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A Phase 2 Trial of Abiraterone Acetate in Japanese Men with Metastatic Castration-resistant Prostate Cancer and without Prior Chemotherapy (JPN-201 Study)

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Objective: Abiraterone acetate has been approved in >70 countries for chemotherapy-naïve metastatic castration-resistant prostate cancer patients. Efficacy and safety of abiraterone acetate (1000 mg/once daily) with prednisolone (5 mg/twice daily) in chemotherapy-naïve Japanese patients with metastatic castration-resistant prostate cancer was evaluated.

Methods: Men, ≥20 years, with prostate-specific antigen levels of ≥5 ng/ml and evidence of progression were enrolled in this Phase 2, multicenter, open-label study. Primary efficacy endpoint was proportion of patients achieving a prostate-specific antigen decline of ≥50% from baseline (prostate-specific antigen response) after 12 week of treatment. Secondary efficacy endpoints and safety were assessed.

Results: A confirmed prostate-specific antigen response was observed in 29/48 (60.4%) patients by week 12; lower limit of two-sided 90% confidence interval was >35% (threshold response rate), demonstrating efficacy of abiraterone acetate. Secondary efficacy endpoints: prostate-specific antigen response rate during treatment period: 62.5%; objective radiographic response, partial response: 4/18 (22.2%) patients; complete response: none; stable disease: 11/18 (61.1%) patients; median percent change in prostate-specific antigen level from baseline at Week 12: −66.62%. Median prostate-specific antigen response duration and progression-free survival were not reached, and median radiographic progression-free survival was 253 days. Of 31/48 (64.6%) patients experienced adverse events of special interest; most common was hepatic function abnormality (37.5%, Grade 3: 10.4%). One Grade 3 hypertension was the only mineralocorticoid adverse event >Grade 1/2.

Conclusions: Efficacy of abiraterone acetate plus prednisolone was demonstrated by decline in prostate-specific antigen levels with evidence of antitumor activity by radiography in Japanese patients with chemotherapy-naïve metastatic castration-resistant prostate cancer. Abiraterone acetate plus prednisolone had an acceptable safety profile.

Clinical trial registration no: NCT01756638.

Key words: abiraterone acetate – chemotherapy-naïve – metastatic castration-resistant prostate cancer – prednisolone – prostate specific antigen

INTRODUCTION

Prostate cancer is one of the most common malignancies in men in Western countries and is the fifth leading cause of death (6.6% of the total men deaths) from cancer in men (1). In Asian countries, prostate cancer is less common (1). However, demographic aging, Westernization of diet and widespread use of prostate-specific antigen (PSA) based screening, has led to detection of an increased number of Japanese patients with prostate cancer. In Japan, 51 534 men were diagnosed with prostate cancer (2008) and 11 143 died of the disease (2012) (2). The number of patients diagnosed annually with this disease is estimated to increase to 118 200 by 2029 (3).

Prostate cancer is highly dependent on androgen levels and the androgen–androgen receptor (AR) axis plays an important role in its growth and sustenance. Metastatic castration-resistant prostate cancer (mCRPC), the terminal stage of the disease, is associated with increased levels of PSA, and may develop in 2–3 years after initiation of androgen deprivation therapies (surgical or medical castration) (4). Until recently, a docetaxel-based regimen was considered the only standard therapy for mCRPC (5) despite resistance (or intolerance) to this therapy and eventual progression of disease (6). Castration-resistant disease is associated with an up-regulation of genes that increase intracellular conversion of adrenal androgens (dehydroepiandrosterone sulfate [DHEA] and androstenedione) to sufficiently high levels of testosterone and dihydrotestosterone that activate the AR (7–10). Reduction in androgen concentrations below castration levels could offer a novel therapeutic approach for improving survival benefits in patients with mCRPC.

Abiraterone acetate (AA) (Zytiga®), a prodrug of abiraterone, is a first-in-class CYP17 (17α-hydroxylase/C17, 20 lyase) inhibitor that selectively inhibits androgen synthesis in testes, adrenal glands and tumor tissues. After oral administration, AA is rapidly converted into its active metabolite, abiraterone. Oral AA (1000 mg) in combination with prednisone 5 mg administered orally twice daily was approved by the US Food and Drug Administration in April 2011 for patients who had received chemotherapy and that approval was expanded for chemo-naïve patients in December 2012. It currently has approval in >70 countries to treat men with mCRPC in settings before and after chemotherapy (11,12). The most common AEs reported in these studies for patients treated with AA plus prednisone were peripheral edema, hypokalemia, urinary tract infection and hypertension (11–16).

Currently, in Japan, there is an unmet need for an effective non-toxic therapy that can prolong survival and prevent progressive disease (PD) in mCRPC patients, as docetaxel therapy is currently the only available option (17–21). In a Japanese Phase 1 study (JPN-101) in chemotherapy-naïve CRPC patients, 1000 mg once daily AA plus prednisolone was selected as the recommended dose owing to its effect of reducing PSA levels and antitumor activity; consistent with prior studies conducted in the USA and UK. Most of the adverse events (AEs) were Grade 1 or 2 and Grade 3 or 4 AEs of hepatic function were clinically manageable, reversible and resolved during the study. In the current study, efficacy of AA based primarily on PSA decline, and its safety profile in chemotherapy-naïve mCRPC patients was evaluated.

PATIENTS AND METHODS

The Independent Ethics Committee or Institutional Review Board approved the protocol and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients or their legally acceptable representatives provided written informed consent before entering the study.

Men with mCRPC, aged ≥20 years, with a PSA level of ≥5 ng/ml and Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 who had not received chemotherapy for prostate cancer, were eligible if they had histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology; with testosterone levels of <50 ng/dl because of surgical or medical castration (treatment with an luteinizing hormone-releasing hormone [LH-RH] analog had to be initiated ≥4 weeks before Cycle 1 Day 1 and continued throughout the study); and had target or non-target metastatic lesions. Evidence of progression consisted of a PSA level of ≥5 ng/ml per Prostate-Specific Antigen Working Group (PSAWG) eligibility criteria or objective progression by Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.0 criteria. For men who had been administered an antiandrogen, disease progression had to be demonstrated following discontinuation of antiandrogen. Patient had to have adequate hematological function and with permitted serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values of <2.5 × ULN were included.

Exclusion criteria were as follows: any major disease including brain metastasis; any currently active second malignancy; history of pituitary or adrenal insufficiency or hyperaldosteronism and medical conditions or comorbidity that could have interfered with their participation in the study. Patients were also excluded if they experienced any toxicities because of prior therapy that had not resolved to a National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0 grade of ≤1.

Study Design

This was a Phase 2, multi-center, open-label, single-arm study conducted at 21 sites in Japan to evaluate the efficacy and safety of AA in chemotherapy-naive mCRPC patients. The study consisted of a screening period (within 14 days before Cycle 1 Day 1), a treatment period (from Cycle 1 Day 1 to documented PD or unacceptable toxicity), and a follow-up period (follow-up for survival every 3 months up to 5 years

after the first dose of study drug or until approval was obtained from the Ministry of Health, Labour and Welfare (MHLW) (whichever is earlier). The data reported in this study are from the second interim report with cutoff date 28 June 2013.

Treatment

Eligible patients received AA 1000 mg (four tablets) orally once daily at least 1 h before a meal and 2 h after a meal. In addition, prednisolone 5 mg was to be taken concomitantly orally, twice daily to reduce the risk of study drug-related AEs (e.g. hypertension, swelling and hypokalemia) accompanied with secondary increases in mineralocorticoid level caused by long-term treatment with AA. A 28-day daily dosing cycle was continued until PD or unacceptable toxicity was observed.

Prior and Concomitant Therapy

Besides prednisolone, administration of LH-RH agonist and antagonist (in patients without orchiectomy), systemic corticosteroid, bisphosphonate and anti-receptor activator of nuclear factor-κB ligand monoclonal antibody concomitantly was permissible.

The prohibited medications included 5α-reductase inhibitor, hormonal therapy (including bicalutamide and flutamide), systemic corticosteroid therapy, radiotherapy, chemotherapy or immunotherapy, systemic ketoconazole or other azole drugs, CYP17 inhibitors and other investigational agents targeting the androgen receptors.

Endpoints

Primary

The primary endpoint was the proportion of patients achieving a PSA decline of $\geq$50% from baseline to 12 weeks of therapy in accordance with PSAWG criteria (PSA response) (confirmed by a subsequent measurement at least 4 weeks later).

Secondary

Secondary endpoints were the duration of a $\geq$50% PSA decline and the proportion of patients achieving PSA response (PSA response rate), serum PSA decline per Prostate Cancer Clinical Trials Working Group (PCWG)2 criteria, radiographic objective response rate (RAD-ORR) measured with RECIST Version 1.0, clinical benefit, as determined by disease stabilization and by changes in ECOG PS, pharmacokinetics, overall survival (OS), PSA-based progression-free survival (PSA-PFS), radiographic progression-free survival (RAD-PFS) and safety. Other secondary endpoints were Brief Pain Inventory-Short Form (BPI-SF) and circulating tumor cell (CTC) responders. BPI-SF was evaluated at screening and at subsequent cycles. The CTC conversion rate was defined as the proportion of patients achieving a decline in CTC count to $<$5.

Pharmacokinetic and Pharmacodynamic Evaluations

Venous blood samples of 2 ml were collected at specific time points for determination of pre- and post-dose plasma concentrations of abiraterone (and if required, selected metabolites). Changes in serum concentration of testosterone and DHEA-S were measured for each patient.

Safety Evaluations

Safety was evaluated based on AEs, clinical laboratory tests (hematology, serum chemistry, urinalysis and drug lymphocyte stimulation test [DLST]), vital sign measurements, physical examinations and electrocardiography (ECG). An assessment of AE severity grade was made using NCI-CTCAE Version 3.0.

Statistical Methods

Sample Size

Assuming an expected response rate of 55% that is 20% higher than the threshold response rate (35%), 45 patients were determined as necessary to demonstrate that the lower limit of the two-sided 90% confidence interval (CI) of the response rate would exceed the threshold response rate with a power of 80%.

Efficacy Analysis

The primary analysis population for efficacy was the full analysis set, which was defined as the patients who received treatment with the study drug at least once and had any post-treatment PSA assessment data. For the primary endpoint, PSA response rate and corresponding 90% CI were calculated. For secondary endpoints and other endpoints, all continuous variables were summarized using descriptive statistics. Categorical variables were summarized using frequencies and percentages. The Kaplan–Meier product-limit method was used to estimate the event-free time for the time-to-event data, along with the corresponding 90% CI. The corresponding 90% CI for the median time estimate was calculated.

Safety Analysis

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0. All reported AEs with onset during the treatment period (i.e. treatment-emergent AEs including AEs that worsened post-baseline) were included in the analysis. For each AE, the proportion of patients who experienced at least one occurrence of the given event was calculated.

RESULTS

A total of 56 patients were screened and 48 completed treatment (Fig. 1). The median age was 70 years (range: 46–89) (Table 1). The median baseline PSA level was 31.4 ng/ml

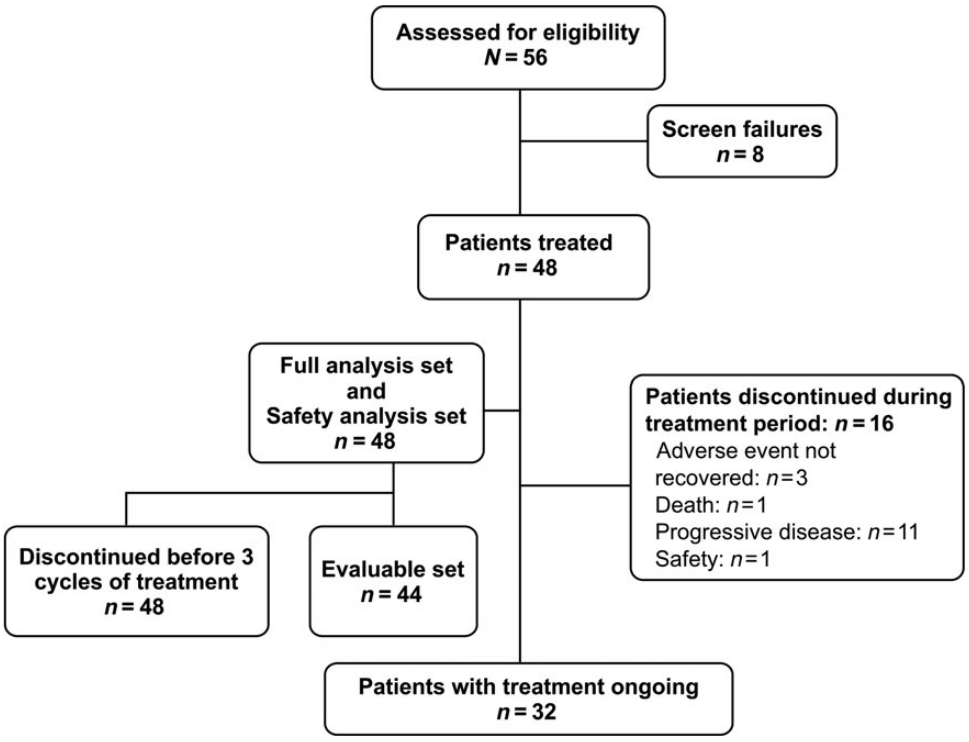

Figure 1. Patient disposition. Full analysis set: patients who received treatment with the study drug at least once and had any post-treatment PSA assessment (used for primary analysis). Evaluable set: consisted of patients with data on tumor assessments or PSA measurements at baseline and post-baseline at least once, and who had received a minimum of three cycles of study drug (≥21 daily doses in the 28-day cycle). Safety analysis set: patients who received treatment with the study drug at least once were included in the safety analysis set.

(range: 6.0–469.0). Demographic, baseline disease and baseline laboratory characteristics for the full analysis set were consistent with the safety analysis set, because the two analysis sets were identical in this study.

All 48 (100%) patients received at least one concomitant medication during the treatment period. Sixteen patients discontinued study treatment by the cutoff date. Most patients ($n = 42/48$, 87.5%) showed compliance with AA, and >95% compliance with prednisolone.

At data cutoff, the median duration of AA treatment was 9.18 months (range: 1.1–12.0). The median number of treatment cycles was 10.0 (range: 2–13), with 42/48 (87.5%) patients having started ≥6 or more cycles. Dose reductions of AA were required for 2/48 (4.2%) patients ($n = 1$, hepatic function abnormal; $n = 1$, other reasons [patient forgot to take medicines]). A total of 16 patients discontinued the study treatment, primarily because of PD ($n = 11$), unresolved AEs ($n = 3$) and safety reasons ($n = 1$).

Efficacy

Primary

Of the 48 patients, 29 (60.4% [90% CI: 47.5–72.3%]) patients achieved a confirmed ≥50% PSA response by Week 12 (Fig. 2A). The lower limit of the two-sided 90% CI (47.5%) was higher than the threshold response rate (35%). The total response rate during the treatment period, including confirmed and unconfirmed responses, was 66.7% (32/48 patients; 90% CI: 53.9–77.8%). The results for the evaluable set (61.4% [27/44 patients; 90% CI: 47.9–73.7%]) were similar to those for the full analysis set, which indicates that the results are stable, regardless of analysis population.

Secondary

The confirmed PSA response rate during the treatment period was 62.5% (30/48 patients; 90% CI: 49.6–74.2%) (Fig. 2B). The total response rate, including confirmed and unconfirmed responses, was 68.8% (33/48 patients; 90% CI: 56.0–79.6%). These results were similar to those by Week 12. Except for one patient who achieved a confirmed PSA response on Day 1 of Cycle 6, all patients with a PSA response achieved the response by Week 12. PSA progression was defined as a ≥50% increase in PSA from nadir, provided the absolute increase was ≥5 ng/ml. Of the 30 patients with a confirmed PSA response during the treatment period, 5 (16.7%) (censored, 25 [83.3%]) had PSA progression by the cutoff date. The median PSA response duration was not reached. The median percent change in PSA level from baseline at Week 12 was −66.62% (range: −100.0%, 105.6%) (Fig. 2A). The majority of patients had a decline in PSA level during the treatment period (Fig. 2B).

Of the 18 patients with measurable lesions, 4/18 (22.2%) achieved partial response (PR) and met the criteria for RAD-ORR. No patients achieved complete response, 11/18 (61.1%) patients were assessed with stable disease (SD) and

Table 1. Demographic characteristics (safety analysis set)

	Abiraterone acetate
Total number of patients	48
Age (years)	
Category, *N* (%)	
<65	9 (18.8)
65–69	13 (27.1)
70–74	11 (22.9)
≥75	15 (31.3)
Median, range	70.0 (46; 89)
Weight (kg), median (range)	63.70 (39.9; 103.2)
Height (cm), median (range)	163.20 (142.3; 182.0)
Body mass index (kg/m^2) median (range)	23.98 (17.5; 31.7)
Gleason score at initial diagnosis	
Category, *N* (%)	
<7	0
7	4 (8.3)
2 + 5 = 7	1 (2.1)
3 + 4 = 7	1 (2.1)
4 + 3 = 7	2 (4.2)
Unknown	0
≥8	43 (89.6)
Unknown	1 (2.1)
Range	7; 10
Duration of disease (years), median (range)	2.10 (0.6; 16.0)
Stage at initial diagnosis (T)	
Category, *N* (%)	
0	0
1	0
2	6 (12.5)
3	28 (58.3)
4	12 (25.0)
Unknown	2 (4.2)
Stage at initial diagnosis (*N*)	
Category, *N* (%)	
0	27 (56.3)
1	21 (43.8)
Unknown	0
Stage at initial diagnosis (M)	
0	15 (31.3)
1	33 (68.8)
Unknown	0
Stage at initial diagnosis	
Category, *N* (%)	
Stage I	0
Stage II	2 (4.2)
Stage III	9 (18.8)
Stage IV	37 (77.1)
Incomplete reporting	0
Evidence of disease progression	
Category, *N* (%)	
PSA only	40 (83.3)
Radiographic progression with or without PSA progression	8 (16.7)
Extent of disease	
Category, *N* (%)	
Abdominal	0
Bone	44 (91.7)
Prostate mass	0
GI	0
Hepatic	1 (2.1)
Lymphatic	19 (39.6)
Pulmonary	0
Skin	0
Other	0
Prior cancer therapy	
Time from initiating LH-RH to first dose (months)	
N	46
Median, range	21.91 (6.2; 191.6)
Previous prostate cancer therapy	
Radiotherapy	13 (27.1)
Surgery	5 (10.4)
Hormone	48 (100.0)
Bicalutamide	45 (93.8)
Flutamide	32 (66.7)
Goserelin acetate	26 (54.2)
Leuprorelin acetate	25 (52.1)
Chlormadinone acetate	5 (10.4)
Orchiectomy	4 (8.3)
Ethinylestradiol	3 (6.3)
Dutasteride	1 (2.1)
Others	10 (20.8)
Number of regimens by prior hormone therapy	
All	
2	12 (25.0%)
3	25 (52.1%)
4	8 (16.7%)
5	3 (6.3%)

Continued

Table 1. *Continued*

	Abiraterone acetate
Anti-androgenic agent	
1	13 (27.1%)
2	25 (52.1%)
3	9 (18.8%)
4	1 (2.1%)
Castration	
1	48 (100.0%)
Estrogen preparation	
1	3 (6.3%)
Other (5a-reductase)	
1	1 (2.1%)
ECOG performance status	
Category, *N* (%)	
0	40 (83.3)
1	8 (16.7)
BPI-SF worst pain score, median (range)	1.0 (0; 9)
Pain	
Category, *N* (%)	
Absent	28 (58.3)
Present	13 (27.1)
Baseline	
PSA (ng/ml), median (range)	31.4 (6.0; 469.0)
Lactate dehydrogenase (IU/l), median (range)	212.0 (164; 1045)
Hemoglobin (g/dl), median (range)	12.9 (10.2; 15.2)
Alkaline phosphatase (IU/l), median (range)	292.0 (139; 2643)

BPI-SF, brief pain inventory-short form; ECOG, Eastern Cancer Organization Grade; GI, gastrointestinal; LH-RH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.
Anti-androgenic agents: bicalutamide, flutamide and chlormadinone acetate.
Estrogen preparations: ethinylestradiol and fosfestrol.
Other (5a-reductase): dutasteride.
Castration: degarelix acetate, goserelin acetate, leuprorelin acetate and orchiectomy

3/18 (16.7%) patients with PD. Of the 48 patients clinical benefit was documented for 36/48 (75.0%) (Table 2). The ECOG PS scores for most patients were maintained at 0 or 1 throughout the treatment period. The median OS was not reached (Fig. 3A). The 6-month survival rate was estimated to be 0.98 (90% CI: 0.90–1.00). Totally, four (8.3%) deaths were reported.

Out of the 48 patients, 20/48 (41.7%) patients had PD in accordance with PSAWG criteria, died or started a secondary antitumor therapy by cutoff date. The median PSA-PFS was not reached (Fig. 3B). The 6-month PSA-PFS was estimated to be 0.703 (90% CI: 0.578–0.797). By the cutoff date, 23/48 patients (47.9%) had PD by RECIST criteria, or died, or started a secondary antitumor therapy. The median RAD-PFS was 253.0 days (90% CI: 246.0, not estimable) (Fig. 3C). The 6-month RAD-PFS was estimated to be 0.638 (90% CI: 0.511–0.741).

In the 13 patients with a BPI baseline worst pain score of ≥4, a response for pain palliation in 9 (69.2%), and pain progression in 2 (15.4%) patients, on the basis of BPI-SF was observed. The median baseline BPI-SF worst pain score was 1.0 (range: 0–9) which decreased to 0 on Day 15 of Cycle 1 and was maintained at 0 throughout the treatment period. The median time to pain progression was not reached (Fig. 3D). The 6-month pain progression-free rate was estimated to be 0.833 (90% CI: 0.557–0.945). Of the 18 patients with baseline CTC count of ≥5, 10 (55.6%) had a post-baseline CTC count of <5.

Safety

In the safety analysis set, 46/48 (95.8%) had at least one AE (Table 3). The most commonly reported AE (≥10% of patients) was hepatic function abnormal ($n = 18$, 37.5%). AEs of special interest were reported for 31/48 patients (64.6%) (Table 4). Most of these AEs were Grade 1/2 in severity. Grade 3 AEs were reported for 7/48 (14.6%) patients, which included hepatic function abnormal (five patients, 10.4%), hypertension (one patient, 2.1%) and cataract (one patient, 2.1%). One death was reported within 30 days after receiving the last dose of study drug and this death was not related to AA. Serious AEs were reported for eight patients (16.7%). Four (8.3%) patients discontinued study treatment because of six AEs (hepatic function abnormal, $n = 3$, Grade 3 and ventricular tachycardia, $n = 1$, Grade 2).

The commonly reported AEs (≥5% of patients) related to prednisolone were diabetes mellitus ($n = 6$, 12.5%), hyperglycemia ($n = 5$, 10.4%), hepatic function abnormal ($n = 5$, 10.4%), cushingoid ($n = 3$, 6.3%) and hypercholesterolemia ($n = 3$, 6.3%) (Table 5). Most laboratory abnormalities were Grade 1/2. Although Grade 3 abnormalities were observed for some hematologic and serum chemistry parameters, shifts from baseline by two or more grades were infrequent. Mean changes from baseline in vital signs and ECG parameters were not considered to be clinically relevant. There were four patients who showed Grade 3 or higher increases in liver function tests and their blood samples were collected for DLST tests. All these patients showed negative DLST result.

Pharmacokinetics and Pharmacodynamics

Mean plasma pre-dose abiraterone concentrations during multiple administrations of AA at the dose of 1000 mg were similar regardless of the visit (mean [SD], 10.6 ng/ml [8.9] to 14.3 ng/ml [18.9]). However, individual plasma abiraterone concentrations post-dose showed large variability as samples were collected during the absorption phase.

Mean serum testosterone concentrations declined from baseline (Cycle 1 Day 1) following multiple administrations of AA and most serum testosterone concentrations and median

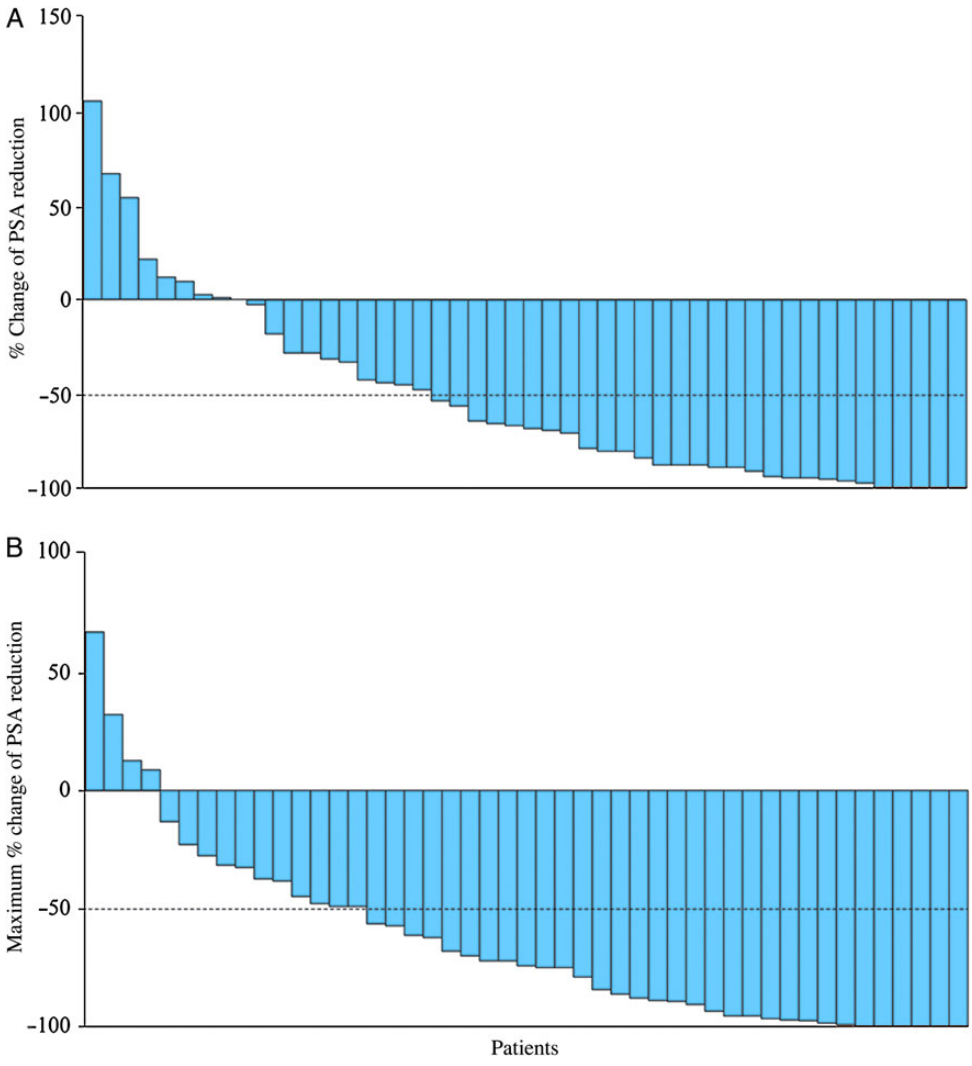

Figure 2. Waterfall plot (A) percent change in prostate-specific antigen (PSA) level from baseline to Week 12, and (B) maximum percent change in PSA during the treatment period (full analysis set).

Table 2. Summary of clinical benefit (full analysis set)

	Abiraterone acetate
Total number of patients	48
Number of patients with clinical benefit[a]	36 (75.0%)
Category, *N* (%)	
PSA response according to PSAWG criteria	30 (83.3%)
Radiographic response[b] by RECIST criteria	4 (11.1%)
Stable disease (by RECIST) lasting 6 months (±8 days)	7 (19.4%)
Improvement by at least 1 unit in ECOG performance status	5 (13.9%)

ECOG, Eastern Cooperative Oncology Group; PSAWG, Prostate-Specific Antigen Working Group; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]Clinical benefit is defined as an observation of at least one of the categories listed in the table.
[b]Radiographic response = complete response or partial response.

serum testosterone concentrations were below the quantification limit (BQL; <0.030 ng/dl). Mean serum DHEA-S concentrations declined from baseline (Cycle 1, Day 1) to BQL (<0.400 μg/dl) level following multiple administrations of AA.

DISCUSSION

Currently, in Japan, there is limited choice for an effective non-toxic alternative for docetaxel-based treatment for preventing disease progression in men with mCRPC. In this study, the mCRPC patients were primarily asymptomatic or mildly symptomatic (BPI-SF, median: 1) with a high burden of disease (Gleason's score of ≥8: 90%). The proportion of patients achieving a ≥50% PSA response rate from baseline to Week 12, primary endpoint, was 60.4%. Since the lower limit of the two-sided 90% CI of this response exceeded the predefined threshold response rate of 35%, efficacy of AA was established. Furthermore, the secondary endpoint, ≥50% PSA

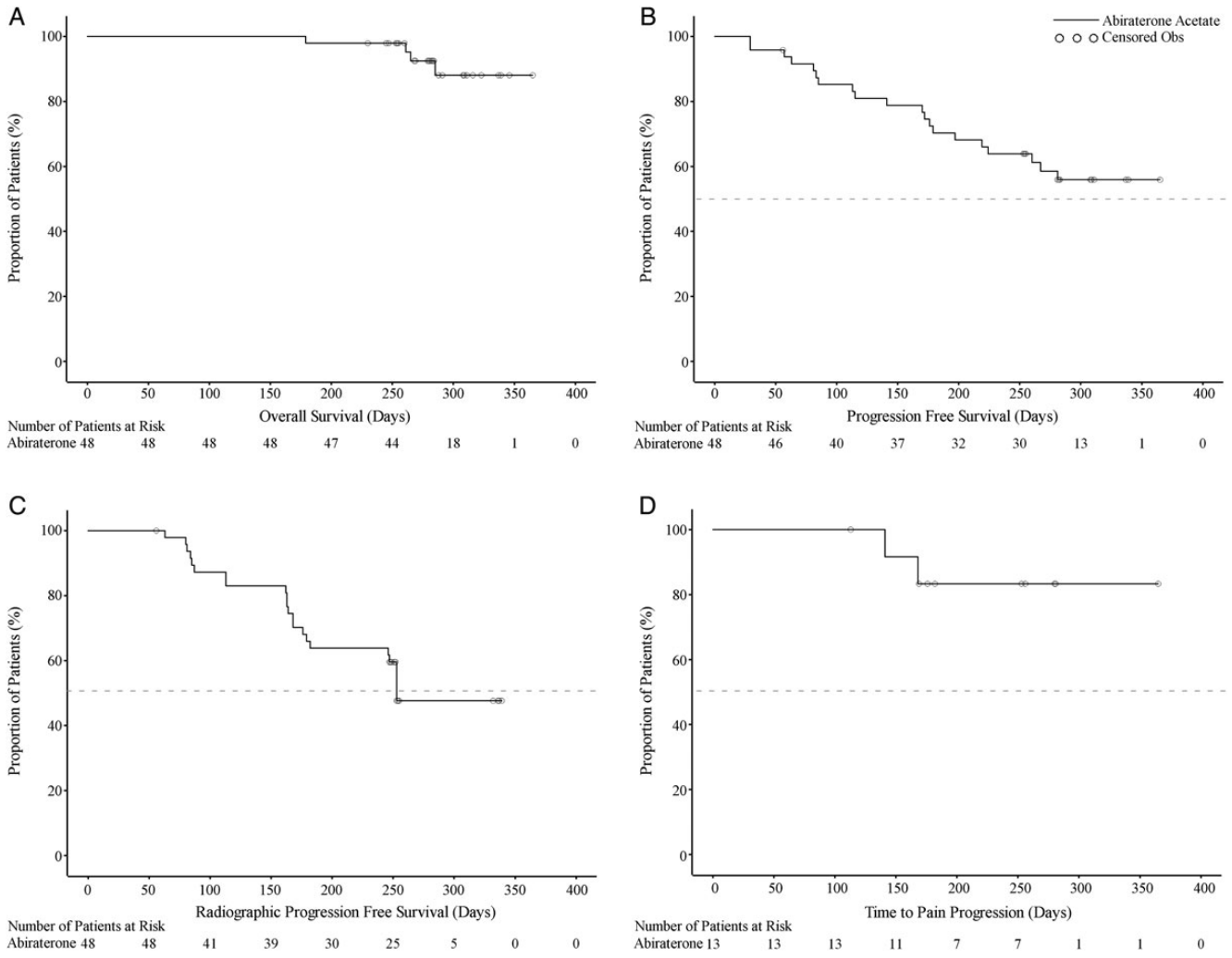

Figure 3. Kaplan–Meier plot (A) overall survival, (B) PSA-based progression-free survival, (C) radiographic progression-free survival (full analysis set) and (D) brief pain inventory-short form time to pain progression. Censored obs: last evaluated observation.

response rate during the treatment period (63%) (median duration 9.18 months) was comparable with the 12-week outcome, suggesting that most patients with a PSA response achieved the response by Week 12. In a Phase 2 study, in chemotherapy-naïve mCRPC non-Japanese patients, the PSA response by Week 12 (67%) and during treatment (79%) was slightly higher, which was attributed to low baseline median PSA level (23 ng/ml) (22). However, in the current study, a subgroup analysis showed that factors such as baseline PSA levels (31.4 ng/ml) did not affect the PSA response (data not shown). The PSA response rate observed in this study was consistent with the results of a Phase 3 study in chemotherapy-naïve non-Japanese patients with a median follow-up of 22.2 months (62%) (12), and an updated analysis (68%) at a median survival of 27.1 month (16).

The outcomes of secondary endpoints showed additional evidence of clinical benefits. The RAD-ORR response of AA based on RECIST was 22% (PR) which was lower than that observed in the Phase 2/3 AA trials in non-Japanese chemotherapy-naïve patients (36–69%) (12,22). Since, the majority of patients were event-free at the time of data cutoff, the median OS and PSA-PFS were not reached. Furthermore, the clinical benefit assessed on the basis of disease stabilization and improved EOCG PS was considerably high (75%). Most patients were without pain or with mild pain at study entry (BPI-SF). Of the 13 patients with a pain score $\geq$4 at baseline, pain intensity was reduced in 69% patients. Additionally, pharmacodynamic assessment showed that median testosterone and mean DHEA-S concentrations declined, and were maintained at BQL levels following multiple administrations of AA.

Majority of the AEs were Grade 1/2 in severity. The percentage of patients with Grade 3/4 severity was lower (40%) in the current study than in the Phase 3 AA trial in chemotherapy-naïve non-Japanese patients (49%) (16). Hepatotoxicity is a known risk of treatment with AA, though the mechanism of AA-induced transaminase elevation is not well understood (12,16). Compared with the global Phase 3 study, Grade 3 AE, hepatotoxicity (6 versus 10%) was higher in the current study, however, the between-study difference

was not remarkable. In contrast to the global study, patients with metastases to liver or metastases to other visceral organ were eligible for the current study, and one patient with liver metastasis was enrolled (Table 1). For management of laboratory abnormality on hepatic function, Grade 3 AST, ALT or total bilirubin increased were managed with interruption of therapy, followed by reinstitution of AA or placebo at a reduced dose only when the toxicity resolved to Grade 1 or baseline. All hepatic function abnormal cases returned to normal, so it was considered as clinically manageable. The incidence of hepatotoxicity was higher in the early phase (<Cycle 4), of the treatment period than in the later phase which was consistent with the global study (12,16). No Grade 3 AEs of cardiac disorders were observed in this study as opposed to 7% AEs in the former study (16). A well-known side effect of AA is mineralocorticoid-related toxicities. Among the 23% patients with mineralocorticoid-related AEs, only one patient (2%) showed Grade 3 severity hypertension that required dose interruption, and these results were consistent with those observed in the Phase 3 trial in non-Japanese patients (most AEs were Grade 1/2, dose interruptions in 1% of patients, treatment discontinuations in <0.5% patients, and no deaths due to these AEs) (12,16).

Frequently reported AEs with the use of prednisolone were generally not contrary to our expectations. An alternative therapy for asymptomatic or minimally symptomatic mCRPC patients in the USA is sipuleucel-T, an immunotherapy that demonstrated survival benefits compared with placebo in a Phase 3 trial (median survival, 25.8 months versus 21.7 months) (23). However, sipuleucel-T treated patients rarely exhibit reduction in PSA level and radiographic volume. Ketoconazole is an unspecific CYP17 inhibitor prescribed by physicians off-label for patients with mCRPC, but Phase 3 randomized trials supporting survival outcomes are lacking and its use is also severely limited due to toxicity. In addition, a recent retrospective study comparing AA and ketoconazole in the treatment of docetaxel-refractory mCRPC patients, demonstrated superiority of AA with respect to OS, RAD-PFS and safety (24). Recently, enzalutamide showed a reduced risk of death of 30% and an 81% decrease in risk of radiographic progression or death compared with placebo in chemotherapy-naïve mCRPC men (25). Due to the lack of head-to-head randomized trials between AA and enzalutamide, the optimal front line and sequential treatment are still uncertain. The limitation of the current study is that it was conducted in

Table 3. Adverse events

	Abiraterone acetate *N* (%)
Total number of patients	48
Patients with AEs	46 (95.8)
Patients with NCI-CTCAE Grade 3–4 AEs	19 (39.6)
Patients with serious AEs	8 (16.7)
Patients with AEs leading to treatment discontinuation	4 (8.3)
Patients with AEs leading to death	1 (2.1)
AEs in >10% patients	
Upper respiratory tract infection	9 (18.8)
Hypercholesterolemia	7 (14.6)
Constipation	7 (14.6)
Diabetes mellitus	6 (12.5)
Hyperglycemia	6 (12.5)

AE, treatment-emergent adverse event.
National Cancer Institute (NCI)—Common Terminology Criteria for Adverse Events (CTCAE).

Table 4. Adverse events of special interest

	Abiraterone acetate				
	Total *N* (%)	Grade 1 *N* (%)	Grade 2 *N* (%)	Grade 3 *N* (%)	Grade 4 *N* (%)
Total no. of patients with AEs	31 (64.6)	10 (20.8)	14 (29.2)	7 (14.6)	0
Hepatotoxicity	21 (43.8)	10 (20.8)	6 (12.5)	5 (10.4)	0
Hypokalemia	7 (14.6)	7 (14.6)	0	0	0
Hypertension	3 (6.3)	0	2 (4.2)	1 (2.1)	0
Osteoporosis	4 (8.3)	2 (4.2)	2 (4.2)	0	0
Cardiac disorders: arrhythmia	2 (4.2)	0	2 (4.2)	0	0
Anemia	2 (4.2)	0	2 (4.2)	0	0
Cardiac disorders: other cardiac disorders	1 (2.1)	1 (2.1)	0	0	0
Cataract (SMQ lens disorders)	1 (2.1)	0	0	1 (2.1)	0
Fluid retention/edema	1 (2.1)	1 (2.1)	0	0	0

AEs, adverse events.

Table 5. Prednisolone-related adverse events (safety analysis set)

	Abiraterone acetate *N* (%)
Total number of patients	48
Total number of patients with AEs	28 (58.3)
Diabetes mellitus	6 (12.5)
Hyperglycemia	5 (10.4)
Hepatic function abnormal	5 (10.4)
Cushingoid	3 (6.3)
Hypercholesterolemia	3 (6.3)
Hypomagnesemia	2 (4.2)
Hypokalemia	2 (4.2)
Hypertension	2 (4.2)
Hot flush	2 (4.2)
Glucose urine present	2 (4.2)
Hypertriglyceridemia	1 (2.1)
Hyperlipidemia	1 (2.1)
Hyper HDL cholesterolemia	1 (2.1)
Cataract	1 (2.1)
Enzyme abnormality	1 (2.1)
Glucose tolerance impaired	1 (2.1)
Flushing	1 (2.1)
Pleurisy	1 (2.1)
Abdominal pain upper	1 (2.1)
Constipation	1 (2.1)
Gastric ulcer	1 (2.1)
Leukocytosis	1 (2.1)
Hyperbilirubinemia	1 (2.1)
Drug eruption	1 (2.1)
Osteoporosis	1 (2.1)
Renal impairment	1 (2.1)
Death	1 (2.1)
Face edema	1 (2.1)
Edema	1 (2.1)
Weight increased	1 (2.1)
Spinal compression fracture	1 (2.1)

AE: adverse events.

chemotherapy-naïve mCRPC patients with fairly good performance status (ECOG PS, 0–1), hence the beneficial outcomes cannot be extrapolated to all mCRPC patients. Nevertheless, based on the favorable long-term survival outcomes and safety reports from global studies, current guidelines recommend the use of AA plus prednisolone as an alternative for chemotherapy for all mCRPC patients (26).

In summary, efficacy of AA plus prednisolone was established based on PSA response rate and its antitumor activity that was confirmed by radiographic objective response. Additional secondary endpoints OS, RAD-PFS, PSA-PFS, clinical benefit based on disease stabilization and EOCG PS improvement support this treatment strategy for routine management of chemotherapy-naïve mCRPC Japanese patients. The combined treatment had an acceptable safety profile consistent with global studies, thus offering a new, effective non-toxic alternative option for the treatment of mCRPC patients in Japan.

Authors' contributions

All authors have contributed to conception, design and interpretation of data. N.M., H.U., Hiroji Uemura, T.S., H.S., T.N. and K.H. were the principal investigators of the study. K.I. was the medical expert and clinical responsible physician and H.A. was the medical advisor. S.O. was Chief of Independent Data Monitoring Committee Members.

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Conflict of interest statement

Dr Keiichiro Imanaka is an employee of Janssen Pharmaceutical K.K., Tokyo, Japan. No conflicts of interest to declare for

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