 (27.3)	10 (30.3)	14 (42.4)	24 (38.1)	12 (19.1)	27 (42.9)
6 months	230 (34.8)	147 (22.2)	284 (43.0)	87 (40.3)	42 (19.4)	87 (40.3)	5 (23.8)	6 (28.6)	10 (47.6)	13 (37.1)	10 (28.6)	12 (34.3)
9 months	199 (37.9)	109 (20.8)	217 (41.3)	56 (35.7)	33 (21.0)	68 (43.3)	5 (41.7)	3 (25.0)	4 (33.3)	7 (36.8)	4 (21.1)	8 (42.1)
FACT-PCS (MID, 2)												
3 months	359 (40.8)	235 (26.7)	285 (32.4)	132 (38.3)	72 (20.9)	141 (40.9)	11 (33.3)	11 (33.3)	11 (33.3)	26 (41.3)	12 (19.1)	25 (39.7)
6 months	272 (40.6)	147 (21.9)	251 (37.5)	91 (40.3)	46 (20.4)	89 (39.4)	7 (33.3)	6 (28.6)	8 (38.1)	20 (57.1)	8 (22.9)	7 (20.0)
9 months	233 (43.5)	110 (20.5)	193 (36.0)	52 (32.7)	29 (18.2)	78 (49.1)	7 (53.9)	2 (15.4)	4 (30.8)	11 (55.0)	1 (5.0)	8 (40.0)

Note: Data are presented as n (%) unless otherwise stated.

Abbreviations: FACT-G, Functional Assessment of Cancer Therapy–General; FACT-PCS, Functional Assessment of Cancer Therapy–Prostate Cancer Subscale.

TABLE S11 Secondary endpoint: treatment response at selected study visits based on MIDs for the EQ-5D-5L, FACT-P, and BPI-SF scales[a]

	Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone (n = 42)			Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 96)		
	Improve	**No change**	**Worsen**	**Improve**	**No change**	**Worsen**
EQ index (MID, 0.12)[b]						
3 months	10 (32.3)	16 (51.6)	5 (16.1)	13 (20.3)	34 (53.1)	17 (26.6)
6 months	4 (19.1)	11 (52.4)	6 (28.6)	9 (25.0)	17 (47.2)	10 (27.8)
9 months	4 (30.8)	6 (46.2)	3 (23.1)	6 (30.0)	7 (35.0)	7 (35.0)
EQ-VAS (MID, 7)[c]						
3 months	10 (32.3)	12 (38.7)	9 (29.0)	14 (21.9)	27 (42.2)	23 (35.9)
6 months	6 (28.6)	7 (33.3)	8 (38.1)	6 (16.7)	17 (47.2)	13 (36.1)
9 months	4 (30.8)	6 (46.2)	3 (23.1)	5 (25.0)	5 (25.0)	10 (50.0)

FACT-P (MID, 6)[d]						
3 months	8 (24.2)	13 (39.4)	12 (36.4)	16 (25.4)	24 (38.1)	23 (36.5)
6 months	6 (28.6)	7 (33.3)	8 (38.1)	15 (42.9)	10 (28.6)	10 (28.6)
9 months	4 (33.3)	6 (50.0)	2 (16.7)	9 (47.4)	2 (10.5)	8 (42.1)
BPI-SF severity (MID, 2)[e]						
3 months	2 (6.5)	24 (77.4)	5 (16.1)	10 (16.7)	38 (63.3)	12 (20.0)
6 months	2 (10.5)	13 (68.4)	4 (21.1)	6 (17.1)	21 (60.0)	8 (22.9)
9 months	NA (NA)	7 (63.6)	4 (36.4)	1 (5.3)	13 (68.4)	5 (26.3)
BPI-SF interference (MID, 1.25)[e]						
3 months	5 (23.9)	19 (53.8)	8 (25.0)	10 (16.7)	35 (58.3)	15 (25.0)
6 months	3 (15.0)	14 (70.0)	3 (15.0)	6 (16.7)	20 (55.6)	10 (27.8)
9 months	1 (8.3)	6 (50.0)	5 (41.7)	5 (26.3)	7 (36.8)	7 (36.8)

Note: Data are presented as n (%) unless stated otherwise.

Abbreviations: BPI-SF, Brief Pain Inventory–Short Form; EQ, EuroQol; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; MID, minimally important difference; VAS, visual analog scale.

[a]Due to patient dropout at months 12, 15, and 18, data are only shown from months 3–9.

[b]On EQ index, 0 = equivalent to dead and 1 = perfect health.

[c]EQ-VAS is measured on a scale from 0–100, with higher values indicating better quality of life.

[d]FACT-P total score (range, 0–156) is the combination of FACT-G (range, 0–108) and FACT-PCS (range, 0–48) subscale scores, with higher scores indicating better quality of life.

[e]BPI-SF severity and interference are measured on a scale from 0–10, with higher scores indicating less pain severity or interference.

TABLE S12 Overview of dosing status, TEAEs, and deaths[a] per 100 patient-years in cohorts 3 and 4

	Enzalutamide cohort 3: chemotherapy naïve + post-abiraterone (n = 42)		**Enzalutamide cohort 4: post-chemotherapy + post-abiraterone (n = 97)**	
Treatment duration, median, days (IQR)	211.0 (80–482)		132.0 (72–234)	
Dosing status per patient[b]				
Dose modifications	5 (11.9)		5 (5.2)	
Dose interruptions	2 (4.8)		7 (7.2)	
	n (%)	IR[c]	n (%)	IR[c]
TEAEs	25 (59.5)	220.8	71 (73.2)	358.3
Treatment-related TEAEs	14 (33.3)	74.6	28 (28.9)	93.5
Serious TEAEs	4 (9.5)	11.9	34 (35.1)	75.9
Serious treatment-related TEAEs	0		2 (2.1)	5.3
TEAEs leading to treatment discontinuation	8 (19.0)	32.8	34 (35.1)	68.8
Treatment-related TEAEs leading to treatment discontinuation	4 (9.5)	14.9	10 (10.3)	26.5
Deaths[a]	2 (4.8)	6.0	11 (11.3)	19.4

Most frequently reported TEAEs (occurring in ≥5% of patients in any cohort)[d]				
Fatigue	6 (14.3)	20.9	19 (19.6)	33.5
Back pain	2 (4.8)	6.0	9 (9.3)	15.9
Asthenia	3 (7.1)	11.9	10 (10.3)	17.6
Decreased appetite	0		8 (8.2)	14.1
Malignant neoplasm progression	2 (4.8)	6.0	15 (15.5)	26.5
Hot flush	3 (7.1)	9.0	0	
Nausea	5 (11.9)	14.9	5 (5.2)	12.4
Constipation	1 (2.4)	3.0	1 (1.0)	1.8
Bone pain	2 (4.8)	6.0	5 (5.2)	8.8
Arthralgia	2 (4.8)	9.0	0	
General physical health deterioration	3 (7.1)	9.0	5 (5.2)	8.8
Anemia	1 (2.4)	3.0	8 (8.2)	21.2

Note: Data presented as n (%) unless otherwise stated. Data from SAF (n = 1732).

Abbreviations: IQR, interquartile range; IR, incidence rate; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

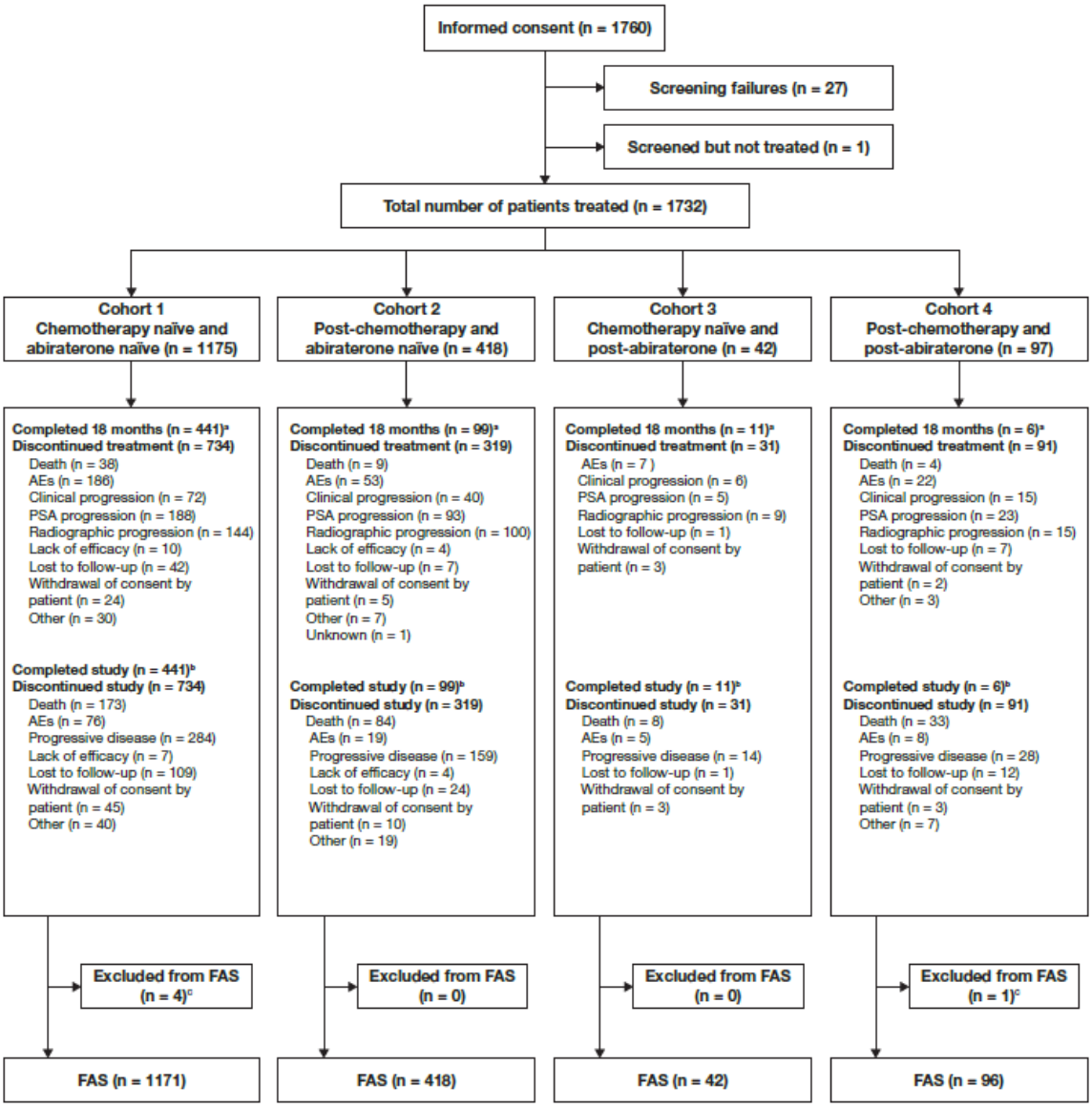
[a]TEAEs and deaths were reported from the time of consent until 30 days following enzalutamide treatment discontinuation.

[b]Patients can be counted in both dose changes and dose interruptions but will only count a maximum of once in each.

[c]The incidence rate, or the number of TEAEs per 100 patient-years, is calculated as: number of TEAEs x 100, divided by the sum of treatment-emergent period duration of all patients treated in the corresponding cohort in years.

[d]TEAEs were sorted by frequency in cohort 1, as this was the largest group.

FIGURE S1 Patient disposition flow chart



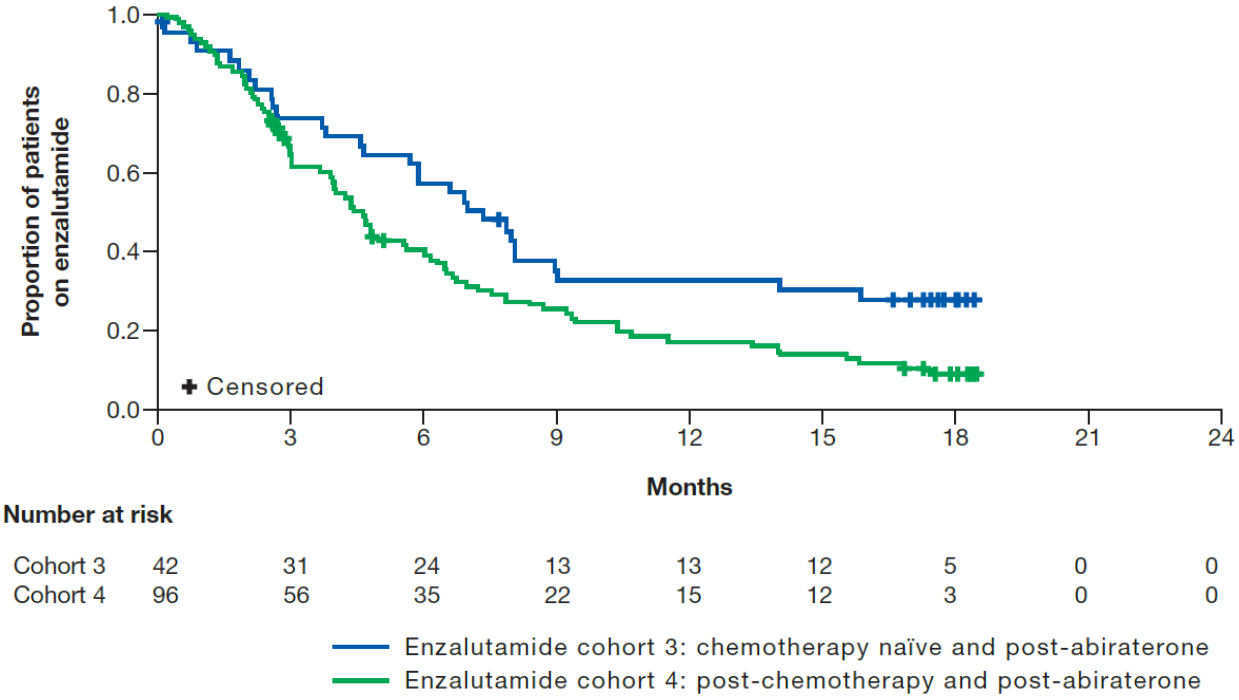
[a]From baseline until end of enzalutamide treatment period (up to a maximum of 18 months).

[b]From baseline until end of study (including follow-up after enzalutamide discontinuation).

[c]Excluded from FAS due to lack of post-baseline assessment.

FAS, full analysis set.

FIGURE S2 Kaplan–Meier estimate of TTF: cohorts 3 and 4

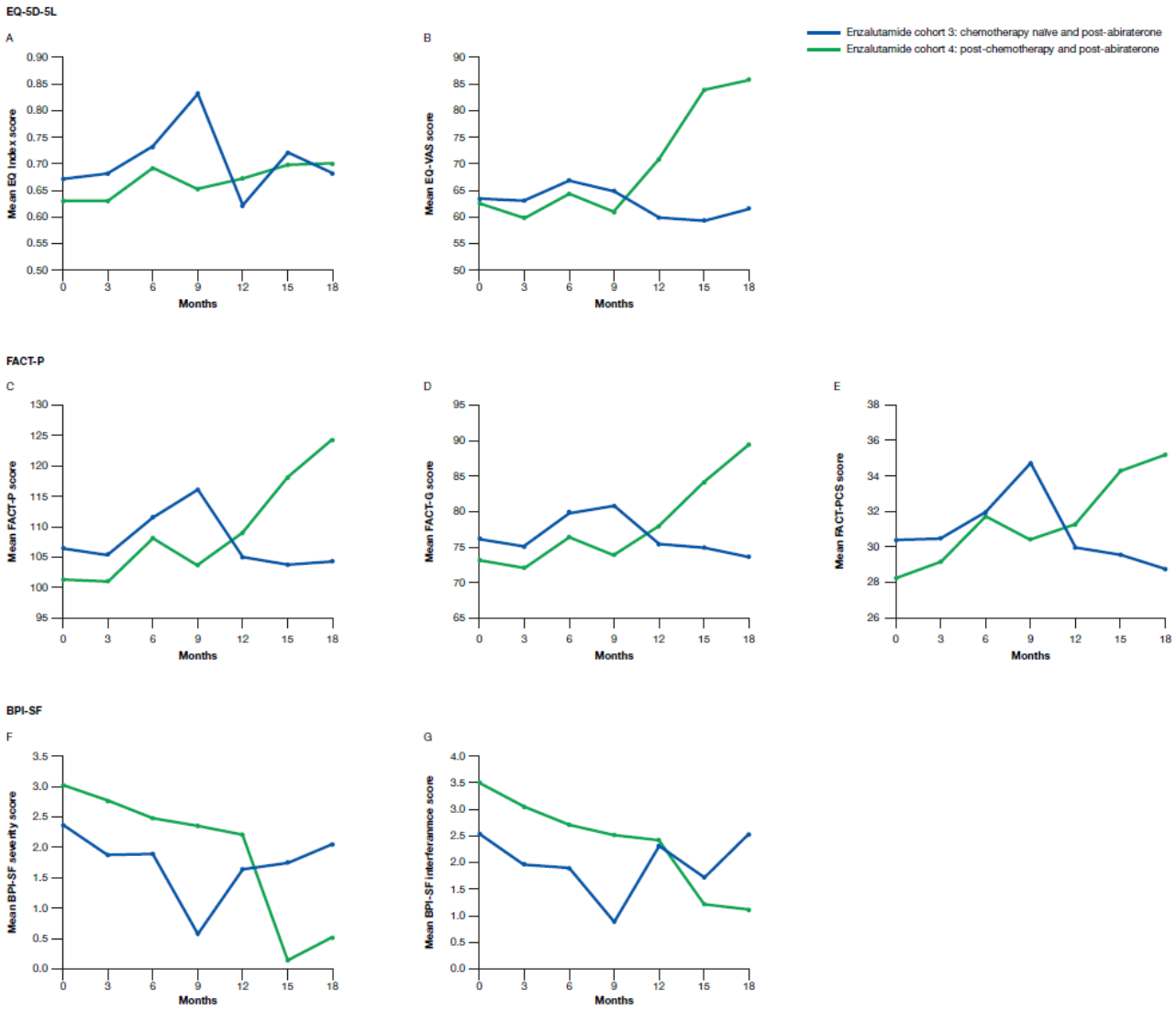


Number at risk

Cohort 3	42	31	24	13	13	12	5	0	0
Cohort 4	96	56	35	22	15	12	3	0	0

Enzalutamide cohort 3: chemotherapy naïve and post-abiraterone
Enzalutamide cohort 4: post-chemotherapy and post-abiraterone

FIGURE S3 Mean EQ-5D-5L (A−B), FACT-P (C−E), and BPI-SF (F−G) scores over time in cohorts 3 and 4



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