



Original Article: Clinical Investigation**Enzalutamide with androgen deprivation therapy in Japanese men with metastatic hormone-sensitive prostate cancer: A subgroup analysis of the phase III ARCHES study**

Taro Iguchi,¹  Go Kimura,² Satoshi Fukasawa,³ Hiroyoshi Suzuki,⁴ Hiroji Uemura,⁵ Kazuo Nishimura,⁶ Hiroaki Matsumoto,⁷  Akira Yokomizo,⁸ Andrew J Armstrong,⁹ Brad Rosbrook,¹⁰ Jennifer Sugg,¹¹ Benoit Baron,^{12,†} Lucy Chen,¹¹ Futoshi Kunieda¹¹ and Arnulf Stenzl¹³

¹Osaka City University Graduate School of Medicine, Osaka, ²Nippon Medical School, Tokyo, ³Chiba Cancer Center, Chiba, ⁴Toho University Sakura Medical Center, Chiba, ⁵Yokohama City University Medical Center, Yokohama, ⁶Osaka International Cancer Institute, Osaka, ⁷Graduate School of Medicine, Yamaguchi University Hospital, Yamaguchi, ⁸Harasanshin Hospital, Fukuoka, Japan, ⁹Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, North Carolina, ¹⁰Pfizer Inc., San Diego, California, ¹¹Astellas Pharma Inc., Northbrook, Illinois, USA, ¹²Astellas Pharma Inc., Leiden, The Netherlands and ¹³Eberhard Karls University of Tübingen, Tübingen, Germany

Abbreviations & Acronyms

ADT = androgen deprivation therapy
AE = adverse event
BPI-SF = Brief Pain Inventory – Short Form
CI = confidence interval
ECOG = Eastern Cooperative Oncology Group
FACT-P = Functional Assessment of Cancer Therapy – Prostate
HR = hazard ratio
ITT = intention-to-treat
mHSPC = metastatic hormone-sensitive prostate cancer
NA = not available
NE = not evaluable
NR = not reached
ORR = objective response rate
OS = overall survival
PSA = prostate-specific antigen
QLQ-PR25 = 25-Item Quality of Life Prostate-Specific Questionnaire
QoL = quality of life
RECIST = Response Evaluation Criteria In Solid Tumors
rPFS = radiographic progression-free survival
SD = standard deviation
SSE = symptomatic skeletal event

Objective: To evaluate the efficacy and safety of enzalutamide plus androgen deprivation therapy in Japanese men with metastatic hormone-sensitive prostate cancer.

Methods: A post-hoc analysis of the Japanese subgroup in the phase III, randomized, multinational ARCHES study (NCT02677896) was carried out. Patients with metastatic hormone-sensitive prostate cancer were randomized to receive enzalutamide or a placebo, plus androgen deprivation therapy, stratified by disease volume and prior docetaxel therapy. The primary end-point was radiographic progression-free survival. Secondary end-points included time to prostate-specific antigen progression and overall survival.

Results: Of 1150 patients, 92 Japanese patients were randomized to enzalutamide ($n = 36$) or a placebo ($n = 56$), plus androgen deprivation therapy; none received prior docetaxel. Enzalutamide plus androgen deprivation therapy reduced the risk of radiographic progression or death in Japanese patients by 61% versus the placebo, similar to the overall population. Similar results were observed with secondary end-points, showing clinical benefit of enzalutamide plus androgen deprivation therapy in Japanese patients. Overall survival data were immature. Grade 3–4 adverse events were reported in 47% and 25% of the enzalutamide and placebo groups, respectively. Nasopharyngitis, hypertension and abnormal hepatic function were reported more frequently in Japanese patients versus the overall population.

Conclusions: Enzalutamide plus androgen deprivation therapy has clinical benefit with a tolerable safety profile in Japanese men with metastatic hormone-sensitive prostate cancer, consistent with the overall population.

Key words: androgen receptor antagonists, enzalutamide, Japan, metastatic prostate cancer.

Correspondence: Taro Iguchi M.D., Ph.D., Department of Urology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno, Osaka 545-8585, Japan. Email: taro@msic.med.osaka-cu.ac.jp

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†Present address: B-value, Leiden, The Netherlands

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Introduction

Prostate cancer ranks sixth in cancer mortality among Japanese men, with an estimated incidence of 78 400 that is steadily rising due to increased PSA testing.^{1,2} Initial therapy for locally advanced and mHSPC, also known as metastatic castration-sensitive prostate cancer, is ADT. In Japan, combined androgen blockade therapy, consisting of ADT with conventional non-steroidal anti-androgens, is commonly prescribed for mHSPC and is associated with significant long-term outcomes.³ No prospective Japanese study, however, has assessed the benefit of combined androgen blockade therapy for mHSPC. Other recommended combination therapies for mHSPC^{4,5} include ADT plus docetaxel,^{6,7} abiraterone and corticosteroids, apalutamide⁸ or enzalutamide.⁹ ADT plus docetaxel or abiraterone and corticosteroids improved survival for patients with metastatic prostate cancer regardless of disease risk or volume.^{10,11}

Apalutamide plus ADT increased rPFS and OS based on interim analyses from the TITAN study.⁸ The 5-year survival rate of 49.1% in Japan reflects the need for additional effective therapies that improve clinical outcomes and extend survival for patients with mHSPC.¹

Enzalutamide, a potent androgen receptor signaling inhibitor,¹² is either approved or under regulatory consideration for approval for castration-resistant prostate cancer, irrespective of the presence of metastases, and mHSPC/metastatic castration-sensitive prostate cancer globally.^{13,14} Recently, the Japan Ministry of Health and Welfare amended the indication for enzalutamide to include mHSPC.¹⁵ In the phase III ARCHES study (NCT02677896), enzalutamide plus ADT significantly reduced the risk of radiographic progression versus placebo plus ADT in mHSPC patients.⁹ Additionally, enzalutamide significantly extended progression-free survival and OS when compared with conventional non-steroidal anti-androgen therapy in the open-label, phase III ENZAMET trial (NCT02446405).¹⁶ The efficacy of enzalutamide for castration-resistant prostate cancer has previously been reported for the Japanese population,¹⁷ but not for Japanese men with mHSPC. Also, post-hoc analyses of the phase III PREVAIL and LATITUDE studies showed slight differences in AE incidence within Japanese patients compared with the overall population.^{18,19} In the present post-hoc analysis, we evaluated the efficacy and safety of enzalutamide plus ADT versus placebo plus ADT in the ARCHES cohort of Japanese men with mHSPC.

Methods

Study design and conduct

The ARCHES study design (NCT02677896) has been previously reported.⁹ The clinical protocol was approved by local independent review boards, and carried out according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. All patients provided informed consent.

Eligible patients were men with pathologically confirmed prostate adenocarcinoma without neuroendocrine differentiation or signet cell/small cell features, had investigator-

confirmed mHSPC and had an ECOG performance status of ≤ 1 at screening. Up to 3 months of prior ADT (or ≤ 6 months if treated with docetaxel) and six or fewer cycles of prior docetaxel were permitted. Patients who experienced disease progression before randomization while receiving ADT and/or docetaxel were excluded.

Enrolled patients were randomized 1:1 to receive enzalutamide (160 mg/day) plus ADT or a placebo plus ADT (Fig. 1). Treatment continued until occurrence of unacceptable toxicity, radiographic progression, initiation of an investigational agent or new therapy, or other discontinuation criteria.

End-points

The primary end-point was rPFS, defined as time from randomization to first evidence of radiographic disease progression (based on central review) or death from any cause within 24 weeks of study drug discontinuation, whichever occurred first. Radiographic disease progression was assessed by independent central review according to RECIST version 1.1 for soft tissue lesions, and protocol-defined criteria for bone lesions. Key secondary end-points were time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, ORR, time to deterioration in urinary symptoms and OS. Other secondary end-points included time to first SSE, time to castration resistance, time to pain progression and time to deterioration of QoL. Safety was also assessed. End-points were previously defined in ARCHES.⁹

Assessments

Efficacy and patient-reported outcome assessments, including imaging, were carried out at screening, week 13 and every subsequent 12 weeks. Patient-reported outcome assessments included FACT-P,²⁰ European Organization for Research and Treatment of Cancer QLQ-PR25²¹ and BPI-SF. PSA levels were assessed at screening, weeks 1, 5 and 13, every subsequent 12 weeks, and 30 days after the last dose or before new antineoplastic therapy initiation, whichever occurred first. Treatment-emergent AEs were graded by the site investigator, as previously described.⁹

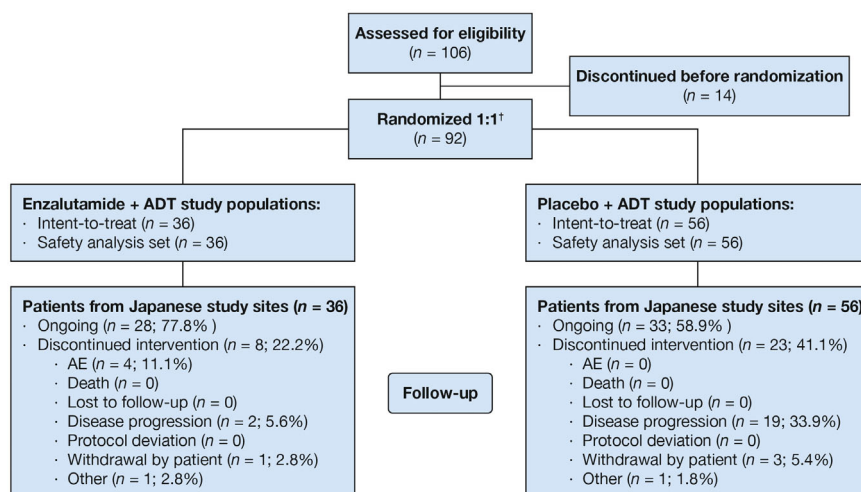


Fig. 1 CONSORT diagram: Japanese subgroup. †Randomization 1:1 was stratified by the volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no cycles, 1–5 cycles or 6 cycles); high volume of disease was defined as the presence of metastases involving the viscera, or in the absence of visceral lesions, four or more bone lesions, one or more of which must have been in a bony structure beyond the vertebral column and pelvic bone, as per the criteria.⁸

Table 1 Baseline characteristics

	Japanese subgroup		Overall ITT population	
	Enzalutamide + ADT (n = 36)	Placebo + ADT (n = 56)	Enzalutamide + ADT (n = 574)	Placebo + ADT (n = 576)
Median age, years (range)	72.0 (58–92)	70.0 (45–88)	70.0 (46–92)	70.0 (42–92)
Age category				
65 years	4 (11.1)	12 (21.4)	148 (25.8)	152 (26.4)
65 to <75 years	20 (55.6)	24 (42.9)	265 (44.6)	255 (44.3)
≥75 years	12 (33.3)	20 (35.7)	170 (29.6)	169 (29.3)
Median weight, kg (range)	65.7 (48–91)	62.0 (39–103)	80.0 (43–163)	80.0 (39–158)
ECOG performance status score on day 1				
0	34 (94.4)	47 (83.9)	448 (78.0)	443 (76.9)
1	2 (5.6)	9 (16.1)	125 (21.8)	133 (23.1)
Total Gleason score at initial diagnosis				
<8	3 (8.3)	9 (16.1)	171 (29.8)	187 (32.5)
≥8	33 (91.7)	47 (83.9)	386 (67.2)	373 (64.8)
Confirmed metastases at screening				
Yes	35 (97.2)	53 (94.6)	536 (93.4)	531 (92.2)
No	1 (2.8)	3 (5.4)	34 (5.9)	45 (7.8)
Unknown	0	0	4 (0.7)	0
Localization of confirmed metastases at screening				
Bone only	17 (47.2)	25 (44.6)	268 (46.7)	245 (42.5)
Soft tissue only	3 (8.3)	3 (5.4)	51 (8.9)	45 (7.8)
Visceral†	3 (8.4)	4 (7.1)	63 (11.0)	63 (11.0)
Bone and soft tissue	15 (41.7)	25 (44.6)	217 (37.8)	241 (41.8)
Distant metastases at initial diagnosis				
M1	36 (100)	53 (94.6)	402 (70.0)	365 (63.4)
M0	0	1 (1.8)	83 (14.5)	86 (14.9)
MX/unknown	0	2 (3.6)	88 (15.3)	125 (21.7)
Disease volume				
Low	13 (36.1)	22 (39.3)	220 (38.3)	203 (35.2)
High	23 (63.9)	34 (60.7)	354 (61.7)	373 (64.8)
Prior local therapy				
Radical prostatectomy	0	1 (1.8)	72 (12.5)	89 (15.5)
Radiation therapy	2 (5.6)	1 (1.8)	94 (16.4)	96 (16.7)
Prior docetaxel chemotherapy				
None	36 (100)	56 (100)	471 (82.1)	474 (82.3)
1–5 cycles	0	0	14 (2.4)	11 (1.9)
6 cycles	0	0	89 (15.5)	91 (15.8)
Prior use of ADT				
None	5 (13.9)	5 (8.9)	39 (6.8)	61 (10.6)
≤3 months	31 (86.1)	50 (89.3)	414 (72.1)	394 (68.4)
>3 months	0	1 (1.8)	121 (21.1)	120 (20.8)
Unknown	0	0	0	1 (0.2)
Prior prostate cancer drug therapy	33 (91.7)	50 (89.3)	514 (89.9)	505 (88.0)
Prior use of anti-androgen	9 (25.0)	23 (41.1)	205 (35.8)	229 (39.9)
Median PSA, µg/mL (range)	16.9 (0–1374)	15.5 (0–2088)	5.4 (0–4824)	5.1 (0–19 000)
Modified QLQ-PR25 urinary symptoms score, mean (SD)‡	29.6 (21.4)	37.8 (25.2)	35.2 (25.3)	35.8 (25.4)
FACT-P total score, mean (SD)§	106.9 (17.3)	105.9 (18.4)	113.9 (19.8)	112.7 (19.0)
BPI-SF pain severity score, mean (SD)¶	0.88 (1.1)	1.25 (1.6)	1.36 (1.8)	1.35 (1.7)

Data are n (%) unless otherwise indicated. MX, distant metastasis cannot be assessed (NE by any modality); M0, no distant metastasis; M1, distant metastasis. †Visceral metastases consists of liver and lung metastases. No patients had both liver and lung metastases at screening. ‡Only items Q31–Q33 from the urinary symptoms subscale were assessed. All items and scale scores of the QLQ-PR25 are linearly transformed to a 0–100 scale. A higher score in the urinary symptoms subscale indicates more symptoms.¹⁷ §The FACT-P total score ranges from 0 to 156, with the higher scores indicating more favorable QoL.¹⁸ ¶The BPI-SF average score ranges from 0 to 10, with higher scores indicating worse pain.

Statistical analysis

Baseline characteristics and efficacy outcomes were evaluated in the ITT population. Safety was assessed in patients who received at least one dose of study drug. Median estimates

and 95% CIs were determined using Kaplan–Meier and Brookmeyer methods, respectively. HRs relative to placebo plus ADT, with <1.00 favoring enzalutamide plus ADT, were determined using Cox regression model stratified for prior docetaxel use and disease volume.

Results

Baseline demographics and patient history

Eligible patients were randomized from March 2016 to January 2018. As of the data cut-off of 14 October 2018,⁹ the median follow-up time in the Japanese subgroup was 15.7 months for enzalutamide plus ADT and 15.5 months for a placebo plus ADT. Of the 1150 patients in ARCHES, 92 were randomized from 19 Japanese study sites (enzalutamide plus ADT, $n = 36$; placebo plus ADT, $n = 56$; Fig. 1). Baseline demographics and disease characteristics, such as disease volume (low vs high), were generally balanced across both treatment arms: 62% of patients had high disease volume and 38% had low disease volume, similar to the overall population (Table 1). Fewer Japanese patients had prior radical prostatectomy (Japan 1.1%; overall 14.0%) or radiation therapy (Japan 3.3%; overall 12.6%) versus the overall population; no Japanese patients had prior docetaxel therapy. Some baseline differences were also observed when compared with the overall population. Japanese patients had 20% lower bodyweight and higher baseline PSA levels.

Additionally, a higher proportion of Japanese patients had an ECOG score of 0, a Gleason score of ≥ 8 and distant metastases at initial diagnosis. At data cut-off, 34% of all Japanese patients discontinued treatment (Fig. 1), with the primary reasons being AEs (enzalutamide plus ADT, $n = 4$ [11%]; placebo plus ADT, $n = 0$ [0%]) and progressive disease (enzalutamide plus ADT, $n = 2$ [5.6%]; placebo plus ADT, $n = 19$ [33.9%]).

Clinical efficacy

Median treatment duration was slightly longer in both arms of the Japanese subgroup (enzalutamide plus ADT 13.7 months; placebo plus ADT 12.3 months) versus the overall population (enzalutamide plus ADT 12.8 months; placebo plus ADT 11.6 months). Enzalutamide plus ADT reduced the risk of radiographic progression or death by 61% compared with the placebo plus ADT (HR 0.39, 95% CI 0.13, 1.18; Table 2; Fig. 2) in Japanese patients, consistent with the overall population. Median rPFS was NR with enzalutamide plus ADT versus 16.8 months with a placebo plus ADT.

Table 2 Primary and secondary end-points

	Japanese subgroup		Overall ITT population	
	Enzalutamide + ADT ($n = 36$)	Placebo + ADT ($n = 56$)	Enzalutamide + ADT ($n = 574$)	Placebo + ADT ($n = 576$)
Primary end-point				
Median rPFS, months (95% CI)	NR (16.5, NR)	16.8 (14.1, NR)	NR (NR, NR)	19.0 (16.6, 22.2)
HR (95% CI)	0.39 (0.13, 1.18)		0.39 (0.30, 0.50)	
Radiographic progression, n (%)	3 (8.3)	13 (23.2)	79 (13.8)	188 (32.6)
Death within 24 weeks of treatment in the absence of radiographic progression, n (%)	1 (2.8)	1 (1.8)	12 (2.1)	13 (2.3)
Key secondary end-points				
Median time to PSA progression, months (95% CI)	NR (NR, NR)	NR (13.9, NR)	NR (NR, NR)	NR (16.6, NR)
HR (95% CI)	0.00 (0.0, NR) [†]		0.19 (0.13, 0.26)	
Median time to initiation of new antineoplastic therapy, months (95% CI)	NR (20.0, NR)	17.2 (13.1, NR)	30.2 (NR, NR)	NR (21.1, NR)
HR (95% CI)	0.24 (0.08, 0.73)		0.28 (0.20, 0.40)	
PSA undetectable (<0.2 ng/mL) rate, [‡] n (%)	25 (71.4)	8 (14.5)	348 (68.1)	89 (17.6)
Rate difference, % (95% CI)	56.9 (39.3, 74.5)		50.5 (45.3, 55.7)	
ORR, [§] n (%)	14 (93.3)	16 (100)	147 (83.1)	116 (63.7)
Rate difference, % (95% CI)	-6.7 (-19.3, 6.0)		19.3 (10.4, 28.2)	
Median time to deterioration of urinary symptoms, [¶] months (95% CI)	11.2 (2.9, NR)	NR (NR, NR)	NR (19.4, NR)	16.8 (14.1, NR)
HR (95% CI)	2.22 (1.10, 4.47)		0.88 (0.72, 1.08)	
Median OS, months (95% CI)	NR (NR, NR)	NR (19.3, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.92 (0.15, 5.52)		0.81 (0.53, 1.25)	
Other secondary end-points				
Median time to first SSE, months (95% CI)	NR (NR, NR)	NR (16.8, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.27 (0.06, 1.24)		0.52 (0.33, 0.80)	
Median time to castration resistance, months (95% CI)	NR (NR, NR)	16.8 (11.1, NR)	NR (NR, NR)	13.8 (11.3, 16.8)
HR (95% CI)	0.15 (0.05, 0.50)		0.28 (0.22, 0.36)	
Median time to deterioration of QoL, ^{††} months (95% CI)	13.8 (2.9, NR)	13.8 (5.6, NR)	11.3 (11.0, 13.8)	11.1 (8.5, 13.8)
HR (95% CI)	1.07 (0.57, 1.99)		0.96 (0.81, 1.14)	
Median time to pain progression, ^{‡‡} months (95% CI)	5.7 (2.9, 8.3)	5.6 (2.8, 14.0)	8.3 (8.3, 10.9)	8.3 (5.7, 8.4)
HR (95% CI)	1.25 (0.71, 2.19)		0.92 (0.78, 1.07)	

[†]No PSA progression events were reported in patients who were treated with enzalutamide plus ADT in the Japanese subgroup. [‡]This analysis was carried out using ITT patients who had detectable PSA values at baseline (enzalutamide plus ADT, $n = 35$; placebo plus ADT, $n = 55$). [§]Objective response is defined as patients achieving a complete or partial response in their soft tissue disease using RECIST version 1.1.²⁴ [¶]A deterioration in urinary symptoms is defined as an increase in the urinary symptoms subscale score by $\geq 50\%$ of the SD observed in the urinary symptoms subscale score at baseline (i.e. Q31–Q33). ^{††}A deterioration in QoL is defined as a decrease of ≥ 10 points in the total FACT-P score from baseline. ^{‡‡}Pain progression is defined as an increase of $\geq 30\%$ from baseline in the average BPI-SF pain severity score.

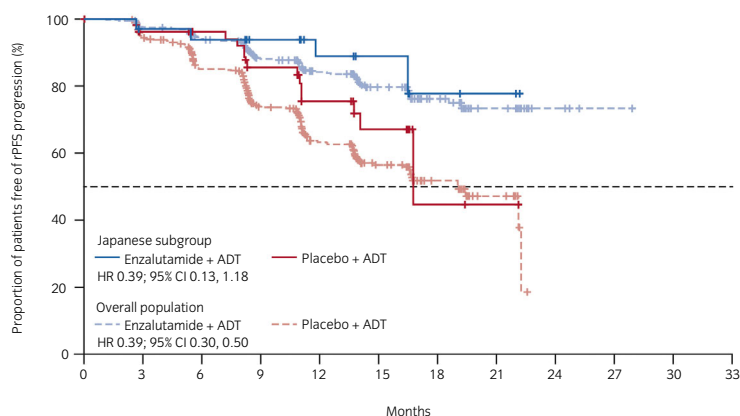


Fig. 2 Kaplan–Meier estimate of time to rPFS in Japanese men and in the overall ARCHES population receiving enzalutamide plus ADT or a placebo plus ADT.

Patients at risk – Japanese subgroup

Enzalutamide + ADT	36	31	30	23	18	8	5	2	0	0	0	0
Placebo + ADT	56	48	46	37	25	14	2	1	0	0	0	0

Patients at risk – Overall population

Enzalutamide + ADT	574	516	493	370	256	144	62	23	4	1	0	0
Placebo + ADT	576	511	445	314	191	106	39	10	0	0	0	0

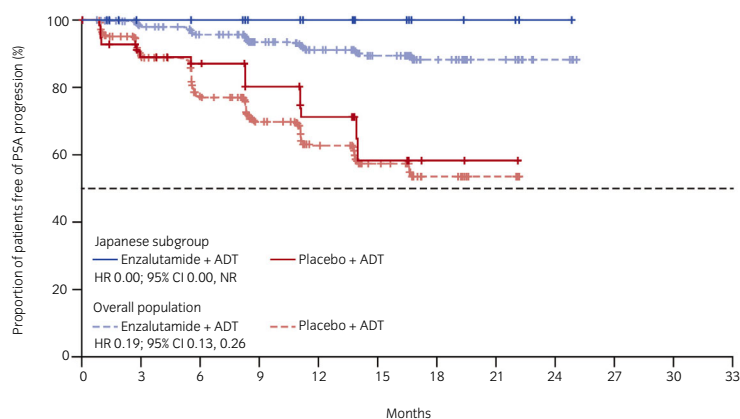


Fig. 3 Kaplan–Meier estimates of time to PSA progression in Japanese men and in the overall ARCHES population receiving enzalutamide plus ADT or a placebo plus ADT.

Patients at risk – Japanese subgroup

Enzalutamide + ADT	36	32	30	23	19	9	6	3	1	0	0	0
Placebo + ADT	56	46	41	31	21	9	2	1	0	0	0	0

Patients at risk – Overall population

Enzalutamide + ADT	574	530	495	371	247	134	58	22	4	0	0	0
Placebo + ADT	576	569	387	257	153	76	25	4	0	0	0	0

The clinical benefit of enzalutamide plus ADT in Japanese patients was also shown in secondary end-points of time to PSA progression (Fig. 3), time to initiation of new antineoplastic therapy (Fig. 4), time to first SSE (Fig. 5), time to castration resistance (Fig. 6) and PSA undetectable rate (Table 2). Bicalutamide was the most commonly chosen new antineoplastic therapy after disease progression, regardless of treatment arm (enzalutamide plus ADT, $n = 3$ [8.3%]; placebo plus ADT, $n = 8$ [14.3%]). ORR among evaluable men with measurable disease ($n = 31$) was comparable between treatment arms (Table 2). At the time of interim analysis, OS data were immature, with five deaths (enzalutamide plus ADT, $n = 2$; placebo plus ADT, $n = 3$; Table 2).

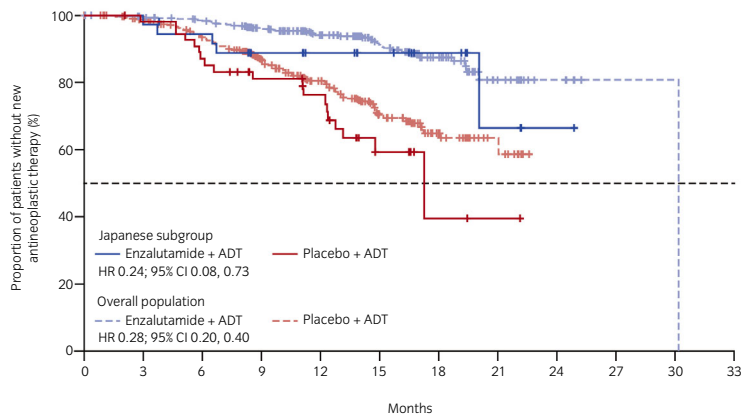
Patient-reported outcomes

QoL at baseline in Japanese patients, measured by FACT-P total score (range 0–156), was high in both treatment arms

(Table 1). Baseline modified QLQ-PR25 urinary symptoms scores were lower in the enzalutamide plus ADT arm (29.6) than the placebo plus ADT arm (37.8); these were similar to treatment groups in the overall population (35.2 and 35.8, respectively; Table 1). The median time to deterioration of QoL and median time to pain progression were comparable between treatment arms (Table 2). The median time to deterioration of urinary symptoms was 11.2 months (95% CI 2.9, NR) in Japanese patients treated with enzalutamide plus ADT and NR with a placebo plus ADT.

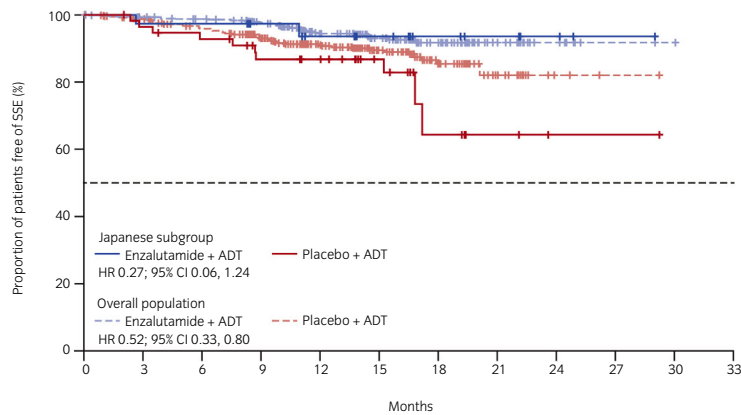
Safety

The incidence of any AE was similar in both treatment arms within the Japanese subgroup compared with the overall population (Table 3). More Japanese patients who received enzalutamide plus ADT reported grade ≥ 3 AEs or serious AEs versus placebo plus ADT; these were generally similar



Patients at risk – Japanese subgroup											
Enzalutamide + ADT	36	35	34	25	21	12	8	3	1	0	0
Placebo + ADT	56	54	47	38	30	13	2	1	0	0	0
Patients at risk – Overall population											
Enzalutamide + ADT	574	559	548	438	299	174	83	28	7	1	0
Placebo + ADT	576	552	515	383	252	140	53	13	0	0	0

Fig. 4 Kaplan–Meier estimates of time to initiation of new antineoplastic therapy in Japanese men and in the overall ARCHES population receiving enzalutamide plus ADT or a placebo plus ADT.



Patients at risk – Japanese subgroup											
Enzalutamide + ADT	36	35	35	27	22	13	8	5	3	1	0
Placebo + ADT	56	53	50	42	35	22	7	3	1	1	0
Patients at risk – Overall population											
Enzalutamide + ADT	574	558	549	448	306	183	91	33	11	2	0
Placebo + ADT	576	552	526	414	283	173	75	19	3	1	0

Fig. 5 Kaplan–Meier estimates of time to first SSE in Japanese men and in the overall ARCHES population receiving enzalutamide plus ADT or a placebo plus ADT.

between treatment groups in the overall population. More Japanese patients versus the overall population who received enzalutamide plus ADT had AEs leading to treatment withdrawal (11.1% vs 7.2%) or dose interruptions (16.7% vs 7.3%). Drug-related AEs leading to treatment withdrawal in Japanese patients who received enzalutamide plus ADT were immune thrombocytopenic purpura ($n = 1$, 2.8%), abnormal hepatic function ($n = 1$, 2.8%) and seizure ($n = 1$, 2.8%); one patient (1.8%) with neuroendocrine carcinoma withdrew from the placebo plus ADT group. No Japanese patients died due to AEs.

A greater proportion of patients who received enzalutamide plus ADT more frequently reported hot flashes, nasopharyngitis, hypertension and abnormal hepatic function than patients who received a placebo plus ADT (Table 4). The most frequently reported AEs of special interest in $\geq 10\%$ of Japanese patients who received enzalutamide plus ADT were rash, hypertension, fractures and musculoskeletal events.

Grade ≥ 3 AEs that were reported more frequently ($>5\%$) in the Japanese subgroup compared with the overall population (enzalutamide plus ADT only) were hypertension (13.9% vs 3.3%) and abnormal hepatic function (5.6% vs 0.3%; Table 4).

Discussion

The present post-hoc analysis of the ARCHES study showed that, similar to the overall population, Japanese men received clinical benefit from enzalutamide plus ADT. The benefit of enzalutamide plus ADT in Japanese patients was shown by the reduced risk of rPFS events and PSA progression, similar to the overall population.⁹

Observed baseline differences between the Japanese subgroup and overall population might be due to country-specific clinical practices. PSA screening is less common in Japan than in Western countries.² Consequently, a higher

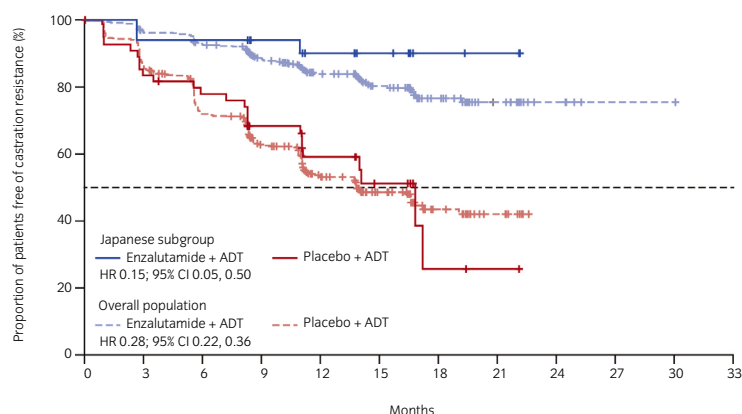


Fig. 6 Kaplan–Meier estimates of time to castration resistance in Japanese men and in the overall ARCHES population receiving enzalutamide plus ADT or a placebo plus ADT.

Patients at risk – Japanese subgroup											
Enzalutamide + ADT	36	31	31	23	18	9	4	2	0	0	0
Placebo + ADT	56	45	41	32	22	12	2	1	0	0	0
Patients at risk – Overall population											
Enzalutamide + ADT	574	514	492	389	262	150	69	26	6	1	1
Placebo + ADT	576	475	392	279	162	91	31	10	0	0	0

Table 3 Overall AE summary

	Japanese subgroup		Overall safety population	
	Enzalutamide + ADT (n = 36)	Placebo + ADT (n = 56)	Enzalutamide + ADT (n = 572)	Placebo + ADT (n = 574)
AEs	32 (88.9)	51 (91.1)	487 (85.1)	493 (85.9)
Grade ≥ 3 AEs	17 (47.2)	14 (25.0)	139 (24.3)	147 (25.6)
Serious AEs	11 (30.6)	9 (16.1)	104 (18.2)	112 (19.5)
AEs leading to dose reduction	1 (2.8)	0	25 (4.4)	11 (1.9)
AEs leading to dose interruption	6 (16.7)	2 (3.6)	42 (7.3)	36 (6.3)
AEs leading to withdrawal of treatment	4 (11.1)	1 (1.8)	41 (7.2)	30 (5.2)
Drug-related AEs	25 (69.4)	30 (53.6)	303 (53.0)	268 (46.7)
Drug-related serious AEs	5 (13.9)	2 (3.6)	22 (3.8)	16 (2.8)
Drug-related AEs leading to withdrawal of treatment	3 (8.3)	1 (1.8)	16 (2.8)	12 (2.1)
AEs leading to death	0	0	14 (2.4)	10 (1.7)

Data are n (%) unless otherwise indicated.

percentage of Japanese prostate cancer diagnoses are advanced de novo metastatic cases (96.7% vs 66.7% of the overall population).⁹ Expectedly, we observed a greater proportion of Japanese patients with Gleason scores ≥ 8 and higher baseline PSA levels compared with the overall population. Additionally, the type of therapy used for prostate cancer might have impacted observed baseline differences and chosen antineoplastic therapy after disease progression. Hormonal therapy with bicalutamide is commonly used as first- and second-line therapy in Japan, whereas local radiation or surgery is preferred in Western countries.^{22,23} Furthermore, docetaxel, a treatment recommended for mHSPC, is not currently covered by public insurance as initial therapy for mHSPC in Japan.

Unlike in the overall population, no differences were observed in ORR between Japanese treatment arms.⁹ This might be due to the small number of Japanese patients with measurable disease at baseline (enzalutamide plus ADT, $n = 15$; placebo plus ADT, $n = 16$) compared with the

overall population (enzalutamide plus ADT, $n = 177$; placebo plus ADT, $n = 182$).²⁴ However, ORR with enzalutamide plus ADT in the overall population resulted in more durable responses, as exemplified by the 61% reduction in risk of radiographic progression over time. We also found that Japanese patients in the placebo plus ADT arm reported higher baseline QLQ-PR25 symptom scores (indicating more urinary symptoms) versus enzalutamide plus ADT; these scores were similar between treatment groups in the overall population. This, alongside the smaller number of patients, might have contributed to the larger treatment difference in time to deterioration of urinary symptoms observed in Japanese patients.

The incidence of AEs was similar between Japanese patients (88.9%) and the overall population (85.1%).⁹ However, Japanese patients reported a higher incidence of grade ≥ 3 AEs in the enzalutamide plus ADT arm (47%) compared with the overall population (24%).⁹ The most frequently reported grade ≥ 3 AEs for enzalutamide plus ADT versus placebo plus ADT in Japanese patients were hypertension

Table 4 Most common AEs and AEs of special interest

	Japanese subgroup				Overall safety population			
	Enzalutamide + ADT (n = 36)		Placebo + ADT (n = 56)		Enzalutamide + ADT (n = 572)		Placebo + ADT (n = 574)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Most common AEs, occurring in ≥10% of patients†								
Hot flash	10 (27.8)	0	12 (21.4)	0	155 (27.1)	2 (0.3)	128 (22.3)	0
Nasopharyngitis	9 (25.0)	0	11 (19.6)	0	23 (4.0)	0	26 (4.5)	0
Hypertension	7 (19.4)	5 (13.9)	3 (5.4)	0	46 (8.0)	19 (3.3)	32 (5.6)	10 (1.7)
Abnormal hepatic function	5 (13.9)	2 (5.6)	3 (5.4)	0	5 (0.9)	2 (0.3)	4 (0.7)	0
Increased weight	3 (8.3)	1 (2.8)	14 (25.0)	0	35 (6.1)	2 (0.3)	44 (7.7)	1 (0.2)
Back pain	3 (8.3)	0	9 (16.1)	1 (1.8)	43 (7.5)	5 (0.9)	62 (10.8)	3 (0.5)
AEs of special interest‡								
Convulsion	1 (2.8)	1 (2.8)	0	0	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Hypertension	7 (19.4)	5 (13.9)	3 (5.4)	0	49 (8.6)	19 (3.3)	36 (6.3)	12 (2.1)
Decreased neutrophil count	1 (2.8)	1 (2.8)	0	0	5 (0.9)	2 (0.3)	4 (0.7)	2 (0.3)
Cognitive/memory impairment	0	0	0	0	26 (4.5)	4 (0.7)	12 (2.1)	0
Ischemic heart disease	2 (5.6)	1 (2.8)	1 (1.8)	1 (1.8)	10 (1.7)	3 (0.5)	8 (1.4)	6 (1.0)
Other selected cardiovascular events	0	0	0	0	13 (2.3)	6 (1.0)	9 (1.6)	5 (0.9)
Fatigue	2 (5.6)	0	2 (3.6)	1 (1.8)	138 (24.1)	10 (1.7)	112 (19.5)	9 (1.6)
Fall	1 (2.8)	0	3 (5.4)	0	21 (3.7)	2 (0.3)	15 (2.6)	1 (0.2)
Fractures	5 (13.9)	2 (5.6)	8 (14.3)	3 (5.4)	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)
Loss of consciousness	1 (2.8)	1 (2.8)	0	0	9 (1.6)	6 (1.0)	1 (0.2)	1 (0.2)
Thrombocytopenia	0	0	0	0	3 (0.5)	0	3 (0.5)	0
Musculoskeletal events	5 (13.9)	0	13 (23.2)	1 (1.8)	151 (26.4)	9 (1.6)	159 (27.7)	12 (2.1)
Severe cutaneous adverse reactions	0	0	1 (1.8)	0	0	0	1 (0.2)	0
Angioedema	2 (5.6)	0	0	0	7 (1.2)	1 (0.2)	1 (0.2)	0
Rash	4 (11.1)	0	1 (1.8)	0	15 (2.6)	0	9 (1.6)	0
Second primary malignancies	1 (2.8)	0	3 (5.4)	2 (3.6)	11 (1.9)	9 (1.6)	11 (1.9)	7 (1.2)

Data are n (%) unless otherwise indicated. †AEs reported in ≥10% of patients in either treatment arm in the Japanese subgroup, listed in descending order by preferred term. None of the most common AEs was grade 5. ‡AEs of special interest were based on prespecified combinations of preferred terms (Medical Dictionary for Regulatory Activities version 21.0) related to the AE of special interest; for example, the combination of preferred terms used to define fatigue as an AE of special interest was fatigue and asthenia.

(14% vs 0%) and abnormal hepatic function (6% vs 0%); these were higher than those reported for the overall population, ranging from 0% to 3% for either AE in both treatment arms. Additionally, Japanese patients treated with enzalutamide plus ADT more frequently reported ischemic heart disease (5.6% vs 1.7%) and fractures (13.9% vs 6.5%) versus the overall population. These data suggest that routine monitoring of hepatic function, blood pressure, cardiovascular risk factors and bone density is warranted, particularly in Japanese men with mHSPC treated with enzalutamide plus ADT. Drug-related AEs leading to withdrawal in Japanese patients were reported by three patients with enzalutamide plus ADT and one with placebo plus ADT, 8.3% and 1.8% of patients in the respective treatment arms. Overall, the smaller number of patients and potential differences in enzalutamide metabolism in Japanese men might contribute to observed AE differences between treatment arms and patient populations.¹⁷

Fatigue and decreased appetite are seriously considered AEs within Japanese clinical practice. In the phase II, randomized, active-controlled OCUU-CRPC study carried out in Japan (NCT02346578; n = 103), the most frequently reported AEs among castration-resistant prostate cancer patients who received enzalutamide were fatigue (19.3%) and decreased appetite (15.4%).²⁵ In this analysis, neither fatigue nor decreased appetite were reported as an AE in >10% of either

treatment arm in the Japanese subgroup. This discrepancy in reported events might be due to differences in disease progression and duration of previous therapies.

The main limitation of this analysis was the small number of patients in the Japanese subgroup; OS analysis was immature, similar to the overall population.⁹ This analysis was not intended to detect differences between treatment arms in the Japanese subgroup, nor between the Japanese subgroup and the overall population. Differences in local treatment practices might have contributed to differences in baseline demographics in Japanese patients compared with the overall population.

Nevertheless, enzalutamide plus ADT showed clinical efficacy compared with a placebo plus ADT in Japanese men with mHSPC, consistent with the results from the ARCHES study.⁹ Enzalutamide plus ADT also had a tolerable safety profile for Japanese men with mHSPC. The efficacy and safety data from the present post-hoc analysis support the use of enzalutamide plus ADT for mHSPC in Japan.

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Conflict of interest

Iguchi reports funding and advisory roles with Astellas and Bayer; and advisory roles with Janssen and Sanofi. Kimura reports honoraria from Bayer, Bristol-Myers Squibb, Novartis, Ono Pharmaceuticals, Pfizer and Roche/Chugai; and a study investigator role with Astellas. Fukasawa reports an advisory role and honoraria from AstraZeneca; honoraria from Astellas, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Ono Pharmaceuticals, Pfizer and Takeda; and a study investigator role with Astellas. Suzuki reports funding and advisory roles with Astellas, Bayer, Daiichi Sankyo, Sanofi and Takeda; advisory roles with AstraZeneca, Eli Lilly, Janssen, MSD, Nihon Medi-Physics and Roche/Chugai; and funding from Kissei, Ono Pharmaceuticals and Pfizer. Uemura reports funding from Bayer, Daiichi Sankyo, Kissei, Roche/Chugai, Sanofi, Taiho and Takeda; advisory roles with AstraZeneca, Daiichi Sankyo and Janssen; and a study investigator role with Astellas. Nishimura reports an advisory role and honoraria from Astellas; advisory roles with AstraZeneca and Janssen; honoraria from Novartis; and funding from Bayer. Matsumoto reports a study investigator role with Astellas. Yokomizo reports an advisory role and honoraria from Bayer; an advisory role with Janssen; honoraria from Astellas and AstraZeneca; and a study investigator role with Astellas. Armstrong reports advisory roles with Astellas, AstraZeneca, Bayer, Clovis Oncology, Dendreon, Janssen, Medivation, Pfizer and Sanofi; honoraria from Dendreon and Janssen; funding from Active Biotech, Astellas, Bayer, Bristol-Myers Squibb, Constellation Pharmaceuticals, Dendreon, Gilead Sciences, Janssen, Medivation, Merck, Novartis, Pfizer, Roche/Genentech and Sanofi; and a patent for circulating tumor cell novel capture technology. Rosbrook is a current employee of Pfizer. Baron is a former employee of Astellas. Sugg, Chen and Kunieda are current employees of Astellas. Stenzl reports an advisory role and funding from Janssen; advisory roles with Alere, Bristol-Myers Squibb, Ipsen, Roche and Stebabiotech; funding from Astellas, AstraZeneca, Karl Storz AG and Medivation; and patents A290/99, AT00/0001 and 2018/6579.

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