The Efficacy of Enzalutamide Plus Androgen Deprivation Therapy on Oligometastatic Hormone-Sensitive Prostate Cancer: Extended *Post Hoc* Analysis of ARCHES

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Objective

- This *post hoc* analysis of ARCHES explored the effect of enzalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in patients with metastatic (m) hormone-sensitive prostate cancer (HSPC) [mHSPC] with bone, soft tissue, or both types of metastases, categorized as oligometastatic (1 to ≤5 metastases) or polymetastatic (≥6 metastases)

Conclusions

- This *post hoc* analysis demonstrates that enzalutamide plus ADT provides clinical benefit in patients with oligometastatic and polymetastatic HSPC with bone, soft tissue, or both types of metastases
- These results validate and support previous findings observed in the bone-only oligometastatic ARCHES population and highlight the utility of enzalutamide, irrespective of metastatic burden or type of oligometastatic disease, in the ARCHES study

References: 1. Astellas Pharma US Inc., Medivation Inc. Available at: https://www.astellas. us/docs/us/12A005-ENZ-WPI.pdf. Accessed October 2021. **2.** Astellas Pharma US Inc. Available at: https://www.ema. europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf. Accessed October 2021. **3.** Astellas Pharma Inc. Available at: https://pins.japic.or.jp/pdf/newPINS/00067392.pdf. Accessed October 2021. **4.** Armstrong AJ et al. J Clin Oncol. 2019;37(32):2974-2986. **5.** Beer TM et al. N Engl J Med. 2014;371:424-433. **6.** Scher HI et al. N Engl J Med. 2012;367(13):1187-1197. **7.** Shore N et al. Lancet Oncol. 2016;17(2):153-163. **8.** Penson DF et al. J Clin Oncol. 2016;34(18):2098-2106. **9.** Hussain M et al. N Engl J Med. 2018;378(26):2465-2474. **10.** Armstrong et al. Ann Oncol. 2021;32(suppl 5):S1300-1301. **11.** Ost P et al. J Clin Oncol. 2018;36(6):446-453. **12.** Phillips R et al. JAMA Oncol. 2020;6:650-659. **13.** Armstrong et al. J Clin Oncol. 2021;39(suppl 15):5071. **14.** Armstrong et al. J Urol. 2021;205(5):1361-1371.

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Plain Language Summary

Video

This poster was previously presented at the 2021 Society of Urologic Oncology (SUO) Annual Meeting.

This presentation is intended for a healthcare provider audience.

Presented at the Journal of the Advanced Practitioner in Oncology (JADPRO) Live Annual Meeting • October 20–23, 2022 • Aurora, CO

Background

- Enzalutamide plus ADT is approved internationally for the treatment of castration-resistant prostate cancer (CRPC)[1–3] and in the United States and Europe for mHSPC[1,2] (also known as metastatic castration-sensitive prostate cancer) based on its established clinical benefit[4–9]
- In the phase 3 ARCHES trial (NCT02677896), enzalutamide plus ADT significantly reduced the risk of radiographic disease progression by 61% (p<0.001) and improved key secondary endpoints versus placebo plus ADT in men with mHSPC[4]
  - Recently reported results showed that after a median follow-up time of 44.6 months, enzalutamide plus ADT improved overall survival (OS) by 34% (p<0.0001); median OS was not reached in either treatment group[10]
- The oligometastatic disease state has become increasingly relevant for prostate cancer management. Current approaches for oligometastatic HSPC management include metastasis-directed radiation or surgery, ADT combined with potent androgen receptor inhibition, or ADT alone. The optimal treatment approach, however, is currently unknown[11,12]
- We previously reported that enzalutamide plus ADT provided clinical benefit for patients with oligometastatic and polymetastatic HSPC with bone-only metastases[13]
  - However, this analysis excluded patients with soft tissue disease (lymph nodal or visceral) to control for potential prognostic effects of variable metastatic spread
  - Additionally, OS was immature at the time of this analysis and could not be examined
- We expand on our analysis of oligometastatic and polymetastatic disease to include patients with bone, soft tissue, or both types of metastases and examine the effect of treatment on OS
  - We also perform sensitivity analyses that exclude patients with visceral metastases, which may be associated with a poorer prognosis[14]

Methods

STUDY DESIGN AND PATIENTS

- In ARCHES,[4] patients with mHSPC (n=1150) were randomized 1:1 to enzalutamide (160 mg/day) plus ADT or placebo plus ADT, stratified by disease volume and prior docetaxel use
- Patients were categorized as having oligometastatic (1 to ≤5 metastases) or polymetastatic (≥6 metastases) disease, based on central review of magnetic resonance imaging, computed tomography, or radionuclide bone scans at screening
- Efficacy outcomes were compared for patients on enzalutamide plus ADT versus placebo plus ADT within the defined groups and against polymetastatic disease
- Additional analyses were conducted on patients without visceral disease to control for possible prognostic influence of visceral metastases

ASSESSMENT

- *Post hoc* analyses were completed for the following endpoints:
  - Primary endpoint: radiographic progression-free survival (rPFS)
  - Secondary endpoints: OS, time to prostate-specific antigen (PSA) progression, time to castration resistance, time to first symptomatic skeletal event, time to initiation of new antineoplastic therapy, and PSA undetectable rate
- All efficacy and safety data are reported with the data cut-off (DCO) date of October 14, 2018 (median follow-up time, 14.4 months), except OS, which is reported with a DCO date of May 28, 2021 (median follow-up time, 44.6 months)

STATISTICAL ANALYSIS

- Kaplan-Meier estimates were used to analyze the primary time-to-event endpoint of rPFS; a two-sided 95% confidence interval (CI) for median time was estimated by using the Brookmeyer and Crowley method
- Hazard ratios (HRs) were estimated from the Cox proportional hazards model
- Similar analyses were performed for selected secondary time-to-event endpoints

Results

PATIENT CHARACTERISTICS

- Of the overall ARCHES population, 1066 patients were diagnosed with bone and/or soft tissue metastases at study initiation
  - Approximately half had oligometastatic disease with ≤5 metastases (enzalutamide plus ADT, n=270; placebo plus ADT, n=250)
- Baseline characteristics were generally comparable between treatment arms; some differences were noted across the metastatic subgroups in baseline PSA, distant metastases at initial diagnosis, Gleason score, and other prognostic variables (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics in Patients With Oligometastatic and Polymetastatic HSPC

Characteristics	Oligometastatic disease[a] ENZA + ADT (n=270)	Oligometastatic disease[a] PBO + ADT (n=250)	Polymetastatic disease[b] ENZA + ADT (n=265)	Polymetastatic disease[b] PBO + ADT (n=281)
Median age, years (range)	70 (46–88)	70 (43–90)	70 (47–92)	69 (42–92)
ECOG PS,[c] n (%)				
0	226 (83.7)	206 (82.4)	195 (73.6)	199 (70.8)
1	43 (15.9)	44 (17.6)	70 (26.4)	82 (29.2)
Total Gleason score at initial diagnosis, n (%)				
<8	94 (34.8)	90 (36.0)	56 (21.1)	75 (26.7)
≥8	170 (63.0)	156 (62.4)	200 (75.5)	194 (69.0)
Distant metastases at initial diagnosis, n (%)				
M0	56 (20.7)	52 (20.8)	21 (7.9)	21 (7.5)
M1	169 (62.6)	134 (53.6)	210 (79.2)	207 (73.7)
MX/unknown	45 (16.7)	64 (25.6)	34 (12.8)	53 (18.9)
Median PSA at study entry,[d] ng/mL (range)	2.82 (0–4823.5)	2.59 (0–469.8)	13.77 (0–4177.0)	9.46 (0–19,000.0)
Cycles of prior docetaxel therapy				
0	224 (83.0)	207 (82.8)	221 (83.4)	231 (82.2)
1–5	4 (1.5)	5 (2.0)	7 (2.6)	5 (1.8)
6	42 (15.6)	38 (15.2)	37 (14.0)	45 (16.0)
Prior local therapy,[e] n (%)				
Radical prostatectomy	51 (18.9)	54 (21.6)	10 (3.8)	22 (7.8)
Radiation therapy	49 (18.1)	47 (18.8)	17 (6.4)	17 (6.0)
Visceral disease,[f] n (%)				
Yes	26 (9.6)	28 (11.2)	45 (17.0)	39 (13.9)
No	92 (34.1)	88 (35.2)	149 (56.2)	153 (54.4)
Target lesions, n (%)	67 (24.8)	56 (22.4)	110 (41.5)	125 (44.5)
Median size of target lesions,[g] mm (range)	32.00 (11.60–113.40)	26.50 (11.00–121.80)	41.05 (12.80–160.50)	37.40 (10.30–121.20)

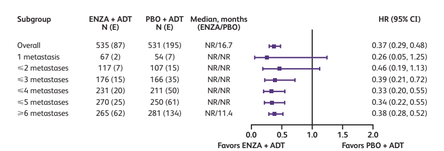
[a]Includes all patients considered to have oligometastatic disease (1 to ≤5 metastases); [b]Polymetastatic disease is defined as having ≥6 metastases; [c]Assessed on day 1 at study entry; [d]PSA level at initial diagnosis of prostate cancer prior to study entry was not collected; [e]Local therapy was defined as previous radical prostatectomy and/or radiation of the prostate area; [f]Of patients with soft tissue metastases. Visceral metastases were defined as metastases to the lung, kidney, liver, adrenal glands, central nervous system, pleura, pleural cavity, and peritoneal sites; [g]Size is calculated as the sum of diameter: longest diameter for non-nodal lesions, short axis for nodal lesions.

ADT=androgen deprivation therapy; ECOG PS=Eastern Cooperative Oncology Group performance status; ENZA=enzalutamide; HSPC=hormone-sensitive prostate cancer; ITT=intent-to-treat; MX=distant metastases cannot be assessed; M0=no distant metastases; M1=distant metastases; PBO=placebo; PSA=prostate-specific antigen.

rPFS AND OS

- Enzalutamide plus ADT reduced the risk of radiographic progression versus placebo plus ADT across all oligometastatic groups (HRs 0.26–0.46) [**Figure 1**] and improved OS (HRs 0.60–0.63) [**Figure 2**]
  - In the largest oligometastatic group (≤5 metastases), enzalutamide plus ADT improved rPFS by 66% compared to placebo plus ADT (HR 0.34; 95% CI 0.22, 0.55) [**Figure 1**] and OS by 40% (HR 0.60; 95% CI 0.42, 0.86) [**Figure 2**]
  - Enzalutamide plus ADT also reduced the risk of radiographic progression compared to placebo plus ADT in patients with polymetastatic disease (HR 0.38; 95% CI 0.28, 0.52) [**Figure 1**] and reduced the risk of death (HR 0.63; 95% CI 0.48, 0.82) [**Figure 2**]
- Patients with oligometastatic disease exhibited a better prognosis than those with polymetastatic disease in both the enzalutamide and placebo plus ADT groups, regardless of the number of metastases used to define the group (**Figures 3** and **4**)
  - HRs versus ≥6 metastases for rPFS ranged from 0.14–0.37 for enzalutamide plus ADT and 0.21–0.40 for placebo plus ADT (**Figure 3**), and for OS (0.26–0.40 and 0.25–0.40, respectively) [**Figure 4**]
- All five oligometastatic groups had similar rPFS and OS outcomes with enzalutamide plus ADT, with minor prognostic differences (**Figures 3** and **4**)
- For patients treated with placebo plus ADT, intergroup variability was noted, with a prognostic impact observed in rPFS for patients with ≥3 metastases (**Figure 3**) and in OS for those with ≥2 metastases (**Figure 4**)

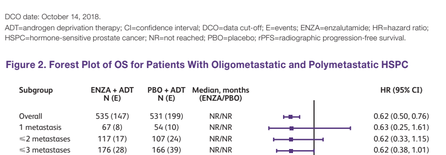
Figure 1. Forest Plot of rPFS for Patients With Oligometastatic and Polymetastatic HSPC



DCO date: October 14, 2018.

ADT=androgen deprivation therapy; CI=confidence interval; DCO=data cut-off; E=events; ENZA=enzalutamide; HR=hazard ratio; HSPC=hormone-sensitive prostate cancer; NR=not reached; PBO=placebo; rPFS=radiographic progression-free survival.

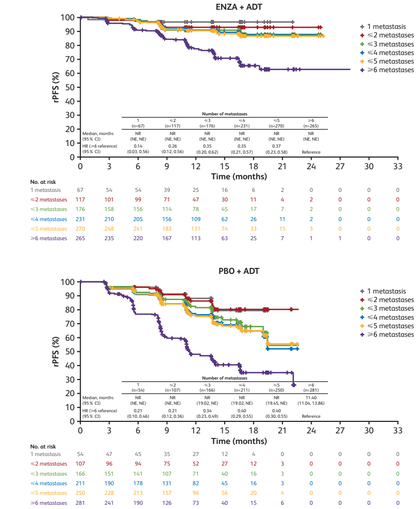
Figure 2. Forest Plot of OS for Patients With Oligometastatic and Polymetastatic HSPC



DCO date: May 28, 2021.

ADT=androgen deprivation therapy; CI=confidence interval; DCO=data cut-off; E=events; ENZA=enzalutamide; HR=hazard ratio; HSPC=hormone-sensitive prostate cancer; NR=not reached; OS=overall survival; PBO=placebo.

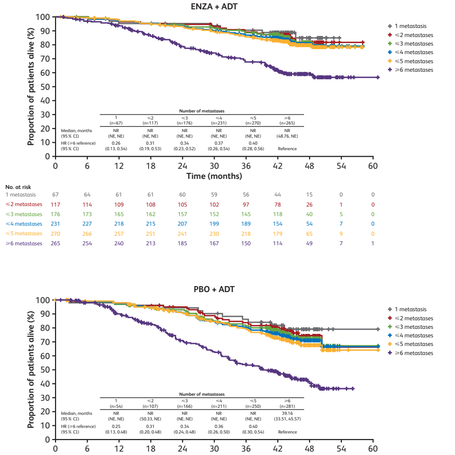
Figure 3. Kaplan-Meier Plot of rPFS for Patients With Oligometastatic and Polymetastatic HSPC



DCO date: October 14, 2018.

ADT=androgen deprivation therapy; CI=confidence interval; DCO=data cut-off; ENZA=enzalutamide; HR=hazard ratio; HSPC=hormone-sensitive prostate cancer; NE=not evaluable; NR=not reached; PBO=placebo; rPFS=radiographic progression-free survival.

Figure 4. Kaplan-Meier Plot of OS for Patients With Oligometastatic and Polymetastatic HSPC



DCO date: May 28, 2021.

ADT=androgen deprivation therapy; CI=confidence interval; DCO=data cut-off; ENZA=enzalutamide; HR=hazard ratio; HSPC=hormone-sensitive prostate cancer; NE=not evaluable; NR=not reached; OS=overall survival; PBO=placebo.

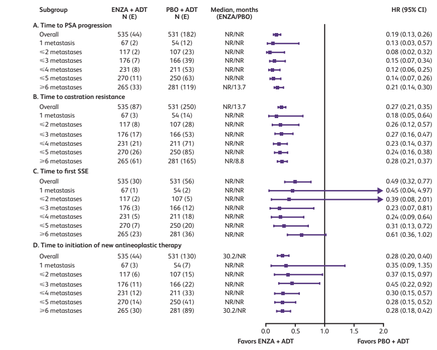
OTHER KEY SECONDARY ENDPOINTS

- The treatment benefits of enzalutamide plus ADT versus placebo plus ADT in the oligometastatic and polymetastatic groups were also observed in additional key secondary endpoints (**Figure 5**)
- Of the patients with detectable PSA at baseline, a greater proportion of those treated with enzalutamide plus ADT achieved an undetectable PSA level (<0.2 ng/mL) than did those treated with placebo plus ADT in the oligometastatic and polymetastatic groups (**Figure 6**)
- When excluding patients with visceral metastases, similar results were observed for rPFS, OS, and across key secondary endpoints (data not shown)

SAFETY

- Patients with oligometastatic disease treated with enzalutamide plus ADT compared with those treated with placebo plus ADT had slightly higher rates of treatment-emergent adverse events (TEAEs) [90.7% vs. 85.5%], similar rates of grade 3/4 TEAEs (20.9% vs. 22.9%), but fewer serious TEAEs (14.6% vs. 19.7%)
  - A greater proportion of patients with oligometastatic disease on enzalutamide plus ADT than those on placebo plus ADT reported musculoskeletal events, fatigue, and cognitive/memory impairment (**Table 2**)
- This observation was inverted for patients with polymetastatic disease. The enzalutamide plus ADT group compared with the placebo plus ADT group had lower rates of TEAEs (80.4% vs. 86.8%), a similar rate of grade 3/4 TEAEs (26.0% vs. 27.4%), but slightly more serious TEAEs (22.6% vs. 20.3%)
  - A slightly greater proportion of patients with polymetastatic disease on enzalutamide plus ADT than those on placebo plus ADT reported hypertension, falls, and fractures, but had a lower risk of musculoskeletal events (**Table 2**)
- Safety observations were consistent when patients with oligometastatic and polymetastatic mHSPC with visceral disease were excluded from the analysis (data not shown)

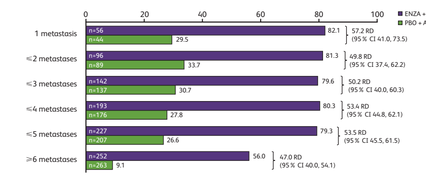
Figure 5. Secondary Endpoints in Patients With Oligometastatic and Polymetastatic mHSPC: Time to A) PSA Progression, B) Castration Resistance, C) First SSE, and D) Initiation of New Antineoplastic Therapy



DCO date: October 14, 2018.

ADT=androgen deprivation therapy; CI=confidence interval; DCO=data cut-off; E=events; ENZA=enzalutamide; HR=hazard ratio; NR=not reached; PBO=placebo; PSA=prostate-specific antigen; SSE=symptomatic skeletal event.

Figure 6. PSA Undetectable Rate[a] in Patients With Oligometastatic and Polymetastatic mHSPC



DCO date: October 14, 2018.

[a]This analysis was conducted using patients who had detectable PSA values at baseline.

ADT=androgen deprivation therapy; CI=confidence interval; DCO=data cut-off; ENZA=enzalutamide; n=number of events; PBO=placebo; PSA=prostate-specific antigen; RD=rate difference.

Table 2. TEAEs of Special Interest in Patients With Oligometastatic and Polymetastatic HSPC

Event, n (%)	Oligometastatic disease[a] ENZA + ADT (n=268)	Oligometastatic disease[a] PBO + ADT (n=249)	Polymetastatic disease[b] ENZA + ADT (n=265)	Polymetastatic disease[b] PBO + ADT (n=281)
Overall	151 (56.3)	132 (53.0)	149 (56.2)	133 (47.3)
Fatigue	81 (30.2)	56 (22.5)	47 (17.7)	44 (15.7)
Musculoskeletal events	79 (29.5)	64 (25.7)	63 (23.8)	82 (29.2)
Hypertension	22 (8.2)	19 (7.6)	23 (8.7)	14 (5.0)
Fractures	16 (6.0)	12 (4.8)	17 (6.4)	12 (4.3)
Cognitive/memory impairment	12 (4.5)	6 (2.4)	10 (3.8)	6 (2.1)
Fall	11 (4.1)	9 (3.6)	10 (3.8)	5 (1.8)
Rash	8 (3.0)	5 (2.0)	7 (2.6)	3 (1.1)
Loss of consciousness	6 (2.2)	1 (0.4)	3 (1.1)	0
Secondary primary malignancies	5 (1.9)	7 (2.8)	6 (2.3)	3 (1.1)
Angioedema	4 (1.5)	0	2 (0.8)	0
Ischemic heart disease	4 (1.5)	4 (1.6)	6 (2.3)	4 (1.4)
Other selected cardiovascular events[c]	3 (1.1)	5 (2.0)	8 (3.0)	4 (1.4)
Decreased neutrophil count	1 (0.4)	3 (1.2)	3 (1.1)	1 (0.4)
Convulsions	1 (0.4)	2 (0.8)	1 (0.4)	0
Thrombocytopenia	0	1 (0.4)	3 (1.1)	2 (0.7)
SCAR	0	0	0	1 (0.4)

DCO date: October 14, 2018.

[a]Includes all patients considered to have oligometastatic disease (1 to ≤5 metastases); [b]Polymetastatic disease is defined as having ≥6 metastases; [c]Other cardiovascular events include cardiac failure, carotid atherosclerosis, cerebellar infarction, cerebral atherosclerosis, cerebral hemorrhage, cerebral infarction, pulmonary edema, transient ischemic attack, subarachnoid hemorrhage, and subdural hematoma.

ADT=androgen deprivation therapy; DCO=data cut-off; ENZA=enzalutamide; HSPC=hormone-sensitive prostate cancer; PBO=placebo; SCAR=severe cutaneous adverse reactions; TEAE=treatment-emergent adverse event.