Clinical Outcomes of Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) with Prostate-Specific Antigen (PSA) Decline to Undetectable Levels on Enzalutamide (ENZA): *Post Hoc* Analysis of ARCHES

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Objective

- **To evaluate whether prostate-specific antigen (PSA) decline to undetectable levels during treatment with enzalutamide (ENZA) + androgen deprivation therapy (ADT) was associated with improved clinical outcomes in patients with metastatic hormone-sensitive prostate cancer (mHSPC)**

Key Findings

- **In ARCHES, 68.6% (n=348) of patients treated with ENZA + ADT reached undetectable PSA levels compared with 17.6% (n=89) of patients treated with placebo (PBO) + ADT**
- **Following ENZA + ADT treatment, patients with undetectable vs. detectable PSA levels had:**
  - **Improved radiographic progression-free survival (rPFS; hazard ratio [HR] 0.14, 95% confidence interval [CI], 0.09–0.23) and overall survival (OS; HR 0.24; 95% CI 0.17–0.34)**
  - **Improved time to PSA progression (HR 0.05; 95% CI 0.02–0.12), new antineoplastic therapy (HR 0.13; 95% CI 0.06–0.26), castration resistance (HR 0.16; 95% CI 0.10–0.25), and time to symptomatic skeletal event (HR 0.40; 95% CI 0.19–0.83)**
  - **Delayed deterioration in overall quality of life (QoL; Time to first deterioration in Functional Assessment of Cancer Therapy-Prostate [FACT-P]; HR 0.78; 95% CI 0.62–0.98)**
- **Compared with patients with undetectable PSA levels, those with undetectable levels had more treatment-emergent adverse events (TEAEs; 86.3% vs. 83.8%) but fewer serious (16.0% vs. 21.4%) and grade 3 or 4 TEAEs (21.3% vs. 26.3%)**
- **Potential predictors for achieving undetectable PSA levels with ENZA + ADT treatment:**
  - **Absence of *de novo* disease (M0 vs. M1: odds ratio [OR] 4.3; p=0.001)**
  - **A low baseline PSA level (≤7.2 ng/mL; OR 3.3; p<0.0001)**

Conclusions

- **In ARCHES, patients treated with ENZA + ADT were approximately 4× more likely to reach undetectable PSA levels than patients treated with PBO + ADT**
- **Patients with mHSPC and undetectable PSA levels following ENZA + ADT treatment had improved rPFS, OS, and secondary clinical outcomes vs. patients with detectable PSA levels after treatment**
- **Patients who achieved PSA decline to undetectable levels on ENZA + ADT had higher FACT-P scores at baseline which were maintained over time, and delayed deterioration in overall QoL vs. those with detectable PSA after treatment. These observations did not apply to patients treated with PBO + ADT**
- **Patients who reached undetectable PSA levels with ENZA + ADT treatment had more TEAEs but fewer serious and grade 3 or 4 TEAEs vs. patients with detectable PSA levels. Safety across treatment arms was similar to that of prior findings**

References: 1. Armstrong AJ et al. *J Clin Oncol*. 2019;37(32):2974–2986. **2.** Armstrong AJ et al. *J Clin Oncol*. 2022;40:1616–1622. **3.** Hussain M et al. *Ann Oncol*. 2020;31:S544–S545. **4.** Hussain M et al. *J Clin Oncol*. 2021;39:94.

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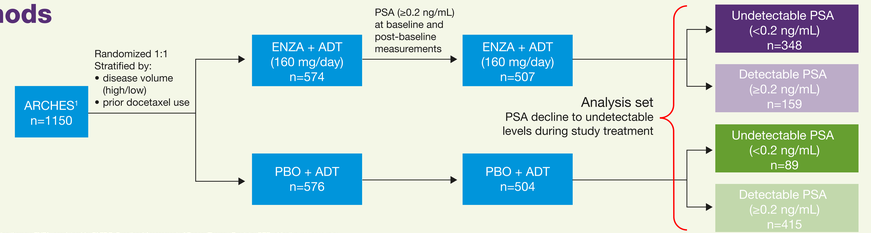
Background and Objectives

- In the Phase 3 ARCHES trial, ENZA + ADT significantly improved rPFS and OS vs. PBO + ADT in men with mHSPC[1,2]
- PSA decline to undetectable levels (<0.2 ng/mL) after treatment with ENZA is associated with improved clinical outcomes in nonmetastatic castration-resistant prostate cancer (nmCRPC)[3,4]
- This ARCHES *post hoc* analysis:
  - Evaluated whether PSA decline to undetectable levels during the study treatment was associated with improved clinical outcomes in patients with mHSPC
  - Determined predictors of PSA decline to undetectable levels for patients treated with ENZA + ADT through a stepwise multivariate analysis

Methods



ADT=androgen deprivation therapy; ENZA=enzalutamide; FACT-P=Functional Assessment of Cancer Therapy-Prostate; ORR=objective response rate; OS=overall survival; PBO=placebo; PSA=prostate-specific antigen; QoL=quality of life; rPFS=radiographic progression-free survival; SSE=symptomatic skeletal event.

- Endpoints assessed: rPFS, OS, time to SSE, time to PSA progression, time to new antineoplastic therapy, time to castration resistance, ORR, QoL (FACT-P), and safety
- Stepwise multivariate analysis was conducted on variables from a univariate logistic regression model

Results

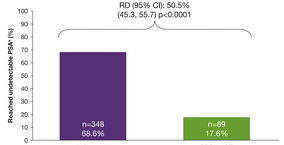
BASELINE CHARACTERISTICS

- PSA undetectable groups had lower baseline PSA levels and a smaller proportion of patients with high-volume disease, Gleason scores of ≥8, and *de novo* mHSPC. Both groups treated with ENZA + ADT had more patients with these poor prognostic factors than did the groups treated with PBO + ADT (see **Supplementary Table 1**, accessible via QR code)

PSA LEVELS

- 68.6% (348/507) of patients treated with ENZA + ADT reached undetectable PSA levels compared with 17.6% (89/507) of patients treated with PBO + ADT (**Figure 1**)

Figure 1. Posttreatment PSA levels



[a]The PSA undetectable rate is defined as the percentage of patients with detectable PSA (>0.2 ng/mL) levels at baseline that become undetectable (<0.2 ng/mL) during the study treatment.

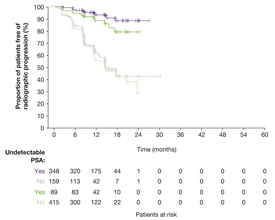
rPFS AND OS

- Reduced risk of death in patients who reached undetectable levels of PSA (**Figure 2**):
  - ENZA + ADT (76%; p<0.0001)
  - PBO + ADT (65%; p=0.0003)

Figure 2. Impact of PSA levels on rPFS and OS

rPFS[a]

Undetectable PSA	No. Subjects	Median	95% CI	HR (95% CI)[b]
Enzalutamide + ADT				
Yes	348	NE	(NE, NE)	0.14
No	159	14.00	(12.39, NE)	(0.09, 0.23)
Placebo + ADT				
Yes	89	NE	(NE, NE)	0.24
No	415	13.86	(12.25, 16.79)	(0.13, 0.43)

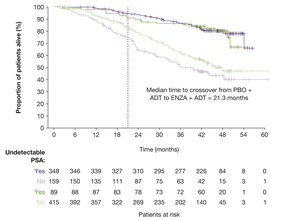


Undetectable PSA:												
Yes	348	320	175	44	1	0	0	0	0	0	0	0
No	159	113	42	7	1	0	0	0	0	0	0	0
Yes	89	83	42	10	0	0	0	0	0	0	0	0
No	415	300	122	22	0	0	0	0	0	0	0	0

Patients at risk

OS[a]

Undetectable PSA	No. Subjects	Median	95% CI	HR (95% CI)[b]
Enzalutamide + ADT				
Yes	348	NE	(54.21, NE)	0.24
No	159	36.44	(29.73, 48.46)	(0.17, 0.34)
Placebo + ADT				
Yes	89	NE	(50.33, NE)	0.35
No	415	47.70	(42.30, NE)	(0.22, 0.57)



Undetectable PSA:												
Yes	348	346	339	327	310	295	277	226	84	8	0	
No	159	150	135	111	87	75	63	42	15	3	1	
Yes	89	88	87	83	78	73	72	60	20	1	0	
No	415	392	357	322	269	235	202	140	45	3	1	

Patients at risk

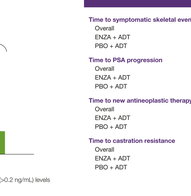
[a]The data cut-off date for rPFS is October 14, 2018, whereas the data cut-off date for OS is May 28, 2021.
ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; ENZA=enzalutamide; NE=not evaluable; OS=overall survival; PBO=placebo; PSA=prostate-specific antigen; RD=rate difference; rPFS=radiographic progression-free survival.

SECONDARY ENDPOINTS

- All secondary efficacy endpoints improved in patients who reached undetectable PSA levels (**Figure 3**)
- Enzalutamide-treated patients who achieved an undetectable PSA had a numerically higher objective response rate[a] compared with those with detectable PSA (88.7% vs. 79.2%) which was not statistically significant (RD 9.5%; 95% CI -1.8%–20.8%); similar results were observed with undetectable vs. detectable PSA for PBO-treated patients (RD 9.0%; 95% CI -12.2%–30.2%)

Figure 3. Secondary endpoints

Subgroup	PSA undetectable N(E)	PSA detectable N(E)	Hazard Ratio (95% CI)	Interaction p-value
Time to symptomatic skeletal event				
Overall	437 (16)	574 (65)	0.28 (0.16, 0.49)	
ENZA + ADT	348 (14)	159 (14)	0.40 (0.19, 0.83)	0.244
PBO + ADT	89 (2)	415 (51)	0.16 (0.04, 0.66)	
Time to PSA progression				
Overall	437 (10)	574 (214)	0.04 (0.02, 0.07)	
ENZA + ADT	348 (6)	159 (37)	0.05 (0.02, 0.12)	0.737
PBO + ADT	89 (4)	415 (177)	0.07 (0.02, 0.17)	
Time to new antineoplastic therapy				
Overall	437 (14)	574 (147)	0.10 (0.06, 0.17)	
ENZA + ADT	348 (10)	159 (29)	0.13 (0.06, 0.26)	0.915
PBO + ADT	89 (4)	415 (118)	0.12 (0.05, 0.33)	
Time to castration resistance				
Overall	437 (16)	574 (280)	0.12 (0.09, 0.17)	
ENZA + ADT	348 (27)	159 (55)	0.16 (0.10, 0.25)	0.998
PBO + ADT	89 (12)	415 (225)	0.16 (0.09, 0.29)	



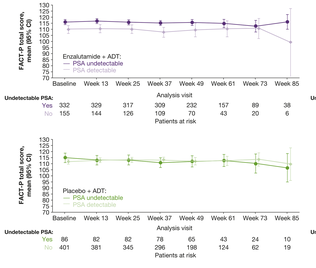
[a]The objective response rate is calculated as the percentage of patients with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease using RECIST version 1.1 at any time during the treatment period as evaluated by independent central review.
ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; E=events; ENZA=enzalutamide; NE=not evaluable; PBO=placebo; PSA=prostate-specific antigen; RD=rate difference.

QUALITY OF LIFE

- Patients with undetectable PSA that were treated with ENZA + ADT had a higher total FACT-P score that was maintained over time, and deterioration in their overall quality of life was delayed compared with patients with detectable PSA after treatment (**Figure 4**)
- These observations did not apply to patients treated with PBO + ADT

Figure 4. FACT-P score

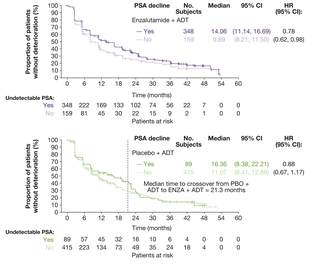
Mean FACT-P Score Over Time[a]



Undetectable PSA:								
Yes	332	329	317	309	232	157	89	38
No	155	144	126	109	70	43	20	6
Yes	86	82	82	78	65	43	24	10
No	401	381	345	296	198	124	62	19

Patients at risk

Time to First Deterioration in FACT-P Total Score[a,b]



PSA decline	No. Subjects	Median	95% CI	HR (95% CI)
Enzalutamide + ADT				
Yes	348	14.06	(11.14, 16.69)	0.78
No	159	9.89	(8.21, 11.56)	(0.62, 0.98)
Placebo + ADT				
Yes	89	16.36	(8.36, 22.21)	0.88
No	415	11.07	(9.41, 12.86)	(0.67, 1.17)

Median time to crossover from PBO + ADT to ENZA + ADT = 21.3 months

Undetectable PSA:												
Yes	348	222	169	133	102	74	56	22	7	0	0	
No	159	81	45	30	22	15	9	2	1	0	0	
Yes	89	57	45	32	16	10	6	4	0	0	0	
No	415	223	134	73	49	35	24	18	4	0	0	

Patients at risk

[a]FACT-P over time and deterioration of FACT-P have different cut-off dates. The former is October 14, 2018, and the latter is May 21, 2021.
[b]The deterioration of QoL is defined as a decrease of ≥10 points in the total FACT-P score from the baseline. In patients with QoL deterioration, the time to deterioration of QoL is defined as the time interval from the date of randomization to the first date a decline of ≥10 points from the baseline in the total FACT-P score is recorded. In patients without FACT-P progression, the time to deterioration of QoL will be censored on the date the last FACT-P total score is calculable.
ADT=androgen deprivation therapy; CI=confidence interval; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio; ENZA=enzalutamide; PBO=placebo; PSA=prostate-specific antigen; QoL=quality of life.

MULTIVARIATE ANALYSIS

Univariate Analysis for Odds to Reach PSA Undetectable levels in ENZA + ADT

Covariate	Comparison	OR (95%CI)	P value
ECOG at study entry	0 vs. ≥1	2.1 (1.4, 3.3)	0.0009
Volume of disease	Low vs. high	2.4 (1.6, 3.6)	<0.0001
Total Gleason score at diagnosis	<8 vs. ≥8	2.5 (1.6, 4.0)	0.0001
Confirmed metastases at screening	No vs. yes	4.0 (1.2, 13.4)	0.03
Localization of confirmed metastases at screening	Bone only vs. bone and soft tissue	2.0 (1.4, 3.0)	0.0006
	Soft tissue only vs. bone and soft tissue	2.2 (1.1, 4.5)	0.03
	Bone, with or without lymph node vs. visceral, with or without bone or lymph node	1.94 (1.1, 3.4)	0.02
Distant metastasis at initial diagnosis	M0 vs. M1	4.1 (1.9, 8.8)	0.0003
	M0 vs. MX/unknown	2.8 (1.1, 6.8)	0.03
Baseline PSA	Baseline PSA	1.0 (1.0, 1.0)	0.0005
	≤Median vs. >median	3.5 (2.3, 5.2)	<0.0001
Alkaline phosphatase	≤Upper limit of normal vs. >upper limit of normal	2.2 (1.5, 3.2)	<0.0001

- Stepwise multivariate analysis was conducted on variables using a univariate logistic regression model to identify clinical factors that significantly correlated with PSA decline to undetectable levels with ENZA + ADT treatment

Multivariate Analysis for Odds to Reach PSA Undetectable levels in ENZA + ADT

Covariate	Comparison	OR (95%CI)	P value
Distant metastasis at initial diagnosis	M0 vs. M1	4.3 (1.8, 10.6)	0.001
Baseline PSA	≤Median[a] vs. >median	3.3 (2.1, 5.2)	<0.0001

- Initial diagnosis (M0 vs. M1: OR 4.33; p=0.0013) and baseline PSA (≤median or >median: OR 3.34; p<0.0001) levels were predictors of undetectable PSA levels in the ENZA arm

[a]Median value of baseline PSA levels in the ENZA + ADT arm was 7.2 ng/mL.
ADT=androgen deprivation therapy; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ENZA=enzalutamide; MX=distant metastases unknown; M0=no distant metastases; M1=distant metastases; OR=odds ratio; PSA=prostate-specific antigen.

SAFETY

- In the full cohort[a], compared with patients with detectable PSA levels, those with undetectable levels had (**Table 1**):
  - More treatment-emergent adverse events (TEAEs) – undetectable: 86.3% vs. detectable: 83.8%
  - Fewer grade 3/4 TEAEs – undetectable: 21.3% vs. detectable: 26.3%
  - Fewer serious TEAEs – undetectable: 16.0% vs. detectable: 21.4%
- Adverse events of special interest (AESIs): no substantial differences between subgroups
- Safety across treatment arms was similar to that of prior findings

Table 1. Safety results

	ENZA + ADT (n=507)		PBO + ADT (n=504)	
AESI, n (%)	Undetectable PSA (n=348)	Detectable PSA (n=159)	Undetectable PSA (n=89)	Detectable PSA (n=415)
Musculoskeletal events	83 (23.9)	38 (23.9)	17 (19.1)	114 (27.5)
Fatigue	74 (21.3)	36 (22.6)	20 (22.5)	68 (16.4)
Hypertension	39 (11.2)	8 (5.0)	5 (5.6)	26 (6.3)
Fractures	24 (6.9)	6 (3.8)	2 (2.2)	19 (4.6)
Cognitive/memory impairment	14 (4.0)	5 (3.1)	4 (4.5)	5 (1.2)
Fall	12 (3.4)	4 (2.5)	4 (4.5)	8 (1.9)
Rash	11 (3.2)	1 (0.6)	2 (2.2)	6 (1.4)
Other cardiovascular events	9 (2.6)	4 (2.5)	4 (4.5)	5 (1.2)
Ischemic heart disease	6 (1.7)	4 (2.5)	1 (1.1)	5 (1.2)
Loss of consciousness	6 (1.7)	1 (0.6)	1 (1.1)	0
Second primary malignancies	6 (1.7)	3 (1.9)	3 (3.4)	7 (1.7)
Angioedema	4 (1.1)	1 (0.6)	0	1 (0.2)
Neutrophil count decreased	4 (1.1)	1 (0.6)	1 (1.1)	2 (0.5)
Convulsion	2 (0.6)	0	0	2 (0.5)
Thrombocytopenia	1 (0.3)	1 (0.6)	0	3 (0.7)
Severe cutaneous adverse reactions (SCAR)	–	0	–	1 (0.2)

[a]The data cut-off date for the safety results is October 14, 2018.
ADT=androgen deprivation therapy; AESI=adverse event of special interest; ENZA=enzalutamide; PBO=placebo; PSA=prostate-specific antigen.