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Phase-1 study of abiraterone acetate in chemotherapy-naïve Japanese patients with castration-resistant prostate cancer

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Key words

Abiraterone acetate, castration-resistant prostate cancer, Japanese patients, phase-1, safety

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Persistent androgen synthesis under castration status in adrenal gland, testes and tumor cells is thought to be one of the major causes of development and progression of castration-resistant prostate cancer (CRPC). Abiraterone acetate (AA), the prodrug of abiraterone, which is an inhibitor of androgen synthesis enzymes, was evaluated for pharmacokinetics, pharmacodynamics, preliminary efficacy and safety in Japanese patients with CRPC in a phase-1, open-label and dose-escalation study. Chemotherapy-naïve Japanese CRPC patients (N = 27) received one of four AA daily doses (250 mg [n = 9], 500 mg [n = 6], 1000 [1 h premeal] mg [n = 6] and 1000 [2 h postmeal] mg [n = 6]) continuously through 28-day treatment cycles. In the first cycle, AA monotherapy was given on days 1–7 for pharmacokinetics, and AA plus prednisone (5 mg twice daily) from days 8 to 28. Of 27 patients, 9 continued treatment with AA until the data cut-off date (18 July 2013). Over the evaluated dose range, plasma abiraterone concentrations increased with dose, with median t_{max} 2–3 h. At each dose level, mean serum corticosterone concentrations increased, while testosterone and dehydroepiandrosterone sulfate concentrations rapidly decreased following a single AA dose and were further reduced to near the quantification limit on day 8 regardless of the dose. At least 3 patients from each dose-group experienced ≥50% prostate-specific antigen reduction, suggesting clinical benefit from AA in Japanese CRPC patients. AA was generally well-tolerated, and, therefore, the recommended AA dosage regimen in Japanese CRPC patients is 1000 mg oral dose under modified fasting conditions (at least 1 h premeal or 2 h postmeal). This study is registered at ClinicalTrials.gov: NCT01186484.

Prostate cancer prevalence has risen in Japan in recent years even though the incidence is lower than in the United States.[1–3] Primary androgen deprivation therapy (ADT) remains the standard-of-care for locally advanced disease in Japanese patients with prostate cancer, compared with surgical castration, radiotherapy or conservative management.[4] Although initial response to ADT is encouraging in most patients, more often the duration of response is limited. Consequently, after approximately 2–3 years, tumors become treatment-resistant and the disease transforms into one with poor prognosis, currently known as castration-resistant prostate cancer (CRPC).[5] In addition to adrenal-derived androgen synthesis, recent studies suggest that androgen levels in the prostate tumor are higher than in plasma due to upregulation of enzymes involved in androgen biosynthesis, and this overrides systemic inhibition by castration.[5–7] Consistent with this, testosterone levels in prostate cancer tissues remain elevated after castration (approximately 25% of precastration levels) even though serum testosterone levels are lowered to <50 ng/dL by inhibiting gonadal androgen synthesis with ADT treatment (surgical or medical castration).[8,9] Therefore, treatment with agents that block testosterone production in the adrenal glands and tumor cells is warranted to mitigate tumor cell proliferation after surgical or medical castration using luteinizing hormone-releasing hormone (LHRH) analogs.[10]

Abiraterone acetate (AA) is an orally active prodrug of abiraterone. Abiraterone irreversibly inhibits cytochrome P450 17a-hydroxylase and C17, 20-lyase enzymes responsible for adrenal, testicular and intratumoral androgen synthesis.[11–15] Targeting the androgen-synthesis pathway in adrenal and prostate cancer tissues can prolong overall survival in patients with metastatic CRPC (mCRPC) who have had docetaxel-containing chemotherapy.[16,17] A recent study conducted in mCRPC patients without any prior exposure to chemotherapy also showed clinical benefits of the compound wherein AA improved radiographic progression-free survival (16.5 months), demonstrated a benefit for overall improved survival, and significantly delayed time for chemotherapy resumption.[17] In

another study, efficacy was reported with a response rate of 47% in CRPC patients who had received prior ketoconazole therapy.[18] Globally, AA is now approved in more than 70 countries for treatment of mCRPC patients without previous chemotherapy exposure and in more than 85 countries for treatment of patients in the postdocetaxel setting.

In global studies, AA has been extensively studied in the USA and EU populations. Because ethnic diversities between Caucasians and Asians could influence the effectiveness of treatment, as well as the types of and susceptibility to adverse effects, studies validating clinical benefits of AA in CRPC patients of different ethnic backgrounds are encouraged.[10] Prior to the present study, with no clinical experience of this drug in Japanese patients, the recommended dose for AA in Japanese CRPC patients had not been established. The objective of the current phase-I study was to evaluate pharmacokinetics, pharmacodynamics, and preliminary efficacy and safety of AA in Japanese CRPC patients.

Methods

Patients. Patients recruited were men aged ≥20 years with histological/cytological confirmation of prostate adenocarcinoma without neuroendocrine differentiation or small cell histology. Patients were required to be chemotherapy-naïve, except those with neoadjuvant or adjuvant chemotherapy exposure that ended at least 1 year before day 1 were also eligible. Other inclusion criteria were: patients who had ADT with LHRH agonists/orchiectomy (testosterone level <0.5 ng/mL); those on LHRH agonist therapy (initiated >4 weeks before day 1 and was to be continued throughout study) without undergoing orchiectomy; prostate-specific antigen (PSA) level ≥2 ng/mL; Eastern Cooperative Oncology Group Performance Status of 0 or 1; disease progression according to Prostate Cancer Clinical Trials Working Group (PCWG2) criteria (increased PSA levels over two consecutive examinations obtained at least 1 week apart after antiandrogen [bicalutamide, flutamide, and chlormadinone acetate] withdrawal) or progressive disease after androgen deprivation for patients with measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria; and documented bone or soft tissue progression.

Patients were ineligible if they had undergone surgery or local prostatic intervention or received radiotherapy or immunotherapy within 4 weeks before AA administration. In addition, history of brain metastasis, an active second malignancy, uncontrolled hypertension, an active autoimmune disease requiring corticosteroid therapy, hormonal therapy with finasteride, dutasteride or herbal medicines known to decrease PSA levels, prior therapy with ketoconazole or CYP17 inhibitors/investigational drugs targeting androgen receptor, history of gastrointestinal disorders that may interfere with AA absorption or pituitary/adrenal insufficiency or hyperaldosteronism, chronic liver disease, myocardial infarction or thrombosis were exclusionary.

Concomitant medications such as 5 α-reductase inhibitor, ketoconazole, or those known to affect endocrine secretion in prostate cancer (diethylstilbestrol, PC-SPES and saw palmetto), herbal supplements, bicalutamide, flutamide, chlormadinone acetate and spironolactone, were prohibited. Concomitant anticancer therapies (chemotherapy, including estramustine, radiotherapy or immunotherapy) were also prohibited. Permissible concomitant medications were non-prednisolone systemic corticosteroid for ≥grade 2 adrenal insufficiency/a life-threatening condition, and LHRH agonists for patients who had not undergone surgical castration.

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements, and are in compliance with the study protocol. The study protocol was reviewed and approved by the Institutional Review Board. All enrolled patients provided written consent for participation.

Study design and treatment. This open-label, dose-escalation study conducted between 28 June 2010 and 18 July 2013 (data cut-off date) at 5 centers in Japan consisted of a screening period (14 days), a recommended dose-determination period (day 1 of cycle 1 up to day 1 of cycle 2), a continuous dosing period (from day 1 of cycle 2) and a postobservation period (30 days after end of treatment). Each treatment cycle was 28 days.

Abiraterone acetate was administered once daily to four sequential cohorts: 250, 500, 1000 (−1 h [1 h premeal]) and 1000 mg (+2 h [2 h postmeal]) through 28-day treatment cycles. In cycle 1, patients received AA monotherapy from days 1 to 7, followed by an AA plus 5 mg prednisone twice daily oral dose from days 8 to 28. In cycle 2 and thereafter, combination therapy (AA plus prednisone 5 mg twice daily) was continued. After an overnight fast, the dose was administered at least 1 h premeal or 2 h postmeal for 250 and 500 mg cohorts, and at specified timings (−1 or +2 h) for 1000 mg cohorts with no food for at least 1 h after dosing. The dose in the subsequent cohort was determined based on the safety and pharmacokinetic data of the previous cohort. If any of the dose increases were not appropriate for the patient for safety-related reasons, the patient then received AA at the original dose. Dose reduction was disallowed in 250 or 500 mg cohorts.

Six patients were to be enrolled in each cohort. The dose escalation was applied to individual patients. Transition of patients to a subsequent cohort or enrollment of additional patients in a preceding cohort was determined depending upon the number of patients experiencing dose limiting toxicity (DLT) during the recommended dose assessment period. DLT was defined as any drug-related adverse event (AE) of ≥grade 3 (except for nausea, vomiting or diarrhea that was controllable by standard therapy). In the case of any DLT, cohort expansion to 3 more patients was required (Fig. 1). In the absence of any DLT, the dose would be considered safe and escalation to the next dose level was allowed. Treatment with AA was continued until disease progression or unacceptable toxicity.

Study evaluations. *Pharmacokinetics.* Blood was sampled from cutaneous veins to determine plasma AA and abiraterone concentrations: at predose, and 0.5, 1, 2, 3, 4, 6 and 12 h postdose on days 1, 7 and 15 in cycle 1; at 24 h postdose on days 2, 8 and 16 in cycle 1; predose on days 6, 14 in cycle 1; and predose on day 1 of cycle 2. A 4-mL cutaneous venous blood was sampled from each patient, collected into vacuum tubes. The tubes were put in an ice bath immediately after sampling. Blood (3 mL) was transferred into polyethylene tubes containing 0.3 mL of 500 mM NaF solution and centrifuged at 1300 RCF (*g*) at 4°C for 10 min. The plasma was immediately stored at −20°C. Samples were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method used in previous studies.[19] The lower limit of quantification (LLOQ) was 0.220 ng/mL for AA and abiraterone. Pharmacokinetic parameters, including area under the

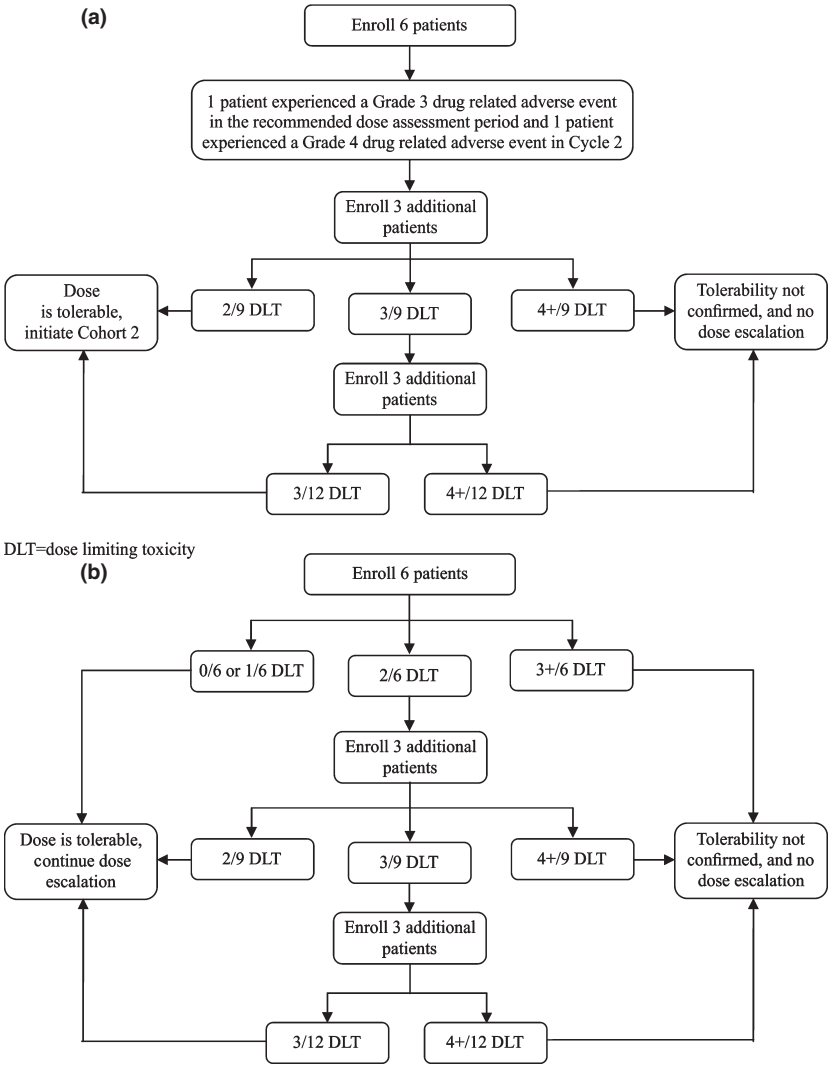

Fig. 1. (a) Evaluation of tolerability and criteria for expansion in cohort 1. DLT, dose limiting toxicity. (b) Evaluation of tolerability and criteria for expansion in cohort 2 or subsequent cohorts. DLT, dose limiting toxicity.

concentration–time curve (AUC), maximum concentration (C_{max}), time to C_{max} (t_{max}) and elimination half-life ($t_{1/2}$) were evaluated for both analytes.

Pharmacodynamic. Blood was sampled at baseline, and days 2 and 8 in cycle 1 (except at screening for testosterone) to determine serum concentrations of corticosterone, testosterone, dehydroepiandrosterone sulfate (DHEA-S) and 11-deoxycorticosterone.

Efficacy. Prostate-specific antigen evaluations were performed at screening and day 1 of every cycle thereafter, based on PSA response rate and PCWG2 criteria. PSA response was defined as ≥50% reduction in PSA levels from baseline, which was confirmed to have been maintained for ≥4 weeks. Objective tumor response was measured in patients with measurable lesions based on RECIST.

Safety. Adverse events, clinical laboratory measurements (hematology, coagulant factors, blood chemistry and urinalysis), 12-led electrocardiograms, vital sign measurements and body weight were monitored throughout the study. Any serious AE (SAE) according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0 or death occurring within 30 days after last AA dose were reported. In the event of dose reduction due to AEs, the timing of AA administration in relation to meal times was the same as that before the onset of such AE.

Statistical analyses. Similar to a global AA phase-1 study,[11] the intention was to enroll 6–12 patients per cohort for the present study, with the sample size not exceeding 63 patients. Pharmacodynamic, pharmacokinetic, safety and efficacy (PSA response rate and 90% confidence interval, and best overall tumor response by RECIST) parameters were descriptively summarized. Pharmacokinetic parameters (C_{max}, t_{max} and AUC_{24}) were estimated using a non-compartment analysis method.

Results

Patient disposition and baseline characteristics. Twenty-seven Japanese patients (cohort 1 [n = 9], cohorts 2–4 [n = 6 each]) were recruited for the present study. One patient withdrew during cycle 1 (500 mg: grade 3 liver function test [LFT] abnormality). In total, 26 patients completed cycle 1 and were shifted to cycle 2. Of these, 17 patients (250 mg [n = 7], 500 mg [n = 4], 1000 [−1 h] mg [n = 5] and 1000 [+2 h] mg [n = 1]) were permanently discontinued after cycle 1 due to disease progression (n = 14) and AE (250 mg [n = 2]: grade 3

LFT abnormality; 1000 [−1 h] mg [n = 1]: hypophosphatemia). On day 1 of cycle 2, 1 patient from the 250 mg cohort was discontinued (grade 3 LFT abnormality) from the study. In total, 9 patients (250 mg [n = 2], 500 mg and 1000 [−1 h] mg [n = 1 each], 1000 [+2 h] mg [n = 5]) continued AA treatment until the data cut-off date.

Median patient age was 72 years (range, 51–80 years), with the majority (85%) aged ≥65 years (Table 1). At baseline, most patients ([n = 25], 93%) had metastases from prostate cancer: bone (n = 19 [70%] and lymph node (n = 9 [33%]) were frequent metastatic sites. The demographic characteristics were generally balanced among all cohorts. Overall, 26 patients had been medically castrated; one had been surgically castrated by orchiectomy. A total of 26 patients had concomitantly used an antiandrogen drug as a prior prostate cancer therapy, 6 had undergone prior radiotherapy and 2 patients either had prior surgery or herbal therapy.

Treatment exposure. Among all patients, the median duration of AA exposure was 28.1 weeks (range: 3.1–156.0 weeks) and the median number of treatment cycles was 7.0 (range: 1–31). Due to a grade 3 LFT abnormality, 1 patient from the 1000 (−1 h) mg cohort had two dose reductions (from 1000 to 750 mg and from 750 to 500 mg) and 1 patient in the 1000 (+2 h) mg cohort had one dose reduction to 750 mg. In the 250 mg cohort, 2 patients had a dose increase to 500 mg, whereas in the 500 mg cohort, the dose was increased to 1000 mg for 1 patient.

Evaluations. *Pharmacokinetics.* Pharmacokinetic parameters of AA in plasma were not estimated as most plasma concentrations were below the quantification limit for all cohorts. Regardless of the dose and dosing frequency and coadministration with/without prednisolone, mean plasma abiraterone concentrations rapidly increased and reached maximum concentrations with median t_{max} of 2–3 h. Mean C_{max} and AUC_{24} values in the 1000 (+2 h) mg cohort were higher than those in the 1000 (−1 h) mg cohort by 3.1–4.2 times after a single dose and by 3.4–4.6 times after multiple doses (Fig. 2). Similarly, multiple doses of AA coadministered with prednisolone increased mean C_{max} and AUC_{24} values in the 1000 (+2 h) mg cohort by 4.1–6 times than those in the 1000 (−1 h) mg cohort. Individual C_{max} and AUC_{24} values of abiraterone after multiple doses with and without prednisolone were not largely different. A steady state was reached by day 7, with accumulation indexes of 1.31–1.74 for C_{max}, and 1.40–1.69 for AUC_{24} irrespective of the dose administered. Exposure of abiraterone was affected by timing between dosing and food. In the 1000 mg cohort, mean C_{max} and AUC_{24} values 2 h postmeal were 3.1–6.0 times higher than those 1 h premeal.

Pharmacodynamics. At each dose level, mean serum corticosterone and 11-deoxycorticosterone concentrations increased rapidly after single AA dose. The mean changes from baseline on day 8 in cycle 1 in corticosterone and 11-deoxycorticosterone levels for the 1000 mg cohorts were higher than for 250 and 500-mg cohorts, with a slightly higher mean change observed for the 1000 (+2 h) mg cohort versus the 1000 (−1 h) mg cohort (Table 2). Meanwhile, mean serum testosterone and DHEA-S concentrations rapidly decreased at each dose level following a single dose of AA, and on day 8 in cycle 1 the concentrations were almost below the quantification limit, regardless of the dose level. The mean change from baseline in testosterone levels on day 8 in cycle 1 ranged from −10.8 to −6.2 ng/dL.

Efficacy. As shown in a waterfall plot (Fig. 3), 20/27 patients achieved ≥50% PSA decline from baseline at one or more evaluation time points during the entire treatment period ([n = 7] 250 mg, [n = 3] 500 mg, [n = 5 each] in 1000 [−1 h] and [+2 h] mg cohorts). Among these patients, ≥50% declines in PSA levels were confirmed to have been maintained for at least 4 weeks in 18/27 (67%) patients. The PSA response rate was highest (83%) in the 1000 (+2 h) mg cohort, followed by 67% in the 1000 (−1 h) mg and the 250-mg cohorts, and 50% in the 500 mg cohort. The mean percentage change from baseline in PSA levels at week 12

Table 1. Demographics and baseline characteristics

Parameters	Abiraterone acetate				
	250 mg (n = 9)	500 mg (n = 6)	1000 (−1 h) mg (n = 6)	1000 (+2 h) mg (n = 6)	Total (N = 27)
Age, years mean (SD)	72.9 (4.34)	68.8 (3.37)	72.2 (7.36)	66.3 (8.57)	70.4 (6.31)
Weight, kg mean (SD)	67.2 (9.62)	66.9 (9.24)	63.7 (10.48)	68.1 (16.14)	66.6 (10.90)
Gleason score, n (%)					
> =8	9 (100.0)	5 (83.3)	3 (50.0)	6 (100.0)	23 (85.2)
7	0	1 (16.7)	2 (33.3)	0	3 (11.1)
Duration of disease, years					
Mean (SD)	4.3 (3.26)	3.6 (1.86)	2.7 (2.33)	2.7 (1.27)	3.4 (2.41)
Baseline serum PSA, ng/mL					
Mean (SD)	162.4 (416.96)	55.1 (43.25)	80.6 (87.86)	22.6 (16.57)	89.3 (241.98)
Disease progression as defined by RECIST, n (%)					
Yes	3 (33.3)	1 (16.7)	3 (50.0)	0	7 (25.9)
No	6 (66.7)	5 (83.3)	3 (50.0)	6 (100.0)	20 (74.1)
PSA progression by PCWG2, n (%)					
Yes	9 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	27 (100.0)
ECOG performance status, n (%)					
0	8 (88.9)	6 (100.0)	6 (100.0)	4 (66.7)	24 (88.9)
1	1 (11.1)	0	0	2 (33.3)	3 (11.1)
Metastasis, n (%)	8 (88.9)	6 (100.0)	6 (100.0)	5 (83.3)	25 (92.6)

ECOG, Easter Cooperative Oncology Group; PCWG2, Prostate Cancer Clinical Trials Working Group; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

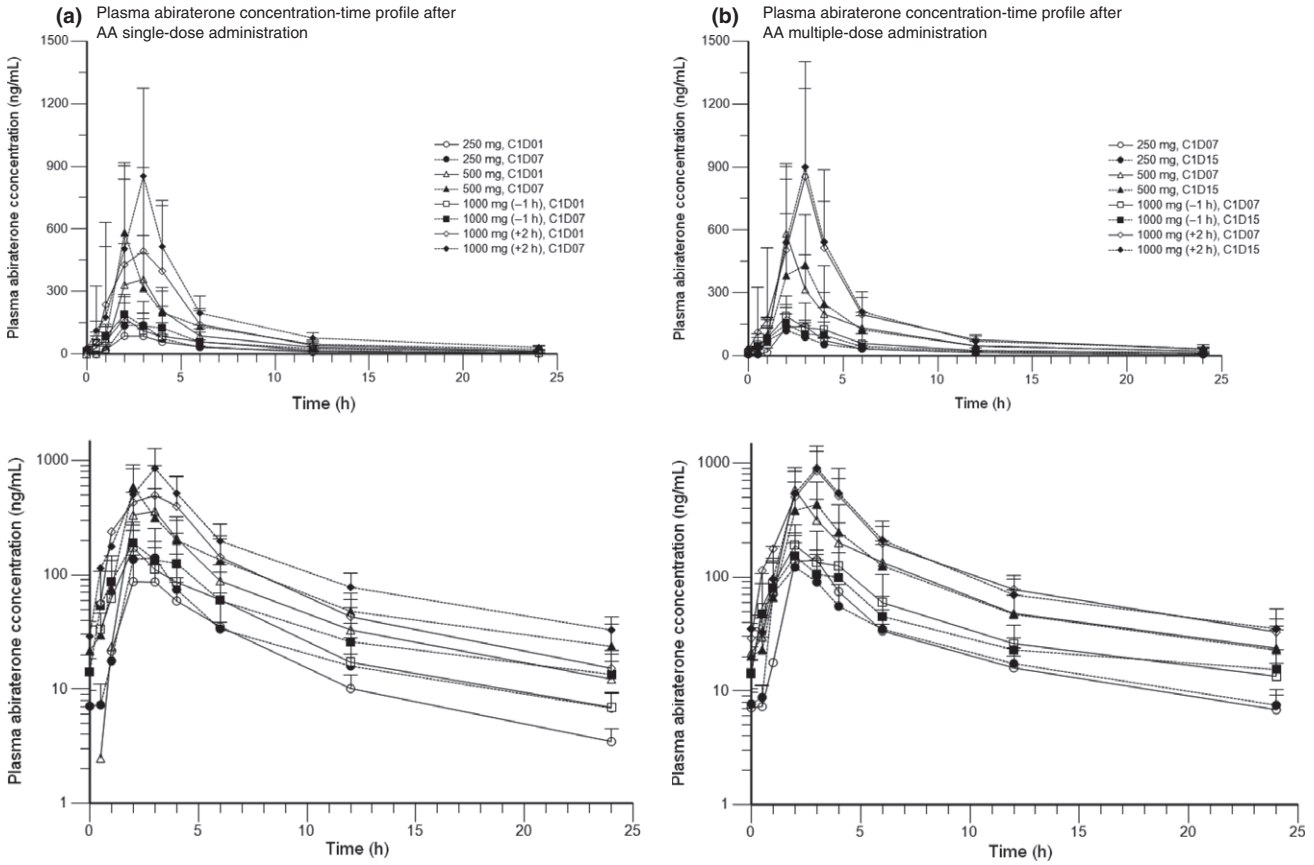

Fig. 2. Mean (SD) plasma abiraterone concentration time profiles following single-dose and multiple-dose administration of abiraterone acetate (Pharmacokinetic analysis set).

Table 2. Serum corticosterone, 11-deoxycorticosterone, testosterone and dehydroepiandrosterone sulfate concentrations (pharmacodynamic analysis set)

	Time points	Abiraterone acetate			
		250 mg (*n* = 9)	500 mg (*n* = 6)	1000 (−1 h) mg (*n* = 6)	1000 (+2 h) mg (*n* = 6)
Corticosterone (ng/dL)	Cycle 1 Day 1, median (range) at baseline	91.0 (0–142)	123.0 (63–272)	93.5 (45–149)	130.0 (32–279)
	Cycle 1 Day 2, mean (SD) change	1097.1 (687.41)	2914.8 (1543.83)	1957.2 (1008.74)	4227.3 (2814.68)
	Cycle 1 Day 8, mean (SD) change	2015.2 (769.39)	4086.5 (2478.82)	5147.8 (1642.75)	6426.2 (2212.64)
11-deoxycorticosterone (ng/dL)	Cycle 1 Day 1, median (range) at baseline	4.5 (4–7)	5.0 (4–10)	7.5 (5–10)	6.0 (4–9)
	Cycle 1 Day 2, mean (SD) change	22.9 (10.13)†	40.3 (16.79)	36.3 (17.22)	45.7 (61.09)
	Cycle 1 Day 8, mean (SD) change	45.9 (13.35)†	78.8 (36.41)	79.2 (51.53)	112.3 (65.15)
Testosterone (ng/dL)	Cycle 1 Day 1, median (range) at baseline	5.0 (2–15)	8.0 (2–14)	14.5 (6–18)	10.0 (7–12)
	Cycle 1 Day 2, mean (SD) change	−3.6 (3.64)	−4.8 (3.06)	−8.0 (3.22)	−7.5 (1.87)
	Cycle 1 Day 8, mean (SD) change	−6.2 (4.06)	−8.2 (3.82)	−10.8 (6.21)	−9.2 (2.32)
DHEA-S (ug/dL)	Cycle 1 Day 1, median (range) at baseline	37.0 (0–68)	33.5 (0–87)	92.5 (0–187)	66.5 (0–142)
	Cycle 1 Day 2, mean (SD) change	−19.1 (13.49)	−28.3 (24.32)	−59.7 (49.87)	−53.3 (34.14)
	Cycle 1 Day 8, mean (SD) change	−35.7 (25.51)	−38.5 (37.31)	−95.3 (77.99)	−76.8 (54.02)

†*n* = 8. DHEA-S, dehydroepiandrosterone sulfate.

was −51.2% for 250 mg; −29.1% for 500 mg; −60.4% for 1000 mg (−1 h); and −37.6% for 1000 mg (+2 h) cohorts.

Based on objective tumor response according to RECIST, 2 patients ([*N* = 1 each] 500 mg and 1000 [−1 h] mg cohorts) had partial response, 5 ([*N* = 1] 250 mg, [*N* = 2 each] 500 and 1000 [−1 h] mg cohorts) had stable disease, and the disease had progressed in 2 patients ([*N* = 1 each] 250 mg and 1000 [+2 h] mg cohorts).

Safety. The overall incidence of AE and drug-related AE was similar among all cohorts. In the high-dose cohort, the overall incidence of AE and grade 3/4 AE was similar for both dose timings (−1 h and +2 h). Overall, no marked

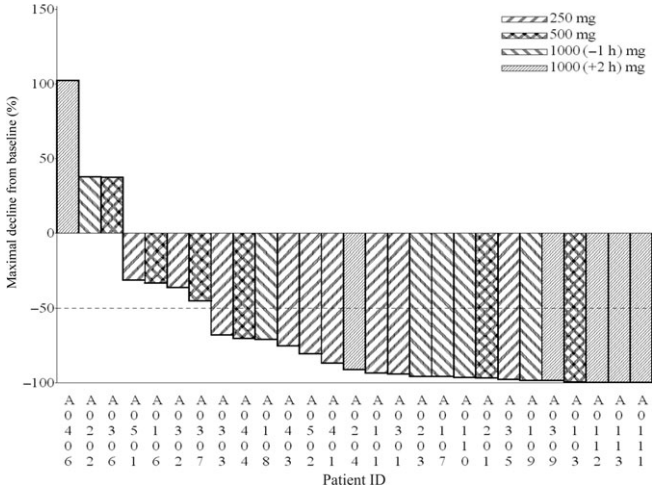

Fig. 3. Waterfall plot of maximum PSA reduction during entire treatment period. PSA response was unconfirmed for 1 patient each from 250 mg (A0502) and 1000 [−1 h] mg (A0110) groups.

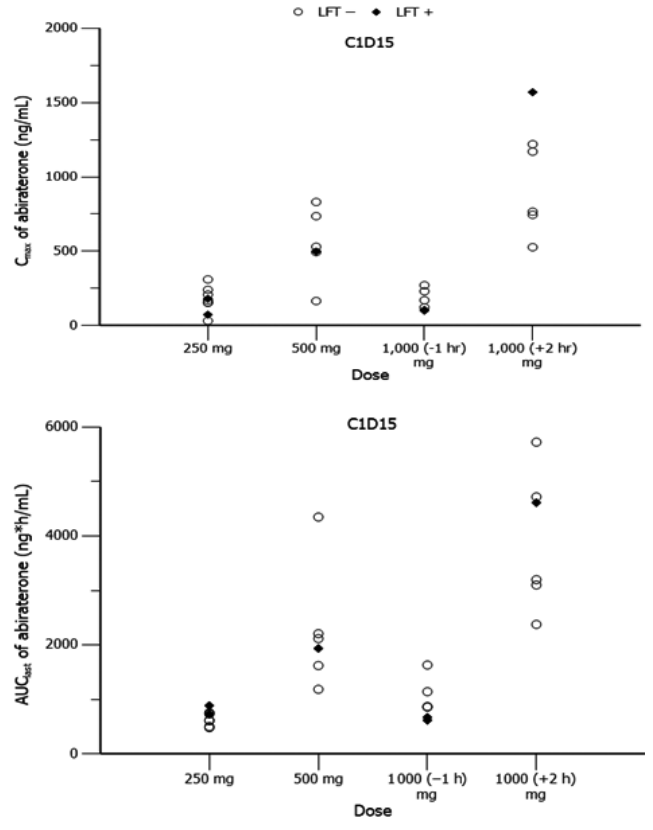

Fig. 4. Comparison of plasma abiraterone exposure at steady state for patients who had positive or negative liver function tests. LFT, liver function test.

difference in the profiles of drug-related AE was found between 2 dose timings during cycle 1. There was no trend signifying increase in overall AE incidence with increase in dose or treatment duration.

Adverse events were observed in all 27 patients and the most frequent (≥10 patients) during the treatment period were: hypoalbuminemia, LFT abnormality, hypokalaemia, hyponatraemia and enzyme abnormality (Table 3). The majority of AE were grade 1/2 in severity; grade 3/4 AE such as LFT abnormality, hypophosphatemia, lymphopenia noted in 6 patients were clinically manageable ([n = 2 each] 250 mg and 1000 [−1 h] mg cohorts; [n = 1 each] 500 mg and 1000 [+2 h] mg cohorts). Four patients experienced eight events of LFT abnormality, leading to treatment discontinuation for 3 patients ([n = 2] 250 mg, [n = 1] 500 mg cohorts), and a dose reduction in 1 patient from the 1000 (−1 h) mg cohort. AE related to pharmacodynamic effects of AA were hypokalemia (grade 3), fluid retention/edema and hypertension (grades 1/2), which occurred in 12 (44.4%), 4 (14.8%) and 6 (22.2%) patients, respectively, but none of them required dose reduction or treatment discontinuation, although one edema peripheral event (250 mg cohort) required treatment interruption. Clinically significant AE were hepatotoxicity (n = 21), hypokalemia (n = 12), hypertension (n = 6), edema (n = 4) and cardiac disorders (n = 2).

Seven patients experienced SAE, with LFT abnormality (6/27 patients) most frequently reported. One patient each from 250, 500 and 1000 (+2 h) mg cohorts experienced DLT of grade 3. These included LFT abnormalities reported in 250 and 500-mg cohorts leading to permanent treatment discontinuation, and hyperamylasemia reported in 1000 (+2 h) mg cohort. No DLT occurred in the 1000 (−1 h) mg cohort. No clinically significant changes were observed in vital signs, body weight or body temperature in all cohorts over the course of treatment. No deaths due to progression of disease or due to any reason were reported as of the cut-off date.

Correlation between plasma abiraterone exposures for patients who had positive or negative liver function test. The relationship between exposure to abiraterone at the steady state (C_{max} and AUC_{last} on day 15 in Cycle 1) and LFT abnormalities was investigated by reviewing ≥grade 3 LFT abnormalities reported in 250 mg (n = 2), 500 mg (n = 1), 1000 (−1 h) mg (n = 2) and 1000 (−2 h) mg (n = 1) cohorts. Comparison of plasma abiraterone exposure for individual patients at the steady state indicated that plasma abiraterone C_{max} and AUC_{last} were not higher in patients who experienced ≥grade 3 LFT abnormalities compared with those with grade 2 or less LFT abnormalities (Fig. 4). In the laboratory tests, no consistent change from baseline was found in mean values of LFT parameters in any cohort (data not shown). Thus, the frequency of LFT abnormalities was independent of AA dose and exposure.

Discussion

This phase-1, multicenter, dose-titration study was designed to validate the clinical utility of the globally-approved AA recommended dose (1000 mg) in chemotherapy-naïve Japanese CRPC patients, and to investigate whether AA dosing needs are different in the Japanese population.

Plasma abiraterone exposure in Japanese CRPC patients increased rapidly, and the steady state was reached by day 7 regardless of the dose and dosing frequency. Similar to the trends observed in non-Japanese healthy participants and patients with mCRPC, plasma abiraterone concentrations peaked at 2–3 h and declined in a biphasic manner.[20, 21] The mean C_{max} and AUC_{24} of plasma abiraterone at doses 250–1000 mg in our study were almost similar or higher compared with those at a 1000 mg dose in a previous study conducted in a non-Japanese population.[20] Moreover, abiraterone pharmacokinetics was influenced by timing between dosing and food intake. When AA 1000 mg multiple doses were administered at

Table 3. Most common (≥5 patients) adverse events during entire treatment period (safety analysis set)

Preferred term	Abiraterone acetate				
	250 mg (*n* = 9)	500 mg (*n* = 6)	1000 (−1 h) mg (*n* = 6)	1000 (+2 h) mg (*n* = 6)	Total (*N* = 27)
Total number of patients with adverse events	9 (100.0)	6 (100.00)	6 (100.0)	6 (100.0)	27 (100.0)
Hypoalbuminaemia	4 (44.4)	3 (50.0)	4 (66.7)	3 (50.0)	14 (51.9)
Liver function abnormality	4 (44.4)	1 (16.7)	4 (66.7)	4 (66.7)	13 (48.1)
Hypokalaemia	5 (55.6)	2 (33.3)	4 (66.7)	1 (16.7)	12 (44.4)
Hyponatraemia	4 (44.4)	3 (50.0)	3 (50.0)	1 (16.7)	11 (40.7)
Enzyme abnormality	3 (33.3)	2 (33.3)	3 (50.0)	2 (33.3)	10 (37.0)
Hypercholesterolaemia	3 (33.3)	1 (16.7)	2 (33.3)	3 (50.0)	9 (33.3)
Hyperkalaemia	2 (22.2)	3 (50.0)	3 (50.0)	1 (16.7)	9 (33.3)
Hypertriglyceridemia	3 (33.3)	0	2 (33.3)	3 (50.0)	8 (29.6)
Anaemia	0	1 (16.7)	2 (33.3)	5 (83.3)	8 (29.6)
Proteinuria	2 (22.2)	2 (33.3)	1 (16.7)	2 (33.3)	7 (25.9)
Hypermagnesaemia	0	1 (16.7)	3 (50.0)	2 (33.3)	6 (22.2)
Upper respiratory tract infection	0	4 (66.7)	1 (16.7)	1 (16.7)	6 (22.2)
Hypertension	2 (22.2)	1 (16.7)	2 (33.3)	1 (16.7)	6 (22.2)
Blood urine present	1 (11.1)	1 (16.7)	1 (16.7)	3 (50.0)	6 (22.2)
Hypophosphataemia	1 (11.1)	1 (16.7)	3 (50.0)	1 (16.7)	6 (22.2)
Hyperglycaemia	2 (22.2)	1 (16.7)	1 (16.7)	2 (33.3)	6 (22.2)
Lymphopenia	1 (11.1)	1 (16.7)	2 (33.3)	1 (16.7)	5 (18.5)
Weight increased	0	1 (16.7)	3 (50.0)	1 (16.7)	5 (18.5)
Hypernatraemia	3 (33.3)	0	1 (16.7)	1 (16.7)	5 (18.5)
Hypocalcaemia	1 (11.1)	2 (33.3)	1 (16.7)	1 (16.7)	5 (18.5)
Hypomegnesaemia	3 (33.3)	0	1 (16.7)	1 (16.7)	5 (18.5)
Rash	4 (44.4)	1 (16.7)	0	0	5 (18.5)

2 h postmeal, abiraterone C_{max} and AUC_{24} were approximately threefold to sixfold higher than when given 1 h premeal. These results indicate that food intake increased systemic abiraterone exposure and the exposure varied greatly depending on the timing of food intake and food composition.[11] Plasma abiraterone concentrations (C_{max} and AUC_{24}) when coadministered twice daily with 5 mg prednisone were similar to those after multiple-dose administration of AA alone. It is worth pointing out that pharmacokinetics of abiraterone remain unaffected with or without the addition of prednisone. Overall, the AA pharmacokinetic profile was comparable between this Japanese study and overseas studies conducted to date.[11,20,21]

In this study, administration of multiple doses of AA (250–1000 mg) to Japanese CRPC patients lowered serum testosterone and DHEA-S levels virtually below LLOQ at all dose levels on day 8, and mean serum corticosterone concentrations on day 8 were higher for the 1000 mg dose than for 250 and 500-mg doses. Of interest, mean changes from baseline in serum corticosterone concentrations were not largely different between 1000 (−1 h) and 1000 (+2 h) mg groups. Results from a previous study using 250–2000 mg multiple doses in non-Japanese mCRPC patients corroborate these findings that AA treatment causes profound suppression of serum testosterone and DHEA-S concentrations, as well as an increase in corticosterone levels, and has durable antitumor activity in Japanese CRPC patients.[11] Considering the pharmacodynamic response observed in the current study, the globally-recommended AA dose of 1000 mg may be more suitable for future studies in the Japanese population than 250 and 500 mg doses.

The findings of our study are encouraging; the overall PSA response rate of 67% in Japanese CRPC patients is comparable to a 66% response rate in a similar phase-1 study in a Western population.[11] Of note, patients treated with the 1000 mg dose in the current study showed greater PSA response (66.7% predose cohort and 83.3% postdose cohort) than those treated with the 500 mg dose (50.0%). Therefore, in light of the pharmacodynamic response and efficacy observations from this study, it is deemed appropriate to select 1000 mg as an appropriate dose for Japanese CRPC patients to maximize treatment benefits from AA.

Overall, the AA safety profile in Japanese CRPC patients was comparable to that in the Western population, except more incidences of LFT abnormalities (≥grade 3) were reported in this study.[11,13,17,21] Notably, abnormal LFT values in those six Japanese CRPC patients returned to their baseline levels or grade 1 or lower after temporary interruption or reduction of the AA dose, and all these events were confirmed to have resolved during the study. One patient with a grade 3 LFT continued AA after two dose reductions. Our observation that their plasma abiraterone exposures overlapped with patients who had negative LFT suggests no correlation between AA pharmacokinetics and incidence of LFT abnormalities. All grade 3/4 LFT abnormalities were considered clinically manageable. The frequency of these events in the current study was neither dose-dependent nor exposure-dependent. Nevertheless, there seems to be no major difference in the incidence of grade 3/4 LFT abnormality between this study and previous studies conducted in the USA and Europe.[16,17] The possibility that LFT abnormalities occur more frequently in Japanese patients than in non-Japanese patients cannot be excluded. Thus, individual LFT parameters need to be more carefully observed in future studies. Of note, no deaths related to LFT abnormality were reported as of the data cut-off date. From above, although limited long-term safety information is available in Japanese patients, no major safety concern was found after treatment with AA plus prednisolone in this population.

In conclusion, the pharmacokinetic profile of abiraterone in Japanese CRPC patients was consistent with the established profile in Western populations. AA was well-tolerated at doses from 250 to 1000 mg at both dose timings and the 1000 mg dose showed better pharmacodynamic response and efficacy than other doses. Thus, the recommended AA dosage regimen in Japanese CRPC patients is a 1000-mg oral dose under modified fasting conditions (at least 1 premeal or 2 h postmeal).

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Disclosure Statement

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