

# Abiraterone acetate, exemestane or the combination in postmenopausal patients with estrogen receptor-positive metastatic breast cancer<sup>†</sup>

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**Background:** Androgen receptor (AR) signaling and incomplete inhibition of estrogen signaling may contribute to metastatic breast cancer (MBC) resistance to a nonsteroidal aromatase inhibitor (NSAI; letrozole or anastrozole). We assessed whether combined inhibition of androgen biosynthesis with abiraterone acetate plus prednisone and estradiol synthesis with exemestane (E) may be of clinical benefit to postmenopausal patients with NSAI-pretreated estrogen receptor-positive (ER+) MBC.

**Patients and methods:** Patients ( $N = 297$ ) were stratified by the number of prior therapies for metastatic disease (0–1 versus 2) and by prior NSAI use (adjuvant versus metastatic), and randomized (1 : 1 : 1) to receive oral once daily 1000 mg abiraterone acetate plus 5 mg prednisone (AA) versus AA with 25 mg E (AAE) versus 25 mg E alone (E). Each treatment arm was well balanced with regard to the proportion of patients with AR-positive breast cancer. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, clinical benefit rate, duration of response, and overall response rate.

**Results:** There was no significant difference in PFS with AA versus E (3.7 versus 3.7 months; hazard ratio [HR] = 1.1; 95% confidence interval [CI] 0.82–1.60;  $P = 0.437$ ) or AAE versus E (4.5 versus 3.7 months; HR = 0.96; 95% CI 0.70–1.32;  $P = 0.794$ ). Increased serum progesterone concentrations were observed in both arms receiving AA, but not with E. Grade 3 or 4 treatment-emergent adverse events associated with AA, including hypokalemia and hypertension, were less common in patients in the E (2.0% and 2.9%, respectively) and AA arms (3.4% and 1.1%, respectively) than in the AAE arm (5.8% for both).

**Conclusions:** Adding AA to E in NSAI-pretreated ER+ MBC patients did not improve PFS compared with treatment with E. An AA-induced progesterone increase may have contributed to this lack of clinical activity.

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**Key words:** abiraterone acetate, androgen receptor, estrogen receptor-positive breast cancer, metastatic breast cancer, postmenopausal breast cancer

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## introduction

Approximately 75% of human breast cancers express the estrogen receptor (ER). A substantial reduction in breast cancer mortality has been reached with endocrine therapy, including nonsteroidal aromatase inhibitors (NSAIs), which inhibit aromatization of androgens and reduce tumor proliferation [1, 2]. Acquired resistance after initial treatment frequently occurs, however, and is a major obstacle in the clinical management of this population.

Active androgen receptor (AR) signaling may contribute to metastatic breast cancer (MBC) resistance to NSAIs. The AR is expressed in 50%–70% of all breast cancers and in ~80%–90% of ER+ breast cancers, indicating potential androgen responsiveness [3, 4]. Furthermore, AR overexpression has been demonstrated in the development of tamoxifen resistance in an ER $\alpha$ + breast cancer *in vitro* and in xenograft models [5]. Other studies have shown that androgens stimulate oncogenic human epidermal growth factor receptor 2 and other signaling pathways by transcriptional upregulation of AR-dependent genes [6]. Due to a potential role of AR, novel anti-androgen signaling therapies may offer new strategies for reversing NSAI resistance.

Improvement of survival outcomes by abiraterone acetate, the prodrug of abiraterone, is attributed to its inhibition of persistent adrenal, testicular and intratumoral androgen synthesis via cytochrome P450 C17 (CYP17) in metastatic castration-resistant prostate cancer [7, 8]. Since abiraterone-induced inhibition of CYP17 decreases the synthesis of both androgens and estrogens, abiraterone plus an NSAI may more adequately inhibit estrogen synthesis in breast cancer patients than NSAIs alone. Antitumor activity of abiraterone acetate has been observed in AR+ and ER+ breast cancer patients resistant to endocrine therapy in a phase I/II trial in postmenopausal breast cancer patients with two or more prior endocrine therapies. Abiraterone acetate reduced both androgen and estradiol concentrations below the limits of detection following 1 month of treatment [9]. Seven of 32 ER+ patients (22%) had stable disease for  $\geq 24$  weeks, with one patient having a confirmed partial response lasting 13.8 months [9].

The objective of this study was to assess the efficacy and safety of abiraterone acetate with or without exemestane (E) versus E alone to support the hypothesis that combined inhibition of androgen and estradiol biosynthesis may provide clinical benefit to patients with NSAI-resistant ER+ postmenopausal breast cancer with and without AR+ disease.

## patients and methods

BCA2001 (NCT01381874) was a phase II, randomized open-label trial conducted in the United States, Europe and Korea. Patients were enrolled from August 2011 to April 2013. The clinical cutoff was 20 September 2013.

### patient population

Eligible patients included postmenopausal women aged  $\geq 18$  years with ER+ MBC sensitive to letrozole or anastrozole before disease progression (stable disease or an objective response for  $\geq 6$  months in the metastatic setting, or relapse free for  $\geq 2$  years in the adjuvant setting). Additional inclusion criteria included  $\leq 2$  prior regimens in the metastatic setting ( $\leq 1$  chemotherapy) and an Eastern Cooperative Oncology Group performance status (ECOG PS) of  $\leq 1$ . Patients were excluded if they had received prior exemestane, ketoconazole (non-topical,  $\geq 7$  days), aminoglutethimide or a CYP17 inhibitor.

## study design and treatments

Patients were stratified according to the number of prior therapies in the metastatic setting (0 or 1 versus 2) and the setting of prior NSAI treatment (adjuvant versus metastatic), and randomized (1 : 1 : 1) to receive 1000 mg abiraterone acetate plus 5 mg prednisone (AA), AA with 25 mg exemestane (AAE), or 25 mg exemestane alone (E) once daily in continuous 28-day cycles.

The primary end point was progression-free survival (PFS), and secondary end points included overall survival (OS), overall response rate (ORR) defined as complete response or partial response confirmed by next assessment at least 28 days later, duration of response, clinical benefit rate (CBR) defined with the same criteria as ORR but also including patients who had at least 6 months of stable disease and blood hormone concentrations.

Clinical assessments were conducted at prespecified visits and included safety evaluations for all patients who received at least one dose of study drug. Patients continued study treatment until disease progression, unacceptable toxicity or death. Patients assigned to the E arm could be switched to the AA arm at disease progression at the investigator's discretion. Patients were then followed every 3 months until death, loss to follow-up, consent withdrawal or discontinuation of AA for this indication. Patients with no disease progression over 12-treatment cycles were allowed to continue study treatment at the investigator's discretion. A planned interim analysis was conducted when 110 PFS events (progression or death) in total were observed. A data review committee monitored treatment efficacy and safety during the trial. The review boards at all participating institutions approved the study, and all patients gave written informed consent.

A central pathology review was planned and conducted for this analysis at PhenoPath Labs (Seattle, WA, USA). Expression of ER (Thermo Fisher #RM-9101-S; clone SP1), progesterone receptor (PR; Dako # M3569, clone PgR636) and AR (Dako, #M3562, clone AR441) were assessed by immunohistochemical staining of formalin-fixed paraffin-embedded tissues (FFPETs) collected from patients at diagnosis. The percentage of positively staining cells, intensity of staining (weak, moderate and strong) and presence of positive internal controls were evaluated. A cutoff of  $\geq 10\%$  was used to define ER+ and PR+ disease for randomization. AR positivity was defined as  $\geq 10\%$  nuclear staining.

Liquid chromatography coupled with tandem mass spectrometry (Applied Biosystems/MDS Analytical Technologies, Foster City, CA, USA) was used to determine testosterone, estradiol and estrone concentrations. Progesterone concentrations were determined using a competitive binding immunoassay (Beckman Coulter Access Progesterone assay, Beckman Coulter, Inc., Brea, CA) and the Dxi 800 instrument (Covance Laboratories, Indianapolis, IN).

## statistical analysis

Enrollment of ~300 patients (100 per arm) was planned. A hazard ratio (HR) of 0.65 (median PFS 6.2 and 4.0 months, respectively) was assumed for each pairwise comparison (AA or AAE compared with E) with an 80% power and two-sided alpha 0.10; ~150 PFS events for each pairwise comparison were required.

Efficacy analyses were conducted on the intent-to-treat population (all patients randomized) or patients having measurable disease at baseline. One interim efficacy/futility analysis was implemented at ~50% of the expected PFS events. Time-to-event (PFS, OS, and duration of response) distribution and median value were estimated using the Kaplan–Meier product–limit method. Stratified Cox proportional hazards model was used to estimate the pairwise HR, and the stratified log-rank test was used in the testing of the treatment effect. ORR and CBR between each treatment pair were estimated using  $\chi^2$  test or Fisher's exact test. No adjustment on the type I error rate was planned for each of the pairwise comparisons.

## results

### patients

Enrollment to the AA arm was discontinued after 89 patients enrolled, as the data review committee determined that the pre-specified futility conditions had been met. Baseline patient demographics and disease characteristics were generally similar among the treatment arms ( $N=297$ ), including prior NSAI for MBC and prior chemotherapy in the adjuvant and/or metastatic setting (Table 1). In total, 181 patients (61%) had a measurable disease at baseline by Response Evaluation Criteria In Solid Tumors and 230 patients (77%) were PR+. The proportion of patients with *de novo* disease was slightly higher in the E arm

**Table 1.** Patient baseline demographics and disease characteristics in the intent-to-treat population

	E (N = 102)	AA (N = 89)	AAE (N = 106)
Age, median (range), years	63 (41–81)	62 (42–83)	64 (37–87)
Race, n (%)			
White	92 (90.2)	76 (85.4)	96 (90.6)
Asian	1 (1.0)	1 (1.1)	5 (4.7)
Black or African American	0	0	0
Other	0	1 (1.1)	1 (0.9)
Not reported	9 (8.8)	11 (12.4)	4 (3.8)
ECOG PS, n (%)			
0	48 (47.1)	52 (59.1)	43 (41.3)
1	54 (52.9)	36 (40.9)	61 (58.7)
PR receptor status, n (%)			
Positive	78 (76.5)	73 (82.0)	79 (74.5)
Negative	24 (23.5)	16 (18.0)	27 (25.5)
Prior NSAI, n (%)			
Adjuvant	36 (35.3)	32 (36.0)	38 (35.8)
Metastatic	66 (64.7)	57 (64.0)	68 (64.2)
Prior chemotherapy	67 (65.7)	59 (66.3)	74 (69.8)
Adjuvant	48 (47.1)	44 (49.4)	46 (43.4)
Metastatic	23 (22.5)	15 (16.9)	28 (26.4)
Measurable disease at baseline, n (%)	63 (61.8)	52 (58.4)	66 (62.3)
<i>De novo</i> MBC, n (%) <sup>a</sup>	23 (22.5)	13 (14.6)	11 (10.4)
Metastasis-free interval, median, months (range) <sup>b</sup>	5.8 (0.7–24.6)	7.5 (0.3–33.9)	6.8 (0.27–27.3)
Site of metastasis, n (%)			
Visceral	47 (46.1)	35 (39.3)	55 (52.4)
Bone	72 (70.6)	69 (77.5)	77 (73.3)
Bone only	24 (23.5)	30 (33.7)	24 (22.9)
Lymph nodes	49 (48.0)	35 (39.3)	40 (38.1)

<sup>a</sup>Patients with time from initial diagnosis of breast cancer to metastatic disease  $\leq 90$  days.

<sup>b</sup>Time from initial diagnosis of breast cancer to metastatic disease (after excluding patients with *de novo* disease).

AA, abiraterone acetate plus prednisone; AAE, abiraterone acetate plus exemestane; E, exemestane; ECOG PS, Eastern Cooperative Oncology Group performance status; NSAI, nonsteroidal aromatase inhibitor; MBC, metastatic breast cancer; PR, progesterone receptor.

versus the AA and AAE arms (22.5%, 14.6% and 10.4%, respectively).

FFPETs were collected at diagnosis from all treated patients ( $N=293$ ). Of these patients, 227 (77%) had AR+ disease. The percentages of patients with AR+ disease in the E, AA and AAE arms were 76.5%, 79.3% and 76.9%, respectively.

At the clinical cutoff, most patients discontinued treatment due to progressive disease: 72.5%, 80.5% and 75.0% of patients in E, AA and AAE arms, respectively (Figure 1). Treatment was ongoing at cutoff for 23 (E), 9 (AA) and 15 (AAE) patients. One patient died in the E arm. Treatment duration among the three arms was comparable, with a median exposure of 3.7 months.

### efficacy outcomes

The median follow-up time for PFS was 11.4 months. Statistically significant improvement in the primary end point of PFS was not observed with AA versus E (3.7 versus 3.7 months, HR = 1.1; 95% CI 0.82–1.60;  $P=0.437$ ) or AAE versus E (4.5 versus 3.7 months; HR = 0.96; 95% CI 0.70–1.32;  $P=0.794$ ; Figure 2A). No difference in PFS between the three arms was observed in the AR+ subpopulation (data not shown). A sensitivity analysis was conducted at different cutoffs for AR positivity. No significant differences in PFS by the level of AR positivity were observed (data not shown). PFS HRs observed in the PR– versus PR+ subgroups differed between the AAE and E arms (HR = 0.545; 95% CI 0.295–1.007 versus HR = 1.138; 95% CI 0.781–1.658, respectively; Figure 2B).

No significant differences among treatment arms were noted for the secondary end points. Median OS has not been reached for any treatment arm. ORR was higher in the AAE arm versus the E arm (12.1% versus 6.3%;  $P=0.366$ ). The median duration of response for patients with a measurable disease at baseline for AAE versus E was 6.9 and 6.5 months, respectively ( $P=0.625$ ). The CBR was higher in the AAE arm (22.7%) versus the E arm (12.7%) ( $P=0.137$ ).

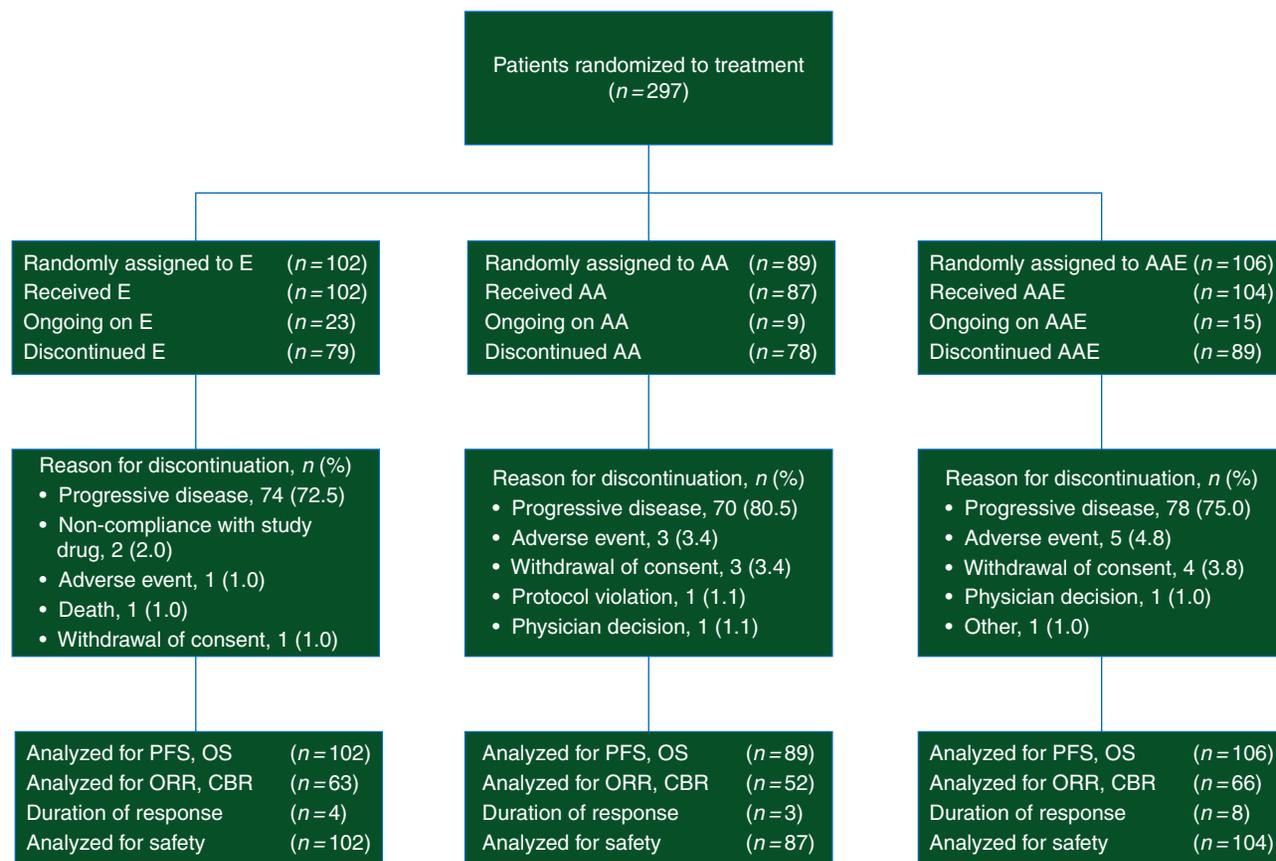
Thirty-one patients crossed over to AA following progression on E. The crossover was discontinued when enrollment to the AA arm was discontinued. No patient, before or after crossover, had a complete response, partial response or  $\geq 6$  months of stable disease upon crossing over to AA.

As expected, a significant ( $P<0.001$ ) decrease in serum testosterone beginning at cycle 2 day 1 was observed for the AA arms (Figure 3A). Reductions in estrone and estradiol were also observed across all treatment arms (Figure 3B and C). Progesterone serum concentrations were significantly ( $P<0.001$ ) increased above the upper limit of normal physiological concentrations for postmenopausal women at cycle 2 day 1 in all patients treated with AA but not with E alone (Figure 3D).

### safety

Treatment-emergent adverse events (TEAEs) occurred in 88 (86.3%), 80 (92.0%) and 93 (89.4%) patients in the E, AA and AAE arms, respectively (Table 2). Twenty-two (25.3%) patients in the AA arm and 34 (32.7%) patients in the AAE arm experienced grade 3/4 TEAEs versus 23 (22.5%) patients observed in the E arm. The majority of these TEAEs ( $\geq 89\%$  in each arm) were not study drug-related.

TEAEs leading to death were reported for 1 (1.0%) and 2 (1.9%) patients in the E and AAE arms, respectively, although



**Figure 1.** Patient enrollment and disposition CONSORT diagram. Percentages are calculated with the number of treated patients in each treatment arm as the denominator. AA, abiraterone acetate; AAE, abiraterone acetate plus exemestane; CBR, clinical benefit rate; E, exemestane; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

none were considered study drug-related (Table 2). Treatment discontinuation due to TEAEs occurred in 2 (2.0%), 4 (4.6%) and 10 (9.6%) patients in the E, AA and AAE arms, respectively. The only TEAEs leading to treatment discontinuation in more than one patient in any arm were vomiting, aspartate aminotransferase (AST) increase and dyspnea (two patients in the AAE arm).

AA-associated TEAEs of special interest occurred in 42 (41.2%), 44 (50.6%) and 56 (53.8%) patients in the E, AA and AAE arms, respectively (Table 2). One grade 4 hypokalemia was observed in each of the AA and E arms. Grade 3/4 hepatic function abnormalities (i.e. AST and alanine aminotransferase increase) occurred in 3.9% and 2.9% of patients in the E arm, 2.3% of patients in the AA arm, and 4.8% and 2.9% of patients in the AAE arm.

## discussion

We present the first randomized study evaluating the efficacy and safety of the androgen biosynthesis inhibitor abiraterone acetate in breast cancer patients. This study did not meet its primary end point of a significant difference in PFS with AA or AAE compared with E alone, but showed modest improvements in secondary end points.

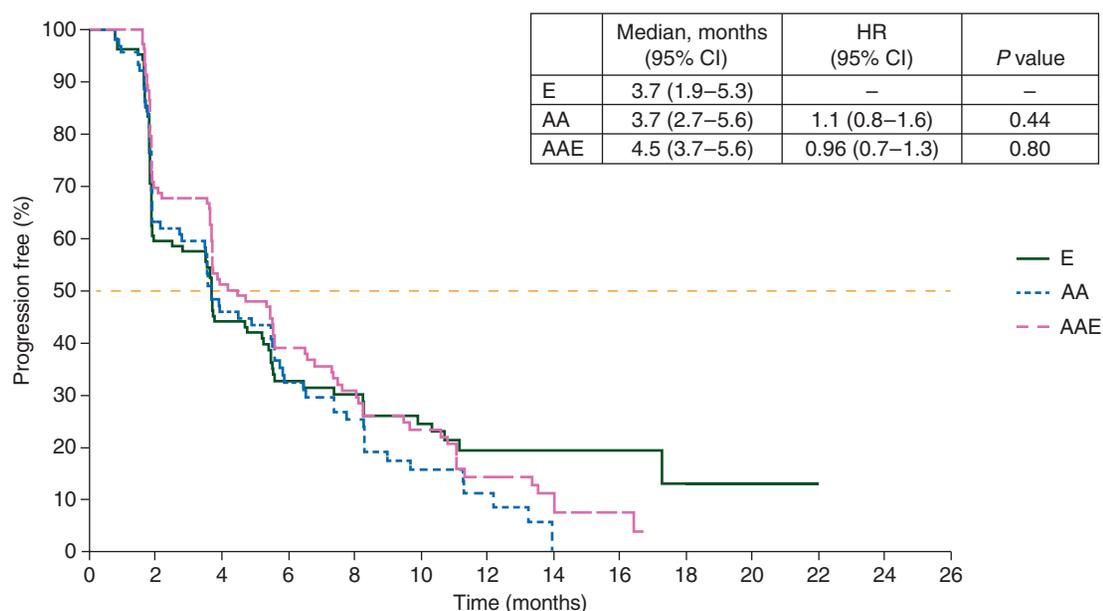
As this study aimed to determine whether AR-mediated signaling plays an important role in NSAI resistance in AR+ disease,

it was designed to show substantial magnitude of PFS benefit between treatment arms. Despite limitations of this study, including small sample size, statistical modeling based on these trial results suggests that a significant improvement in clinical outcomes would likely not be achieved with a larger trial. Therefore, a phase III trial will not be pursued.

Although we demonstrated that abiraterone inhibits testosterone as well as estradiol and estrone synthesis (Figure 3), the lack of superior efficacy of AAE may imply that AR signaling is not an important driver of breast cancer growth following NSAI therapy. At present, it has not been demonstrated that AR signaling drives *de novo* or acquired resistance to endocrine therapy [6], although some preclinical studies suggest that this is true [5, 10].

The AA-induced increases in serum progesterone concentrations observed in all patients may have attenuated any antitumor activity due to androgen biosynthesis inhibition in this study. AA-mediated inhibition of androgen biosynthesis may lead to a subsequent diversion into the progesterone synthetic pathway via adrenal dehydroepiandrosterone and pregnenolone [11]. AA-induced elevated progesterone concentrations could then provide a growth stimulus through the PR or through other mechanisms [12–14].

In patients with ER+ breast cancer, the causes of NSAI resistance are probably multifactorial, including differences in germline pharmacogenomics and somatic changes in tumor biology.

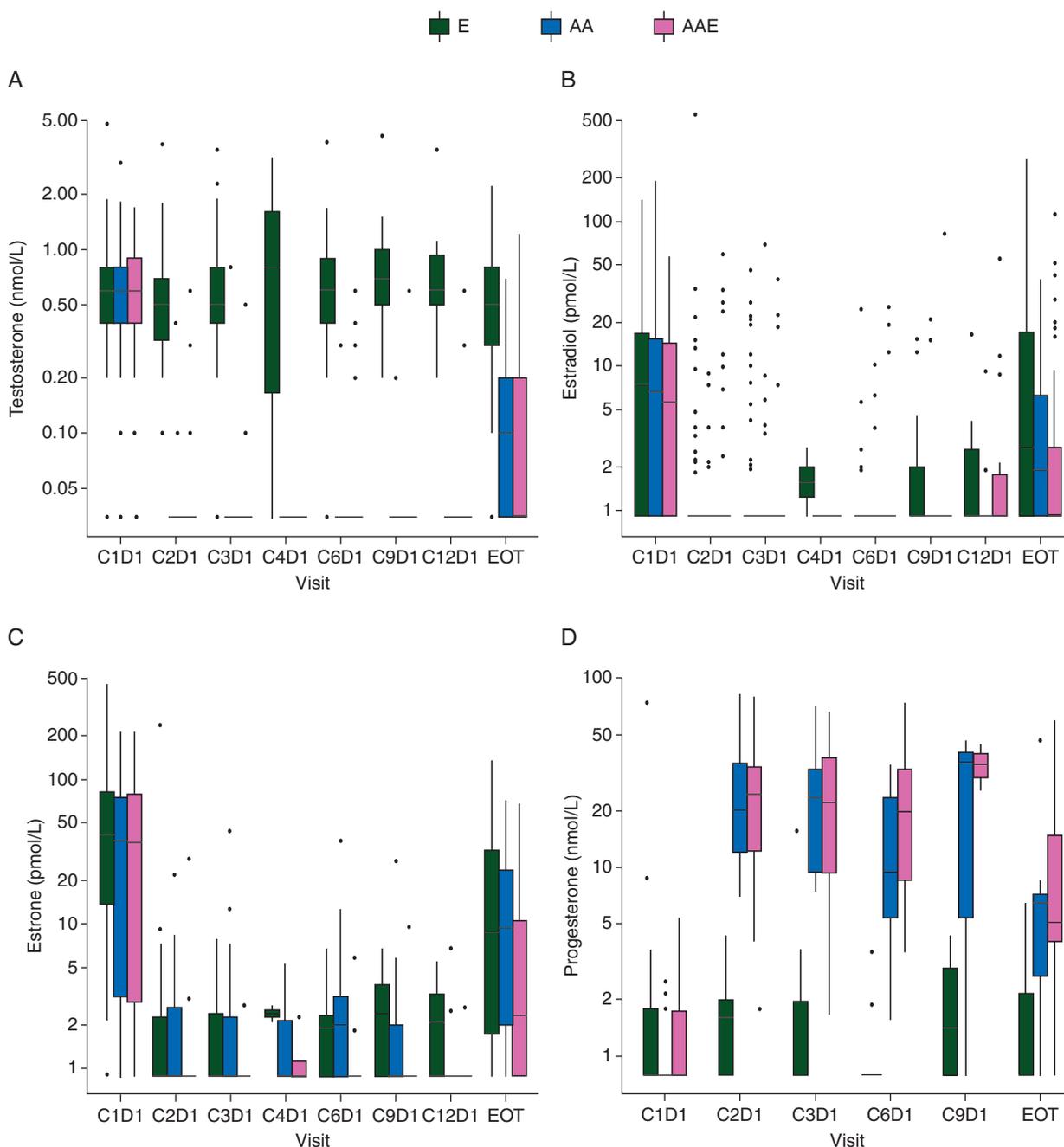


Variable	Subgroup	Median (months)		HR and 95% CI	HR	95% CI	Events/N	
		AAE	E				AAE	E
All subjects	ALL	4.47	3.68		0.972	0.706–1.339	82/106	75/102
No. of prior therapies	0 or 1	3.71	3.65		1.000	0.685–1.458	60/76	53/74
	2	6.51	5.26		0.826	0.450–1.515	22/30	22/28
Setting of prior treatment	Adjuvant	4.73	3.68		0.852	0.491–1.479	26/38	26/36
	Metastatic	4.17	3.71		1.031	0.696–1.527	56/68	49/66
Baseline ECOG status	0	6.57	3.66		0.890	0.554–1.429	35/43	37/48
	1	3.75	3.71		1.046	0.677–1.617	47/61	38/54
No. of prior chemotherapies	0	3.71	3.71		1.137	0.789–1.638	63/78	57/79
	1	6.51	2.20		0.593	0.303–1.162	19/28	18/23
Age	< Median	5.36	1.91		0.719	0.448–1.154	36/46	37/48
	≥ Median	3.75	4.76		1.216	0.786–1.881	46/60	38/54
Region	NA	5.45	1.87		1.001	0.353–2.840	8/8	7/9
	WE	3.71	3.60		0.971	0.655–1.440	54/67	51/61
	EE	6.51	5.55		0.974	0.482–1.970	16/26	16/31
	OTH	5.59	0.85		0.000	<0.001, NE	4/5	1/1
Site of metastatic disease	Visceral	4.17	1.87		0.510	0.323–0.804	43/55	41/47
	Non-visceral	4.73	5.55		1.561	0.973–2.505	39/50	34/55
	Bone only	3.71	3.75		2.092	1.044–4.189	24/24	14/24
PR status	Positive	4.17	3.75		1.138	0.781–1.658	61/79	52/78
	Negative	4.47	2.22		0.545	0.295–1.007	21/27	23/24
De novo MBC	Yes	6.01	3.55		0.678	0.303–1.519	9/11	19/23
	No	4.17	3.71		1.040	0.728–1.485	73/94	56/79

**Figure 2.** Progression-free survival of the intent-to-treat population. AA, abiraterone acetate; AAE, abiraterone acetate plus exemestane; CI, confidence interval; E, exemestane; ECOG, Eastern Cooperative Oncology Group; EE, Eastern Europe; HR, hazard ratio; MBC, metastatic breast cancer; NA, North America; OTH, other; WE, Western Europe.

In such cases, simple reduction in estrogen and androgen concentrations may be insufficient to overcome the acquired resistance due to these mutations.

Although the safety analysis is limited by the small number of patients in each treatment arm, the frequency and clinical pattern of AEs, including those of special interest (e.g. hypertension, fluid



**Figure 3.** Box plot of serum endocrine analysis by visit: (A) testosterone, (B) estradiol, (C) estrone and (D) progesterone. The lower limit of quantification was 2 ng/dl (0.07 nmol/l) for testosterone, 0.5 pg/ml (1.8 pmol/l) for estradiol and estrone, and 0.5 ng/ml (1.6 nmol/l) for progesterone. Dashed lines at base of the box plots represent undetectable levels. Dots represent outliers. AA, abiraterone acetate; AAE, abiraterone acetate plus exemestane; C, cycle; D, day; E, exemestane; EOT, end of treatment.

retention and edema, hypokalemia; Table 2), are consistent with the safety profile of AA in patients with metastatic castration-resistant prostate cancer [7, 8].

In conclusion, we have shown that although abiraterone inhibited androgen biosynthesis in postmenopausal patients with ER+, AR+ NSAI-resistant MBC, elevated progesterone concentrations induced by AA and/or the heterogeneous mechanisms of resistance to NSAIs in this patient population may explain the lack of superiority of the combination of an

NSAI and AA over E. It is possible that AAE is more effective in patients with ER+ PR-negative disease; this hypothesis would need prospective evaluation. These trial results do not exclude the possibility of clinical benefit from AR-signaling disruption in NSAI-resistant ER+ postmenopausal breast cancer as AA demonstrated similar activity to E alone. Further studies of survival outcomes by AR status are ongoing. Additional biomarker analyses are being conducted to potentially identify patient subgroups that manifest AA sensitivity or resistance and to evaluate

**Table 2.** Treatment-emergent adverse events in the safety population

	E (N = 102)			AA (N = 87)			AAE (N = 104)		
No. of patients with TEAEs (%) <sup>a</sup>	88 (86.3)			80 (92.0)			93 (89.4)		
Drug-related <sup>a,b</sup>	50 (49.0)			51 (58.6)			64 (61.5)		
Number of patients with grade 3–4 TEAEs (%)	21 (20.6)			22 (25.3)			34 (32.7)		
Drug-related <sup>b</sup>	4 (3.9)			8 (9.2)			11 (10.6)		
Number of patients with serious TEAEs (%) <sup>a</sup>	11 (10.8)			16 (18.4)			25 (24.0)		
Drug-related <sup>a,b</sup>	1 (1.0)			5 (5.7)			2 (1.9)		
Number of patients with TEAEs leading to treatment discontinuation (%) <sup>a</sup>	6 (5.9)			4 (4.6)			10 (9.6)		
Drug-related <sup>a,b</sup>	4 (3.9)			2 (2.3)			5 (4.8)		
Number of patients with TEAEs leading to death (%)	1 (1.0)			0			2 (1.9)		
Drug-related <sup>b</sup>	0			0			0		
Most frequent TEAEs, <i>n</i> (%) <sup>a,c</sup>	Gr 1/2	Gr 3/4	Total	Gr 1/2	Gr 3/4	Total	Gr 1/2	Gr 3/4	Total
Fatigue	24 (24)	1 (1)	25 (25)	19 (22)	3 (3)	22 (25)	18 (17)	2 (2)	20 (19)
Nausea	18 (18)	0	18 (18)	18 (21)	2 (2)	20 (23)	20 (19)	0	20 (19)
Bone pain	16 (16)	1 (1)	18 (18)	9 (10)	2 (2)	11 (13)	13 (13)	0	13 (13)
Arthralgia	17 (17)	0	17 (17)	7 (8)	0	7 (8)	9 (9)	0	9 (9)
Hot flush	13 (13)	0	13 (13)	14 (16)	0	14 (16)	9 (9)	0	9 (9)
Back pain	10 (10)	1 (1)	12 (12)	14 (16)	2 (2)	16 (18)	17 (16)	0	17 (16)
Decreased appetite	10 (10)	0	10 (10)	13 (15)	0	13 (15)	15 (14)	2 (2)	17 (16)
Constipation	9 (9)	0	9 (9)	13 (15)	0	13 (15)	13 (13)	0	13 (13)
Vomiting	6 (6)	1 (1)	7 (7)	11 (13)	0	11 (13)	18 (17)	3 (3)	21 (20)
Hypokalemia	3 (3)	2 (2)	5 (5)	16 (18)	3 (3)	19 (22)	7 (7)	6 (6)	13 (13)
TEAEs of special interest, grade 3/4, <i>n</i> (%)	Grade 3	Grade 4		Grade 3	Grade 4		Grade 3	Grade 4	
AST increase	3 (3)	1 (1)		2 (2)	0		5 (5)	0	
ALT increase	3 (3)	0		2 (2)	0		3 (3)	0	
Hypertension	3 (3)	0		1 (1)	0		6 (6)	0	
Cardiac disorders <sup>d</sup>	0	1 (1)		2 (2)	0		2 (2)	0	
Hypokalemia	1 (1)	1 (1)		2 (2)	1 (1)		6 (6)	0	
Fluid retention/edema	1 (1)	0		1 (1)	0		2 (2)	0	

<sup>a</sup>Adverse events with toxicity grade 5 are not included.

<sup>b</sup>Adverse events with relationship to the study drugs (AAE and/or E) reported as possible, probable or very likely in each treatment arm are classified as drug-related adverse events.

<sup>c</sup>TEAE in at least 15% of patients in any treatment arm.

<sup>d</sup>Arrhythmias and other cardiac disorders, including chest pain, left ventricular hypertrophy and sinus bradycardia.

AA, abiraterone acetate plus prednisone; AAE, abiraterone acetate plus exemestane; ALT, alanine aminotransferase; AST, aspartate aminotransferase; E, exemestane; Gr, grade; TEAE, treatment-emergent adverse event.

a potential association between AA-induced serum progesterone elevation and PFS.

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