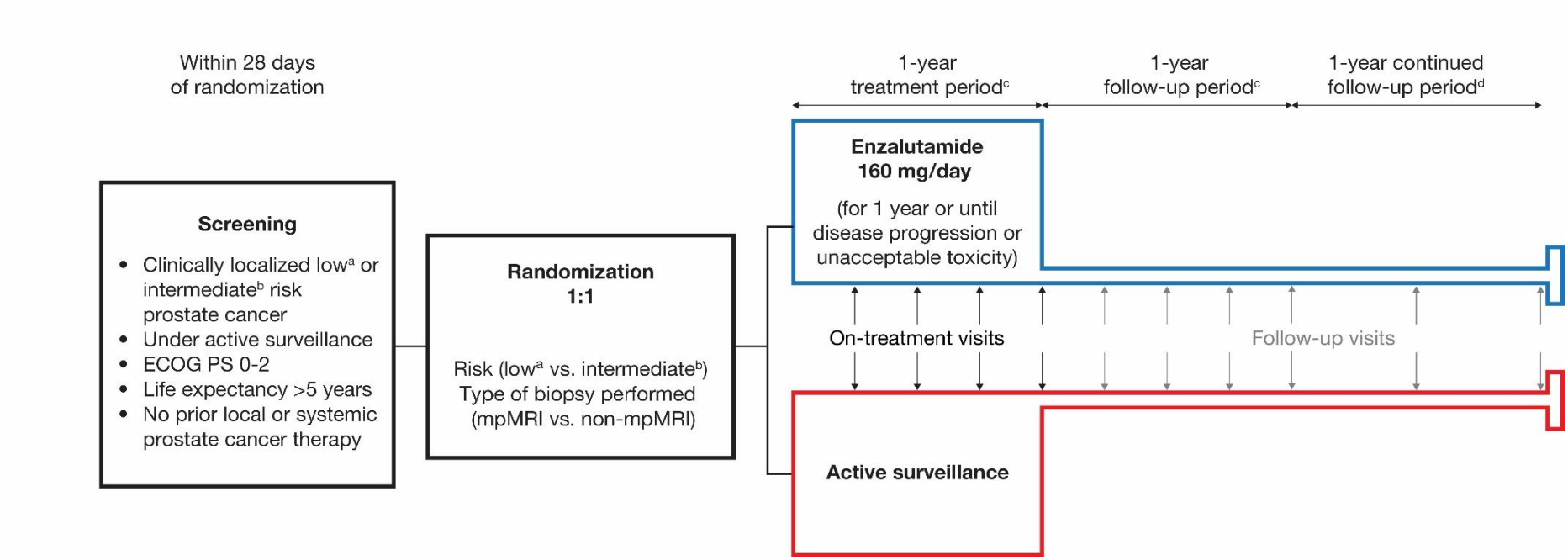
Supplemental Online Content

Shore ND, Renzulli J, Fleshner NE, et al. Enzalutamide monotherapy vs active surveillance in patients with low-risk or intermediate-risklocalized prostate cancer: the ENACT randomized clinical trial *JAMA Oncol.* Published online June 16, 2022. doi:10.1001/jamaoncol.2022.1641

This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Study Design



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; GS, Gleason score; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate-specific antigen.

[a] Low risk defined as T1c-T2a, PSA <10 ng/mL, N0, M0, and GS ≤6.

[b] Intermediate risk defined as T2b-T2c, PSA <20 ng/mL, N0, M0, and GS ≤7 (3+4 pattern only).

[c] During the 1-year treatment period and 1-year follow-up period, visits were every 3 months.

[d] During the 1-year continued follow-up period, visits were every 6 months until the last patient completed their 24-month visit.

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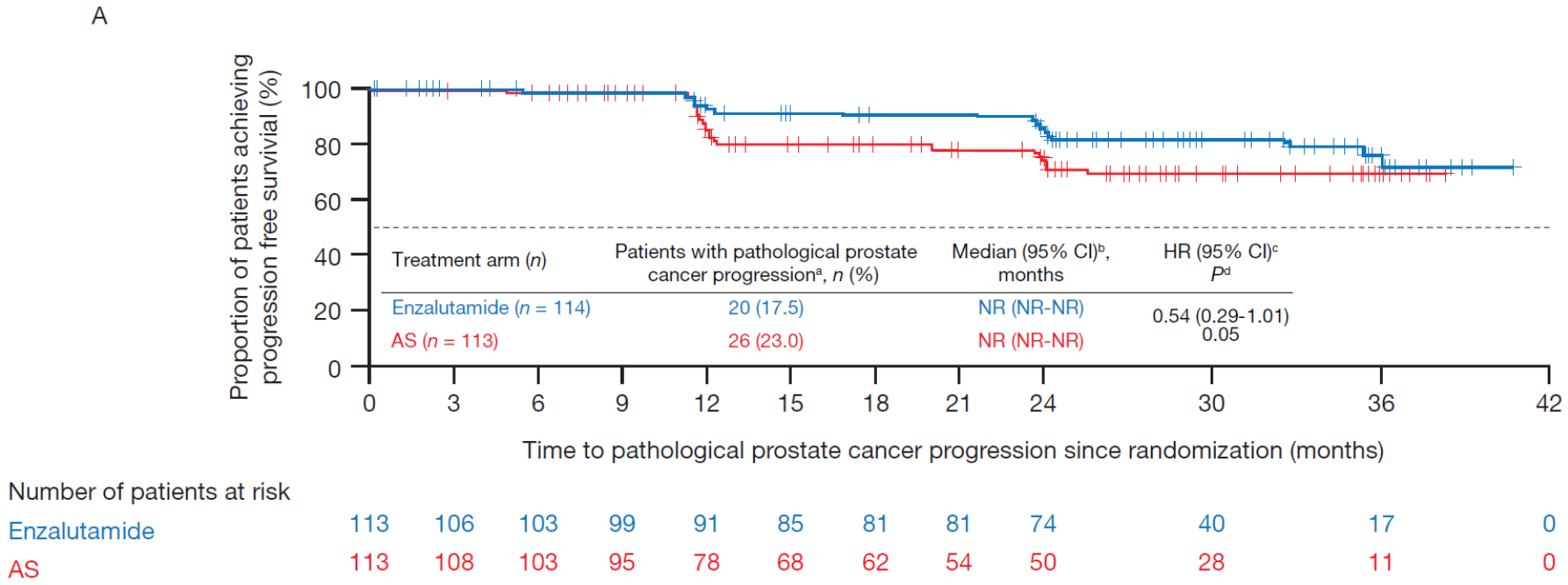
eFigure 2. Time to Prostate Cancer Progression by (A) Pathological and (B) Therapeutic Progression



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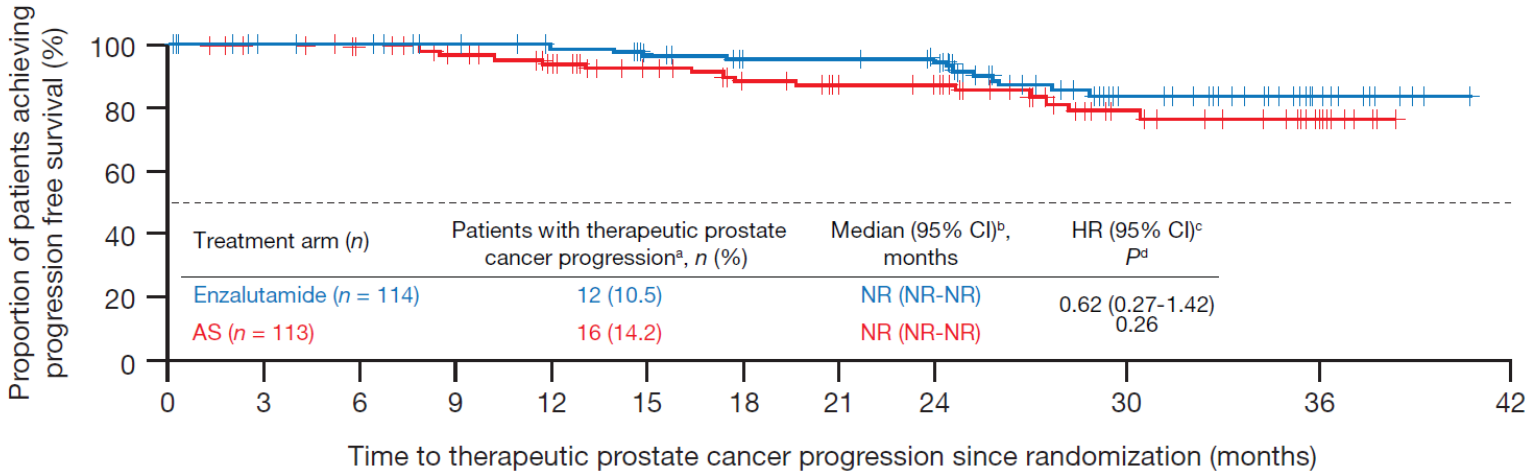

Number of patients at risk

Enzalutamide	113	106	104	99	95	88	81	81	77	41	17	0
AS	113	108	103	96	88	71	63	55	53	29	12	0

Abbreviations: AS, active surveillance; CI, confidence interval; HR, hazard ratio; NR, not reached.

Pathological progression defined as an increase in primary or secondary Gleason score pattern by ≥1 or higher proportion of cancer-positive cores (≥15% increase). Therapeutic progression defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy, radiation, focal therapy, or systemic therapy).

[a]Patients with no prostate cancer progression at the time of study completion, discontinuation, or death were censored at the last assessment date. Patients switching therapy during the study were censored at the time of the initial therapy switch, and patients discontinuing therapy were censored at the time of study discontinuation.

[b]Calculated using a two-sided, log-rank test.

[c]Calculated using a Cox regression model assuming proportional hazards with treatment group, stratification factors, age, race, and time since prostate cancer diagnosis as fixed effects, and study site and patient as random effects. HR <1 favors enzalutamide.

[d]Calculated using a two-sided, stratified, log-rank test.

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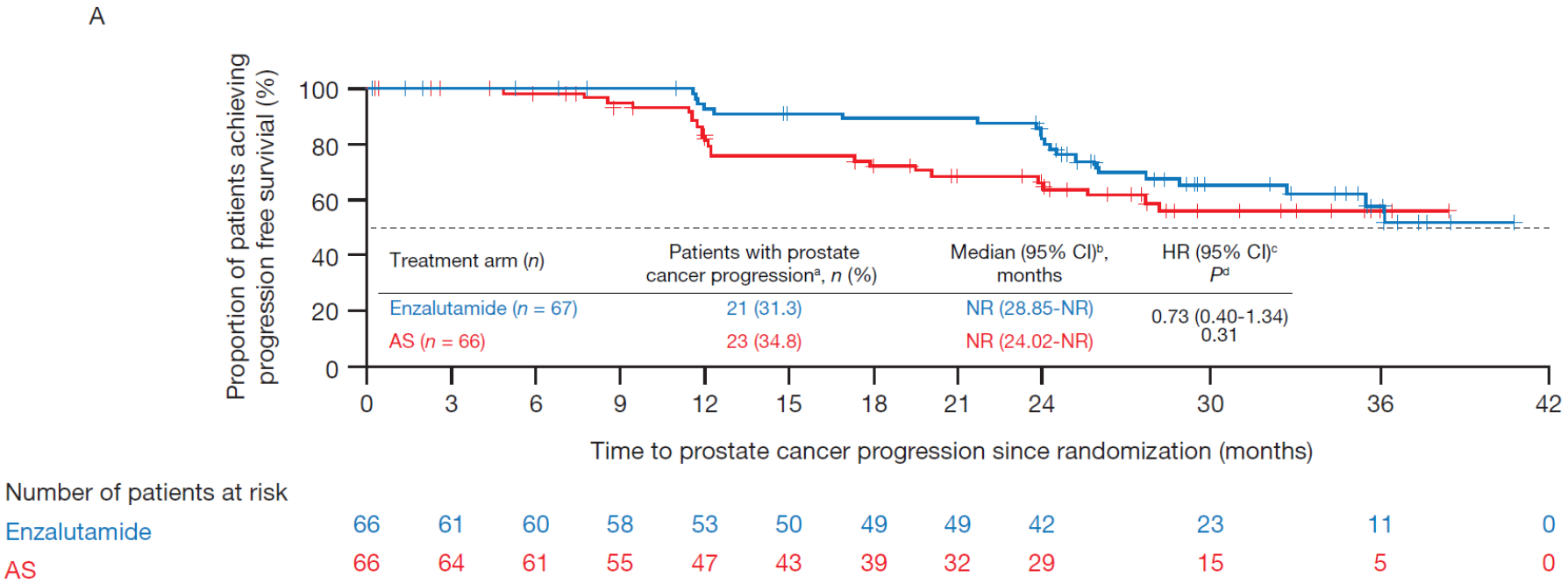
eFigure 3. Time to Pathological or Therapeutic Prostate Cancer Progression by (A) Low and (B) High GS



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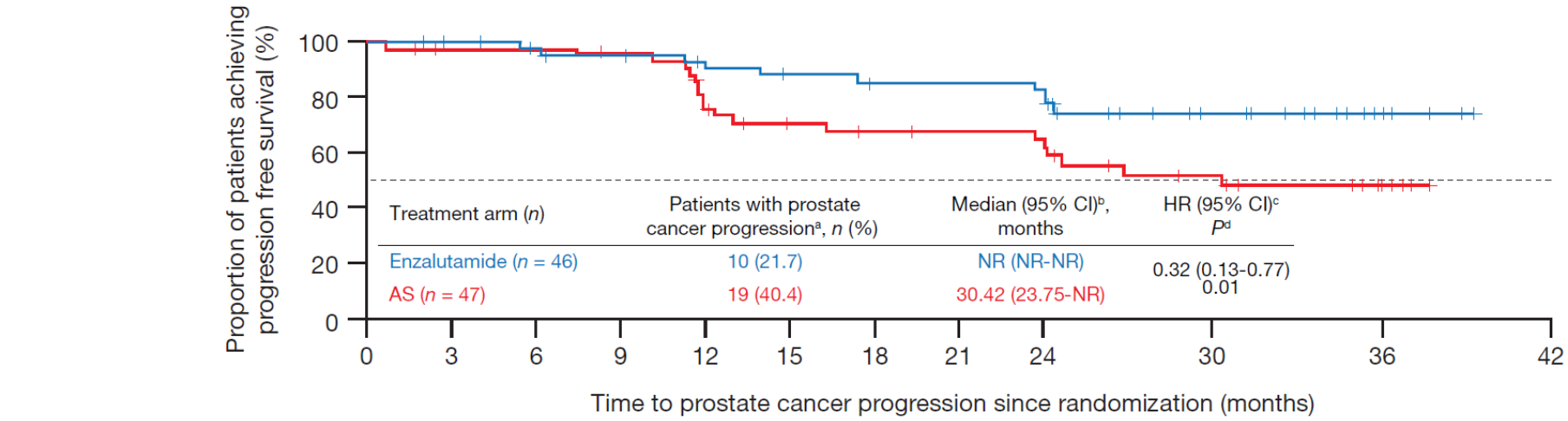

Number of patients at risk												
Enzalutamide	46	44	42	40	37	34	32	32	31	17	6	0
AS	47	44	42	40	30	25	23	22	21	13	6	0

Abbreviations: AS, active surveillance; CI, confidence interval; GS, Gleason score; HR, hazard ratio; NR, not reached.

Pathological progression defined as an increase in primary or secondary Gleason pattern by ≥1 or higher proportion of cancer-positive cores (≥15% increase). Therapeutic progression defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy, radiation, focal therapy, or systemic therapy). Low GS defined as a GS of 6. High GS defined as a GS of 7 (3+4 pattern only).

[a] Patients with no prostate cancer progression at the time of study completion, discontinuation, or death were censored at the last assessment date. Patients switching therapy during the study were censored at the time of the initial therapy switch, and patients discontinuing therapy were censored at the time of study discontinuation.

[b] Calculated using a two-sided, log-rank test.

[c] Calculated using a Cox regression model assuming proportional hazards with treatment group, stratification factors, age, race, and time since prostate cancer diagnosis as fixed effects, and study site and patient as random effects. HR <1 favors enzalutamide.

[d] Calculated using a two-sided, stratified, log-rank test.

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eTable 1. Incidence of Prostate Cancer Progression (Pathological vs. Therapeutic) by Risk (Low vs. Intermediate)

***n* (%)**	**Enzalutamide**	**AS**
Pathological progression (*n* = 46)		
Low risk	11 (23.9)	14 (30.4)
Intermediate risk	9 (19.6)	12 (26.1)
Therapeutic progression (*n* = 28)		
Low risk	5 (17.9)	5 (17.9)
Intermediate risk	7 (25.0)	11 (39.3)

Abbreviations: AS, active surveillance; GS, Gleason score; PSA, prostate-specific antigen.

Pathological progression defined as an increase in primary or secondary Gleason pattern by ≥1 or higher proportion of cancer-positive cores (≥15% increase). Therapeutic progression defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy, radiation, focal therapy, or systemic therapy). Low-risk prostate cancer defined per National Comprehensive Cancer Network guidelines as T1c-T2a, PSA <10 ng/mL, N0, M0, and GS ≤6. Intermediate-risk prostate cancer defined per National Comprehensive Cancer Network guidelines as T2b-T2c, PSA <20 ng/mL, N0, M0, and GS ≤7 (3+4 pattern only).

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eTable 2. Additional Analyses of Primary and Secondary Efficacy Endpoints in Patients With Consistent Biopsy Type

Endpoint	Enzalutamide		AS
Time to pathological or therapeutic prostate cancer progression	*n* = 96		*n* = 81
Progression events[a], *n* (%)	22 (22.9)		27 (33.3)
Median (95% CI)[b]	NR (36.14-NR)		NR (25.59-NR)
HR (95% CI)[c]		0.45 (0.24-0.84)	
P[d]		**.01**	
Incidence of pathological or therapeutic prostate cancer progression at 1 year	*n* = 95		*n* = 81
Progression events, *n* (%)	8 (8.3)		19 (23.5)
OR[e] (95% CI)[f]		0.2 (0.09-0.60)	
P[f]		**<.01**	
Incidence of pathological or therapeutic prostate cancer progression at 2 years	*n* = 78		*n* = 44
Progression events, *n* (%)	10 (12.8)		5 (11.4)
OR[e] (95% CI)[f]		1.1 (0.31-3.57)	
P[f]		0.93	
Incidence of negative biopsy at 1 year	*n* =96		*n* = 81
Biopsy result, *n* (%)			
Negative	31 (32.3)		10 (12.3)

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Endpoint	Enzalutamide	AS
Positive	44 (45.8)	50 (61.7)
Unknown	21 (21.9)	21 (25.9)
OR[e] (95% CI)[g]	3.5 (1.54-8.08)	
P[h]	**<.01**	
Incidence of negative biopsy at 2 years	*n* = 84	*n* = 53
Biopsy result, *n* (%)		
Negative	18 (21.4)	8 (15.1)
Positive	38 (45.2)	25 (47.2)
Unknown	28 (33.3)	20 (37.7)
OR[e] (95% CI)[g]	1.5 (0.53-4.12)	
P[h]	0.44	
Percentage of cancer-positive cores at 1 year[i]	*n* = 74	*n* = 53
LS mean change from baseline ± SE[j] (95% CI)	−13.19 ± 2.61 (−18.34, −8.04)	−4.77 ± 2.70 (−10.10, 0.56)
Difference in LS means ± SE (95% CI)	−8.42 ± 2.59 (−13.52, −3.32)	
P[k]	**<.01**	
Percentage of cancer-positive cores at 2 years[i]	*n* = 43	*n* = 29
LS mean change from baseline ± SE[j] (95% CI)	−6.19 ± 3.01 (−12.14, −0.25)	−6.25 ± 3.09 (−12.35, −0.15)
Difference in LS means ± SE (95% CI)	0.06 ± 3.47 (−6.79, 6.90)	

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Endpoint	Enzalutamide	AS
P[k]	.99	
Time to PSA progression	*n* = 96	*n* = 81
Progression events[a], *n* (%)	79 (82.3)	66 (81.5)
Median (95% CI)[b]	14.82 (14.75-14.95)	8.77 (6.05-11.53)
HR (95% CI)[c]	0.58 (0.40-0.84)	
P[d]	**<.01**	
Incidence of a secondary rise in serum PSA at 1 year	*n* = 96	*n* = 81
PSA response[l], *n* (%)	26 (27.1)	56 (69.1)
OR[e] (95% CI)[g]	0.2 (0.08-0.31)	
P[h]	**<.001**	
Incidence of a secondary rise in serum PSA at 2 years	*n* = 84	*n* = 53
PSA response[l], *n* (%)	77 (91.7)	51 (96.2)
OR[e] (95% CI)[g]	0.7 (0.15-2.94)	
P[h]	0.59	

Abbreviations: AS, active surveillance; CI, confidence interval; HR, hazard ratio; LS, least squares; NR, not reached; OR, odds ratio; PSA, prostate-specific antigen; SE, standard error.

Analyses performed in patients with consistent biopsy type at screening, month 12, and month 24, or screening and month 12, or screening and month 24, or those with just a screening biopsy and no follow-up biopsy. Pathological progression defined as an increase in primary or secondary Gleason pattern by ≥1 or higher proportion of cancer-positive cores (≥15% increase). Therapeutic progression defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy, radiation, focal therapy, or systemic therapy).

[a] Patients with no prostate cancer progression at the time of study completion, discontinuation, or death were censored at the last assessment date. Patients switching therapy during the study were censored at the time of the initial therapy switch and patients discontinuing therapy were censored at the time of study discontinuation.

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[b] Calculated using a two-sided, log-rank test.

[c] Calculated using a Cox regression model assuming proportional hazards with treatment group, stratification factors, age, race, and time since prostate cancer diagnosis as fixed effects, and study site and patient as random effects. HR <1 favors enzalutamide.

[d] Calculated using a two-sided, stratified, log-rank test.

[e] Calculated using an exact logistic regression model with treatment group, stratification factors, age, race, and time since prostate cancer diagnosis as fixed effects, and study site and patient as random effects.

[f] Calculated based on Wald's Chi-square from the logistic regression model.

[g] Calculated based on exact binomial distribution.

[h] Calculated based on exact binomial distribution from the logistic regression model.

[i] Analyzed using a mixed-model-repeated-measures model, with treatment group, stratification factors, visit, visit-by-treatment, and baseline score as fixed effects, and study site and patient as random effects.

[j] Most recent biopsy taken during the 6 months prior to screening.

[k] Bonferroni-Holm used to adjust for multiplicity.

[l] PSA response defined as a secondary rise in serum PSA ≥25% of baseline, or ≥25% above nadir, or an absolute increase of ≥2 ng/mL.

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eTable 3. Overview of AEs

n (%)	During 1-year treatment period[a]		During 1-year follow-up period[b]		During 1-year continued follow-up period[c]	
	Enzalutamide *n* = 112	AS *n* = 113	Enzalutamide *n* = 112	AS *n* = 113	Enzalutamide *n* = 112	AS *n* = 113
AEs	103 (92.0)	62 (54.9)	44 (39.3)	26 (23.0)	16 (14.3)	12 (10.6)
SAEs	9 (8.0)	5 (4.4)	8 (7.1)	3 (2.7)	4 (3.6)	2 (1.8)
AEs leading to death	1 (0.9)	0	0	0	2 (1.8)	0
Drug-related AEs	99 (88.4)	N/A	N/A	N/A	N/A	N/A
Drug-related SAEs	3 (2.7)	N/A	N/A	N/A	N/A	N/A
Drug-related AEs leading to discontinuation of study drug	8 (7.1)	N/A	N/A	N/A	N/A	N/A
AEs reported in ≥5% of patients in any treatment arm during any study period[d]						
Fatigue	62 (55.4)	4 (3.5)	2 (1.8)	1 (0.9)	0	0
Gynecomastia	41 (36.6)	2 (1.8)	2 (1.8)	1 (0.9)	0	0
Nipple pain	34 (30.4)	0	0	0	0	0
Breast tenderness	26 (25.9)	1 (0.9)	0	0	0	0
Erectile dysfunction	20 (17.9)	2 (1.8)	2 (1.8)	2 (1.8)	0	0
Alopecia	11 (9.8)	0	0	0	0	0
Decreased libido	9 (8.0)	1 (0.9)	1 (0.9)	0	0	0

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n (%)	During 1-year treatment period[a]		During 1-year follow-up period[b]		During 1-year continued follow-up period[c]	
	Enzalutamide *n* = 112	AS *n* = 113	Enzalutamide *n* = 112	AS *n* = 113	Enzalutamide *n* = 112	AS *n* = 113
Hypertension	8 (7.1)	8 (7.1)	2 (1.8)	5 (4.4)	1 (0.9)	1 (0.9)
Breast enlargement	7 (6.3)	0	0	0	0	0
Diarrhea	6 (5.4)	0	0	1 (0.9)	0	0
Hot flush	6 (5.4)	0	0	0	0	0
Nausea	6 (5.4)	0	1 (0.9)	1 (0.9)	0	0
Pollakiuria	6 (5.4)	4 (3.5)	1 (0.9)	0	1 (0.9)	0
Upper respiratory tract infection	6 (5.4)	4 (3.5)	6 (5.4)	1 (0.9)	1 (0.9)	1 (0.9)
Weight decreased	6 (5.4)	0	0	1 (0.9)	0	1 (0.9)

Abbreviations: AE, adverse event; AS, active surveillance; N/A, not applicable; NR, not reported; SAE, serious adverse events.

[a] From date of first dose (enzalutamide) or randomization (AS) until date discontinued or completed 12 months on study + 30 days.

[b] From date completed 12 months on study + 31 days until date discontinued or completed 24 months on study.

[c] From date completed 24 months on study + 1 day until date discontinued or completed study.

[d] AEs coded using Medical Dictionary for Regulatory Activities, version 23.0.

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