Table 3. **Efficacy Analysis on the Basis of Local and Central Assessment.***

Variable	Everolimus and Exemestane (N=485)	Placebo and Exemestane (N=239)	P Value	Hazard Ratio (95% CI)
Local assessment				
Progression-free survival				
Events — no. (%)	202 (42)	157 (66)	<0.001	0.43 (0.35–0.54)
Duration — mo				
Median	6.9	2.8		
95% CI	6.4–8.1	2.8–4.1		
Best overall response — %				
Complete response	0.4	0.0		
Partial response	9.1	0.4		
Stable disease	70.1	58.6		
Progressive disease	9.9	31.4		
Unknown or too early	10.5	9.6		
Objective response — % (95% CI)	9.5 (7.0–12.4)	0.4 (0.0–2.3)	<0.001	
Central assessment				
Progression-free survival				
Events — no. (%)	114 (24)	104 (44)	<0.001	0.36 (0.27–0.47)
Duration — mo				
Median	10.6	4.1		
95% CI	9.5–NR	2.8–5.8		
Best overall response — %				
Complete response	0.0	0.0		
Partial response	7.0	0.4		
Stable disease	74.6	64.4		
Progressive disease	5.6	21.8		
Unknown or too early	12.8	13.4		
Objective response — % (95% CI)	7.0 (4.9–9.7)	0.4 (0.0–2.3)	<0.001	

* NR denotes not reached.

pares favorably with that of the limited options available to this group of patients with HR-positive advanced breast cancer. The ER down-regulator fulvestrant (at a standard dose of 250 mg monthly) was associated with activity similar to that of exemestane, with a median progression-free survival of 3.7 months.[6] High-dose fulvestrant (500 mg monthly), as compared with standard-dose fulvestrant, provided only a modest improvement in median progression-free survival, from 5.5 to 6.5 months (hazard ratio, 0.80; P=0.006). This improvement was less clear in patients whose most recent therapy was an aromatase inhibitor (hazard ratio, 0.85; P=0.20) and in those who were considered to have had a response to the most recent endocrine therapy (hazard ratio, 0.85; P=0.12).[7] Our results also compare favorably to those shown with capecitabine and taxanes or anthracyclines, with a median progression-free survival duration of 6.2 months and 8.2 months, respectively, in patients with HR-positive disease.[21]

Combination therapy was associated with a higher incidence of adverse events than exemestane alone. The adverse events observed with everolimus plus exemestane are consistent with those reported with everolimus and other rapamycin analogues and include stomatitis, fatigue and asthenia, diarrhea, cough, pyrexia, and hy-

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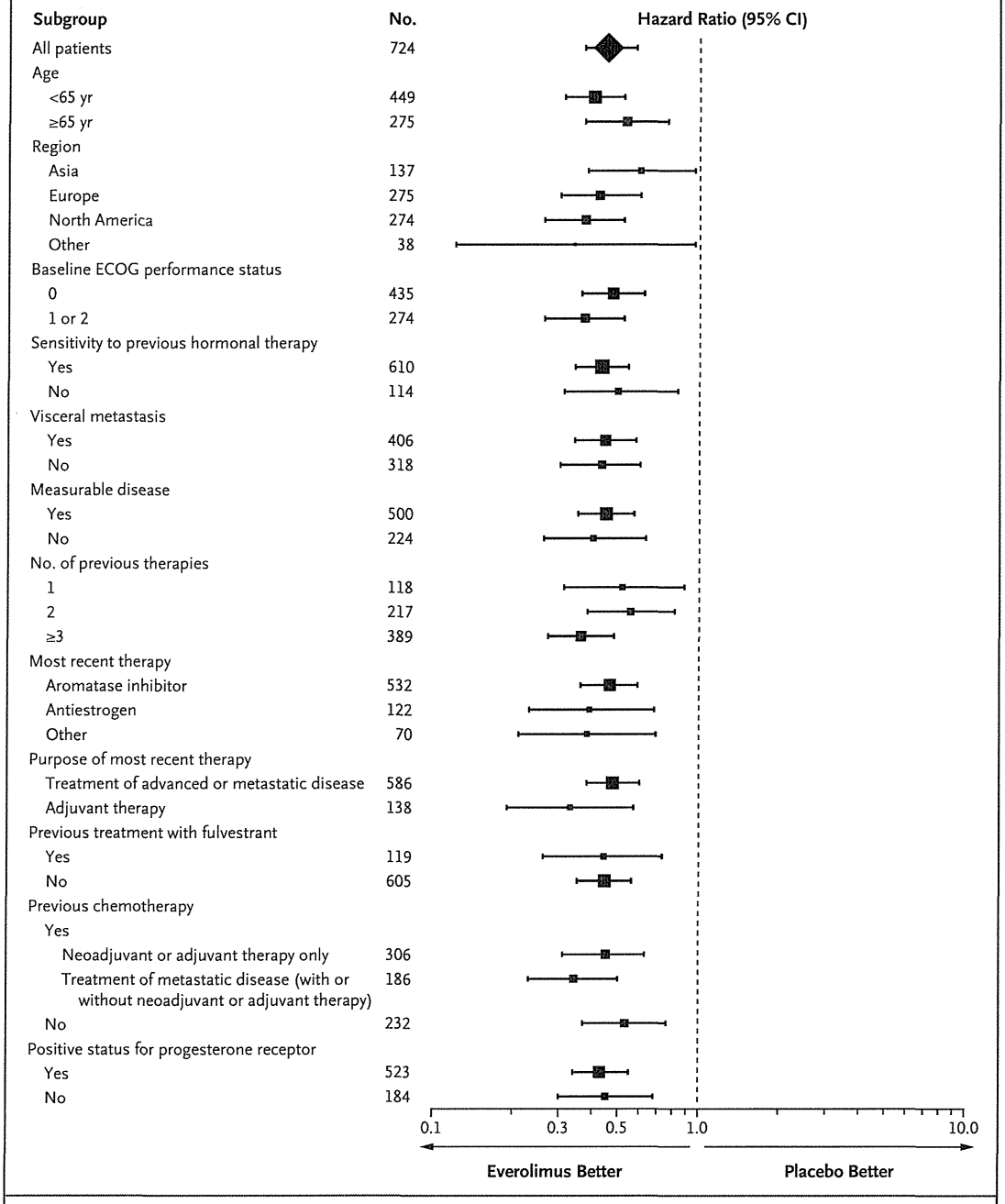

Figure 2. Consistency of Results for Progression-free Survival across the Various Subgroups.

Scores for Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with 0 indicating that the patient is fully active, 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, and 2 indicating that the patient is ambulatory and capable of all self-care but unable to work. The number of patients may not add up to 724 owing to missing baseline data. The size of each square is proportional to the number of patients in the subgroup. The data are shown on a semi-logarithmic scale.

perglycemia.[22,23] In the current study, a high percentage of patients discontinued everolimus because of a lack of tolerability. The longer treatment duration in the combination-therapy group might have contributed to the high discontinuation rate. Careful monitoring of patients and increased physician awareness of the safety profile of everolimus are warranted.

In summary, we report a phase 3 trial in patients with HR-positive advanced breast cancer showing that the addition of everolimus to endocrine therapy results in an improved clinical outcome. This benefit should be weighed against the side effects observed with everolimus. The potential of everolimus to benefit patient survival is not yet known.

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Original Article

Safety, Efficacy and Pharmacokinetics of Neratinib (HKI-272) in Japanese Patients with Advanced Solid Tumors: A Phase 1 Dose-escalation Study

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Objective: Neratinib (HKI-272), a potent, irreversible, small-molecule, orally administered, pan-ErbB inhibitor that blocks signal transduction via inhibition of three epidermal growth factor receptors [ErbB1, ErbB2 (Her2) and ErbB4], is being developed for the treatment of solid tumors, including breast cancer. This Phase 1 dose-escalation study assessed the safety, tolerability, maximum-tolerated dose, antitumor activity and pharmacokinetics of neratinib in Japanese patients with advanced solid tumors.

Methods: Patients received neratinib 80, 160, 240 or 320 mg orally; each patient enrolled in only one dose cohort. Patients received a single dose in week 1, followed by daily continuous doses. Blood samples collected were on days 1 and 21 for pharmacokinetic analyses.

Results: Twenty-one patients were enrolled (3 breast cancer; 17 colorectal cancer; 1 gastric cancer). Neratinib-related adverse events (all grades) included diarrhea (20 patients), fatigue (14 patients), nausea and abdominal pain (9 patients each) and anorexia (8 patients). Grade $\geq$3 neratinib-related adverse events in two or more patients were diarrhea and anorexia (two patients each). Dose-limiting toxicities were diarrhea and anorexia (two patients, 320 mg dose). The maximum-tolerated dose and recommended dose was neratinib 240 mg once daily. Of 21 evaluable patients, 2 with breast cancer had partial response, 3 had stable disease $\geq$24 weeks, 7 had stable disease $\geq$16 weeks and 9 had progressive disease. Pharmacokinetic analyses indicated that neratinib exposures increased with dose.

Conclusions: The safety, efficacy and pharmacokinetic profiles of neratinib are consistent with those reported for non-Japanese patients and warrant further investigation of neratinib in Japanese patients with solid tumors.

Key words: ErbB2 – maximum-tolerated dose – neratinib – Phase I clinical trial – treatment efficacy

INTRODUCTION

Dysregulation of growth factor signaling due to hyperactivation of the epidermal growth factor receptor (EGFR/ErbB) family of tyrosine kinase receptors has been observed in several cancer types (1) and is associated with increased proliferation, angiogenesis, metastasis and decreased apoptosis (2). Due to its implication in tumorigenesis, inhibition of

this family of kinase receptors may be a novel and viable treatment option for patients who are intolerant to chemotherapy or those refractory to the current standard of care.

Several drugs have been developed and marketed that selectively inhibit the ErbB receptor kinases, such as the small-molecule, reversible, adenosine triphosphate-competitive inhibitors erlotinib and gefitinib, which target ErbB1 (3,4), and lapatinib, which targets both ErbB1 and ErbB2 (Her2) (5). Monoclonal antibodies have also demonstrated antitumor activity, such as trastuzumab, which binds to ErbB2 (6), and panitumumab and cetuximab, which bind to ErbB1 (7,8). There are, however, various limitations to the safety and efficacy of these drugs. For example, gefitinib and erlotinib provide progression-free survival (PFS) times of only 9–13 months in patients with non-small cell lung cancer showing EGFR mutations. Likewise, trastuzumab is associated with response rates of only 15–26% when given as monotherapy (9,10) and 42% in combination with paclitaxel for the treatment of patients with metastatic breast cancer (11). Trastuzumab is also associated with cardiac toxicity, particularly in patients previously treated with anthracyclines (12,13).

Neratinib (HKI-272) is a potent, orally administered, small-molecule, pan-ErbB inhibitor that irreversibly blocks signal transduction via inhibition of ErbB1, ErbB2 and ErbB4 (14–16). Neratinib has shown promising antitumor activity in a variety of solid tumors, including breast cancer and non-small cell lung cancer (17,18). In addition, neratinib can potentially overcome the acquired resistance of the EGFR 'gatekeeper' T790M mutation. This mutation typically develops in the tumors of lung cancer patients that harbor the EGFR kinase domain-sensitizing mutation after treatment with reversible inhibitors such as gefitinib or erlotinib and subsequent disease progression (19–22).

In the Phase 1, first-in-human dose-escalation study of neratinib in patients with solid tumors that was conducted in the USA, the maximum-tolerated dose (MTD) of neratinib was found to be 320 mg once daily (17). In addition, neratinib exposure was dose-dependent and the pharmacokinetic (PK) results favored a once-daily dosing regimen (17). Neratinib was also clinically active in patients with advanced and/or metastatic ErbB2-positive breast cancer, even under conditions of trastuzumab resistance, and was well tolerated as a once-daily orally dosed agent (17). However, due to the primary dose-limiting toxicity (DLT) of diarrhea, the therapeutic dose was limited to 240 mg once daily in later Phase 2 studies. In patients with advanced ErbB2-positive breast cancer, the 16-week PFS rates were 59 and 78% for patients with prior trastuzumab and no prior trastuzumab treatments, respectively, and the objective response rates (ORRs) were 24 and 56%, respectively (18).

Because the efficacy and safety of drugs, such as gefitinib and sunitinib, can vary between Western and Asian populations (23), we assessed the safety and tolerability, and determined the MTD of oral neratinib in Japanese patients with solid tumors in this Phase 1 study. The preliminary antitumor activity and the PK profile of neratinib in the same patient population were also evaluated.

PATIENTS AND METHODS

Study Design

This was a multicenter, open-label, Phase 1, ascending single and multiple oral dose study conducted in Japan to determine the safety, tolerability, MTD, antitumor activity and PK of neratinib in Japanese patients with advanced solid tumors. Each patient participated in only one dose cohort (three to six patients) and received a single dose of neratinib. After a 1-week observation period, patients received neratinib as a continual oral daily dose for up to 6 months (six cycles), or longer at the same dose level if neratinib was well tolerated and the patient showed no evidence of progressive disease (PD).

This study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the ethical principles that have origins in the Declaration of Helsinki. The study protocol was approved by an Institutional Review Board and written informed consent was obtained from all patients before their enrollment in this study.

Patient Eligibility

Patients were eligible for enrollment if they were $\geq$20 years of age and had a histologic/cytologic diagnosis of metastatic or advanced cancer that had failed to respond to standard effective therapy or for which no standard effective treatment was available, a life expectancy of $\geq$12 weeks and a measurable lesion as defined by modified Response Evaluation Criteria in Solid Tumors guidelines. Other key inclusion criteria were a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, an absolute neutrophil count of $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, creatinine level $\leq 1.5\times$ the upper limit of normal and total bilirubin $\leq 1.5\times$ the upper limit of normal.

The main exclusion criteria were the following: anticancer chemotherapy, radiotherapy, immunotherapy or investigational agents within 4 weeks before treatment day 1; prior treatment with anthracyclines with a cumulative dose of doxorubicin or equivalent >400 mg/m^2; automatic electrocardiogram (ECG)-corrected QT (QTc) interval reading at screening >470 ms; left ventricular ejection fraction (LVEF) below the institutional range of normal as measured by echocardiogram; significant gastrointestinal disorders with diarrhea as a major symptom; and a history of clinically significant cardiac disease, including congestive heart failure, myocardial infarction and significant arrhythmia.

Dose Escalation

Neratinib was administered orally once daily with food, preferably in the morning. After administration of the single dose and a 1-week observation period, patients were treated at the same dose level with continual oral daily doses in 28-day cycles. Dose cohorts consisted of neratinib 80, 160, 240 and 320 mg. The starting dose was based on the results

of the Phase 1, first-in-human study of neratinib in patients with solid tumors that was conducted in the USA, in which neratinib-related Grade 3 adverse events (AEs) were not reported at doses $\leq$80 mg (17). The decision to proceed to the next dose level was made after the last patient in a cohort had been evaluated through ~14 days of continuous daily administration. Enrollment at the next dose level occurred according to the following criteria: if no patients experienced a DLT, then three–six patients were enrolled at the next dose level; if one patient experienced a DLT, then an additional six patients were treated at the same dose level and the dose escalated if no more than one of those patients had a DLT. If two or more patients at a dose level experienced a DLT by day 14 of continuous daily dosing, dose escalation stopped and the previous dose level was considered the MTD. If a patient in any dose cohort had a toxicity that met the definition of DLT, then the patient's dose was reduced by one dose level, and if the patient experienced a second DLT, then the dose was further decreased by one dose level. No more than two dose reductions were allowed for any patient.

A DLT was defined as any neratinib-related non-hematologic Grade 3 or any Grade 4 AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, with the exception of Grade 3 nausea, vomiting, diarrhea or rash, unless the patient was receiving appropriate medical therapy. Additional DLTs included Grade 2 or 3 diarrhea lasting >2 days, for which the patient was receiving appropriate medical therapy or for that which was associated with fever or dehydration. DLTs were assessed during the first 21 days following the administration of the first dose in the continual single-dose period.

Evaluation of Patients

Safety evaluations were based on the incidence and severity of AEs, the DLTs at each dose level and changes in clinical laboratory test results over time. AEs were monitored and recorded continuously during the study, while laboratory evaluations were conducted at screening; on day 1 of the single-dose period; on days 1, 7, 14 and 21 of cycle 1 of the continuous dosing period; on days 1 and 14 of cycles 2 through 6; and at the final evaluation (30 days after the last dose). Other safety assessments included vital signs, interim history, radiographs, cardiac evaluations, echocardiogram and ECGs. The efficacy population included all patients who received $\geq$2 weeks of neratinib therapy and underwent $\geq$1 tumor assessment ~8 weeks after starting continual daily neratinib administration. In addition, patients with disease progression prior to receiving 14 days of neratinib therapy were considered evaluable for efficacy.

PK Analyses

Timed blood samples for PK analyses of neratinib were collected on day 1 and on day 14 (study day 21) of continual daily dose administration. Samples were collected at 0 h (pre-dose) and at 1, 2, 4, 6, 8 and 24 h after dose administration. Samples were also collected at 48 h after dose administration on day 1 of the single-dose period. Plasma neratinib concentrations were measured using a validated liquid chromatography/tandem mass spectrometry method. PK analyses were performed for each patient using non-compartmental methods (24) with WinNonLin® Enterprise application, version 5.1 (Pharsight Corporation, CA, USA). The parameters determined included the following: observed maximum concentration (C_{max}), area under the concentration–time curve (AUC) from time zero extrapolated to infinite time ($AUC_{0-\infty}$), AUC at steady state (AUC_{ss}), AUC from time 0–24 h (AUC_{0-24h}), time of maximum concentration (t_{max}), terminal-phase elimination half-life ($t_{1/2}$), the apparent volume of distribution for the terminal disposition phase (V_z/F) and the apparent oral clearance (CL/F).

The preliminary assessment of dose proportionality was evaluated by the following power model:

$$C_{max}, \quad AUC_{0-\infty} \quad \text{or} \quad AUC_{ss} = \alpha \times dose^{\beta} \qquad (1)$$

where α is the coefficient and β is the exponent of the linear-regression model on log-transformed parameters, C_{max}, $AUC_{0-\infty}$, AUC_{ss} and dose. The 95% confidence intervals (CIs) for the exponents were also calculated. The validity of the power model was evaluated by performing a lack-of-fit test. A P-value for the lack-of-fit test of <0.05 would imply that there was a significant lack of fit in the power model and that the point estimate derived from the power model was not valid.

Determination of Sample Size

Approximately 28 patients were to be enrolled in this study. This estimate was based on a maximum of 6 patients per dose cohort over approximately four dose levels and enrolling 4–7 additional patients (total 10 patients) at the recommended dose. The actual number of patients enrolled was dependent on the tolerability of neratinib and the number of dose levels required to attain the MTD.

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of three to six patients, if the true underlying rates of DLT were 0.1, 0.2, 0.3, 0.4 and 0.5, there would be 0.91, 0.71, 0.49, 0.31 and 0.17 chances, respectively, of escalating to the next higher dose level. If the frequencies of AEs of Grade $\geq$3 were 0.1, 0.25 and 0.5, the probabilities of detecting one or more such events in six patients receiving neratinib would be 0.469, 0.822 and 0.984, respectively, and the probabilities of detecting one or more such events in 10 patients would be 0.651, 0.944 and 0.999, respectively.

Table 1. Patients' demographics and baseline characteristics

Characteristic	Dose cohorts, mg neratinib				
	80 ($n = 3$)	160 ($n = 3$)	240 ($n = 10$)	320 ($n = 5$)	Total ($n = 21$)
Median age, years (range)	54 (44–63)	47 (44–54)	64.5 (39–78)	61 (47–66)	61 (39–78)
Primary diagnosis, *n* (%)					
Breast cancer	0	1	1	1	3 (14)
Colorectal cancer	3	1	9	4	17 (81)
Gastric cancer	0	1	0	0	1 (5)
ECOG performance status, *n* (%)					
0	3	3	9	4	19 (91)
1	0	0	1	1	2 (10)
Prior chemotherapy, immunotherapy or hormonal therapy, *n* (%)					
Yes	3	3	10	5	21 (100)
Prior chemotherapy, *n* (%)					
2	2	1	4	1	8 (38)
3	0	0	2	2	4 (19)
4	0	0	2	1	3 (14)
5	0	1	0	0	1 (5)
6	1	0	1	1	3 (14)
9	0	0	1	0	1 (5)
12	0	1	0	0	1 (5)
Prior radiotherapy, *n* (%)					
Yes	0	1	3	0	4 (19)
No	3	2	7	5	17 (81)
Prior surgical therapy/cancer biopsy, *n* (%)					
Yes	3	3	10	5	21 (100)

ECOG, Eastern Cooperative Oncology Group.

RESULTS

Patient Characteristics

A total of 21 patients (median age: 61 years; range: 39–78 years) were enrolled in this study from March 2007 to March 2009. The baseline characteristics of the 21 patients are presented in Table 1. Seventeen patients had a primary diagnosis of colorectal cancer, three had a diagnosis of breast cancer and one had a diagnosis of gastric cancer. All 21 (100%) patients had an ECOG performance status of 0 or 1. All patients had received prior cancer-related surgery and chemotherapy and four had received prior radiotherapy.

Dose Escalation of Neratinib

Diarrhea and anorexia were the only reported DLTs for two (40%) patients in the 320 mg dose cohort in this study; one patient had Grade 3 diarrhea and Grade 3 anorexia, and the other patient had Grade 2 diarrhea and Grade 3 anorexia. Neratinib 240 mg was determined to be the MTD and was thus used for the expanded MTD cohort. Therefore, the 240 mg cohort was expanded to include an additional seven patients to confirm the safety and tolerability of the MTD of neratinib.

Safety

All 21 (100%) patients completed the single-dose period and then started the continual daily dose period. The median duration of treatment in the continual daily dose period was 14.9 weeks (range: 2.1–39.9 weeks). The median relative dose intensity was 1.00 for each dose level (range in 240 mg: 0.75–1.00), indicating that patients received close to the initial scheduled daily dose.

All 21 patients experienced AEs that were considered neratinib-related (Table 2). The most common neratinib-related AEs were: diarrhea (20 patients, 95%); fatigue (14, 67%); nausea and abdominal pain (9, 43%

Table 2. Neratinib-related adverse events of all grades that occurred in ≥15% of patients and of Grade ≥3 that occurred in one or more patients from screening visit until 30 days after last dose of neratinib

Adverse event	Dose cohorts, mg neratinib				
	80 ($n = 3$)	160 ($n = 3$)	240 ($n = 10$)	320 ($n = 5$)	Total ($n = 21$)
Diarrhea	2	3	10	5	20 (95)
Grade ≥3	0	1	0	1	2 (10)
Fatigue	1	3	6	4	14 (67)
Abdominal pain	1	2	4	2	9 (43)
Nausea	0	3	3	3	9 (43)
Anorexia	0	1	5	2	8 (38)
Grade ≥3	0	0	0	2	2 (10)
Aspartate aminotransferase increased	1	1	4	2	8 (38)
Grade ≥3	0	0	1	0	1 (5)
Blood alkaline phosphatase increased	0	1	6	1	8 (38)
Hemoglobin decreased	0	1	4	3	8 (38)
Alanine aminotransferase increased	1	0	4	2	7 (33)
Grade ≥3	0	0	1	0	1 (5)
Blood albumin decreased	2	1	2	2	7 (33)
Weight decreased	0	1	3	3	7 (33)
Blood triglycerides increased	1	2	2	1	6 (29)
Rash	2	0	3	1	6 (29)
Blood creatine phosphokinase increased	0	0	2	3	5 (24)
Hyperglycemia	1	0	3	1	5 (24)
Pyrexia	0	0	3	2	5 (24)
Vomiting	0	1	3	1	5 (24)
Blood creatinine increased	0	1	1	2	4 (19)
Stomatitis	1	0	2	1	4 (19)
Neutropenia	0	1	0	1	2 (10)
Grade ≥3	0	0	0	1	1 (5)
Esophageal varices	0	0	1	0	1 (5)
Grade ≥3	0	0	1	0	1 (5)

each); increased aspartate aminotransferase levels, increased blood alkaline phosphatase levels, decreased hemoglobin levels and anorexia (8, 38% each); and increased alanine aminotransferase levels, decreased blood albumin levels and decreased weight (7, 33% each). Anorexia and diarrhea were the most common Grade ≥3 neratinib-related AEs (2, 10% each; Table 2). The median onset of diarrhea was 10.0 days

Table 3. Best overall response in the evaluable population

Response	Dose cohorts, mg neratinib				
	80 ($n = 3$)	160 ($n = 3$)	240 ($n = 10$)	320 ($n = 5$)	Total ($n = 21$)
CR, *n*	0	0	0	0	0
PR, *n*	0	0	1	1	2
ORR, %	0	0	10.0	20.0	9.5
SD, *n*					
≥16 weeks	1	1	4	1	7
≥24 weeks	0	0	2	1	3
CBR, %	0	0	30.0	40.0	23.8
PD, *n*	2	2	3	2	9

CR, complete response; PR, partial response; ORR, objective response rate (CR + PR); SD, stable disease; CBR, clinical benefit rate (CR + PR + SD ≥24 weeks); PD, progressive disease.

and the median duration was 2.0 days. Even though all diarrhea AEs were considered neratinib-related, no patient had a Grade ≥4 event. Diarrhea was managed by dose interruption, dose reduction and appropriate medication and resolved in 90% of the patients. Cardiovascular AEs were reported for one patient who had an LVEF that decreased from normal at baseline to <50%. However, the decrease in LVEF was related to the patient's underlying disease of sinus bradycardia and was considered not related to neratinib therapy by the treating investigator.

Serious AEs were reported for six patients; anorexia and fatigue (two patients each); hydronephrosis, nausea, dysphagia, esophageal varices and dyspnea (one patient each). One neratinib-related serious AE, esophageal varices, was reported for a patient in the 240 mg cohort. No patient discontinued treatment and was withdrawn from this study due to an AE, and no deaths were reported during the study or within 30 days after the last dose was administered.

A total of three (14%) patients had dose reductions due to AEs; two patients in the 320 mg cohort had diarrhea and anorexia, and one patient in the 240 mg cohort had diarrhea. All AEs that led to dose reductions were considered neratinib-related.

Antitumor Activity

All 21 patients were considered evaluable for efficacy (Table 3). Two of the three patients with primary diagnoses of breast cancer had a partial response (PR). ErbB2 status was positive for one of these two patients but unknown for the other patient; both patients had received a prior trastuzumab-containing regimen. Three patients had stable disease (SD) ≥24 weeks, seven patients had SD ≥16 weeks and nine patients had PD. The ORR [complete response (CR) + PR] for all patients was 9.5% (95% CI: 1.2–30.4)

Table 4. Pharmacokinetic parameters of neratinib in Japanese patients with advanced solid tumors

Dose cohort, mg (*n*)	Parameter, mean (CV%)						
	C_{max} (ng/ml)	t_{max}[a] (h)	$t_{1/2}$ (h)	AUC[b] (ng×h/ml)	CL/F (l/h/kg)	V_z/F (l/kg)	*R*
Study day 1							
80 (3)	33.3 (43)	4.0 (2.0–8.0)	NC	NC	NC	NC	NA
160 (3)	51.4 (43)	3.9 (3.9–4.0)	11.1 (28)	638 (66)	5.8 (61)	84 (45)	NA
240 (10)	76.3 (41)	5.9 (2.0–8.0)	14.3 (19)[c]	1640 (48)[c]	3.7 (97)[c]	65 (63)[c]	NA
320 (5)	93.2 (40)	4.0 (3.9–7.9)	16.0 (13)	2290 (46)	3.0 (61)	71 (69)	NA
Study day 21							
80 (3)	41.9 (62)	4.0 (2.0–6.0)	17.6 (50)	581 (46)	2.7 (35)	76 (81)	1.5 (49)[d]
160 (3)	57.4 (80)	3.9 (2.0–4.0)	12.7 (27)	688 (79)	12.0 (129)	192 (122)	1.3 (60)
240 (10)	81.5 (56)	4.0 (2.0-7.9)	22.7 (88)[e]	1110 (59)[e]	5.4 (74)[e]	149 (74)[e]	1.2 (43)[e]
320 (3)	143.0 (34)	3.9 (0.0-5.9)	22.1 (12)[d]	2040 (10)[d]	2.5 (6)[d]	80 (18)[d]	1.3 (4)[d]

CV%, percent coefficient of variation; C_{max}, peak concentration; t_{max}, time to peak concentration; $t_{1/2}$, terminal phase elimination half-life; AUC, area under the concentration–time curve; CL/F, apparent oral dose clearance; V_z/F, apparent volume of distribution; *R*, accumulation ratio (quotient of AUC_{ss} on day 1 to AUC_{0-24h} on study day 21); NC, not calculated; NA, not applicable.
[a]t_{max} reported as median (range: minimum–maximum).
[b]Reported as AUC from time zero extrapolated to infinite time ($AUC_{0-\infty}$) for study day 1, and the steady-state AUC (AUC_{ss}) for study day 21.
[c]$n = 8$.
[d]$n = 2$.
[e]$n = 9$.

and the clinical benefit rate (CR + PR + SD ≥24 weeks) was 23.8% (95% CI: 8.2–47.2). Durations of response for the two patients with PR were 16.1 and 32.3 weeks, respectively. The median duration of SD was 16.7 weeks (95% CI: 16.3–24.1) among 10 patients with SD. The median time to progression was 16.1 weeks (95% CI: 8.4–17.0) for all patients.

Pharmacokinetics

Plasma samples for PK analyses were available for all 21 patients who received neratinib doses ranging from 80 to 320 mg. Samples collected within 5 days after dose reduction were not included in the PK analysis. The PK parameters are summarized in Table 4. Following single doses of neratinib from 80 to 320 mg on study day 1, the absorption of neratinib was relatively slow with a median t_{max} of 4–6 h and mean $t_{1/2}$ for the 160–320 mg dose cohorts ranged from 11 to 16 h (percent coefficient of variation, 13–28%). Multiple-dose exposure was 1.2- to 1.5-fold greater than single-dose exposure across the entire dose range, as assessed by the mean accumulation ratio (*R*, AUC_{ss} on study day 21 to AUC_{0-24h} on study day 1; Table 4). These results suggest that there is no major accumulation of neratinib after repeated daily administration to patients with solid tumors.

After single and multiple oral doses of neratinib, C_{max}, $AUC_{0-\infty}$ and AUC_{ss} appeared to increase with the increasing dose (Fig. 1). The power-model assessment confirmed the dose proportionality of neratinib administration. For day 1, exponents for C_{max} and $AUC_{0-\infty}$ were 0.73 and 1.28, respectively, and the corresponding 95% CIs of the exponents were 0.23–1.24 and 0.32–2.24. For day 21, the exponents for C_{max} and AUC_{ss} were 0.88 and 0.78, respectively, and the corresponding 95% CIs of the exponents were 0.03–1.73 and −0.17–1.73. For all of the parameters on days 1 and 21, the CIs contained one, suggesting that there is no lack of dose proportionality. In addition, the lack-of-fit tests for the models were not statistically significant, thus suggesting a linear relationship for C_{max}, $AUC_{0-\infty}$ and AUC_{ss} versus dose.

A comparison of our PK results in our Japanese patients versus patients in the neratinib study that was conducted in the USA (17), using our in-house data, is presented in Fig. 2. Although the variability in C_{max}, $AUC_{0-\infty}$ and AUC_{ss} is large, there is overlap of the PK exposures between the Japanese and US studies. This comparison suggests that there are no relevant differences in the PK between Japanese patients and those patients (92% white) in the US study.

DISCUSSION

In this Phase 1 study, neratinib as a single agent was administered to Japanese patients with advanced solid tumors. The reported DLTs were Grades 2 and 3 diarrhea and Grade 3 anorexia for two patients in the 320 mg dose cohorts; therefore, the MTD of neratinib for Japanese patients was determined to be 240 mg once daily. In comparison, the MTD was found to be 320 mg once daily in the Phase 1

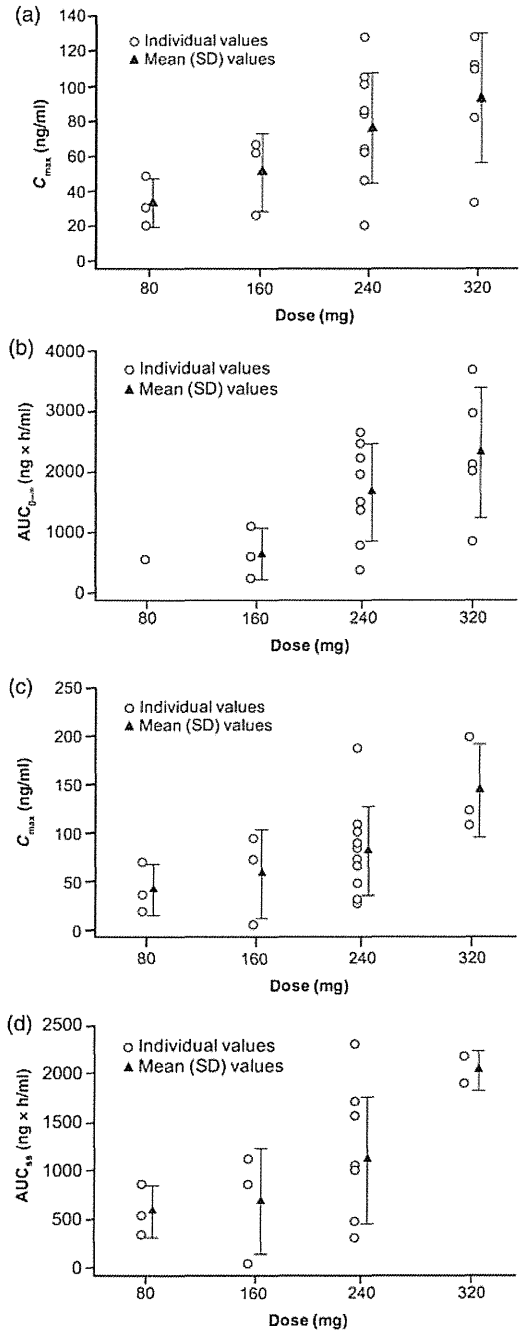

Figure 1. Individual and mean (SD) plasma neratinib exposures versus dose on study day 1 (a) C_{max} versus dose and (b) $AUC_{0-\infty}$ versus dose, and study day 21 (c) C_{max} versus dose and (d) $AUC_{0-\infty}$ versus dose. Patients with advanced solid tumors received single ascending oral doses of neratinib once daily. SD, standard deviation; C_{max}, peak concentration; $AUC_{0-\infty}$, area under the concentration–time curve from time zero extrapolated to infinite time.

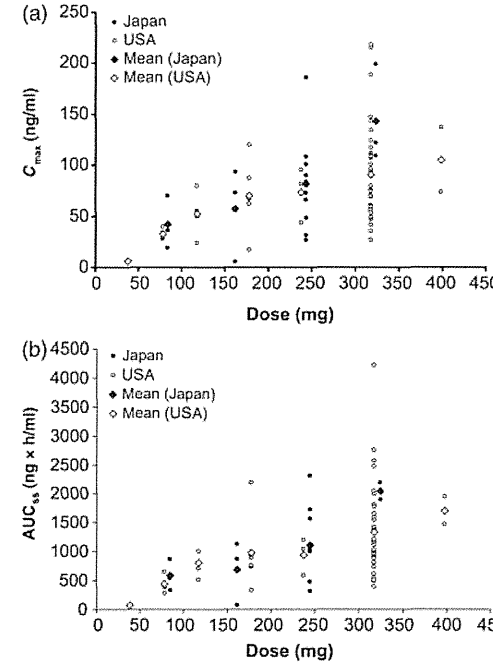

Figure 2. Comparison of neratinib exposures on study day 21: Japan versus US studies. Patients with advanced solid tumors received single ascending oral doses of neratinib once daily; (a) C_{max} versus dose and (b) AUC_{ss} versus dose. C_{max}, peak concentration; AUC_{ss}, area under the concentration–time curve at steady state.

study of neratinib that was conducted in the USA in 72 patients (92% white, 6% black or Hispanic, 1% Asian and 1% Middle Eastern) with advanced solid tumors; the DLT was Grade 3 diarrhea [1 (17%) patient in the neratinib 180 mg dose group and 5 (83%) patients in the 400 mg dose group] (17). However, due to gastrointestinal AEs, the recommended dose in ongoing Phase 3 studies is 240 mg once daily. Although diarrhea was expected in this study and was reported in 20 (95%) patients, no patients were withdrawn from the study or had a serious AE of diarrhea. Diarrhea was managed by dose interruption, dose reduction and appropriate anti-diarrhea medication.

Neratinib demonstrated promising efficacy results in Japanese patients with advanced solid tumors: PR was observed in two (10%) patients with breast cancer; three (14%) patients had SD $\geq$24 weeks and seven (33%) patients had SD $\geq$16 weeks.

PK analyses revealed that after single and multiple oral doses of neratinib, exposures (C_{max}, $AUC_{0-\infty}$ and AUC_{ss}) increased in a dose-dependent manner from 80 to 320 mg. Multiple-dose exposures were 1.2- to 1.5-fold greater than single-dose exposures across the entire dose range, thus suggesting that there was no major accumulation of neratinib after repeated daily administration of neratinib in cancer patients. The mean elimination $t_{1/2}$ on day 1 at the recommended dose of 240 mg was 14.3 h and supports a once-daily dosing regimen. Our PK data are also consistent with that reported for the US Phase 1 study of neratinib and suggest that there are no relevant differences in the PK profiles between Japanese and white patients with cancer.

This study investigated doses of neratinib from 80 to 320 mg daily. The starting dose was chosen based on information from Phase 1 study conducted in the USA (17). In the US study, diarrhea was the main DLT, with five patients in the 400 mg cohort reporting Grade 3 diarrhea. The MTD

in the US study was, therefore, established as 320 mg. In the US study, neratinib-related Grade 3 AEs were not reported at doses $\leq$80 mg. Therefore, a starting dose level of 80 mg was chosen for the current study. Based on the results of pre-clinical toxicity studies, this starting dose (80 mg/body = 48 mg/m^2 based on 1.65 m^2 human body surface area) is one-fifth of the highest non-severely toxic dosage of 45 mg/kg/day (266 mg/m^2/day, with conversion factor of 5.9), which was the highest dose used in a 4-week rat study (data on file). This dose did not elicit severe or life-threatening toxicity. This clinical dose is also supported by dosages [up to 6 mg/kg/day or 107 mg/m^2 (conversion factor of 17.9)] that did not elicit severe or life-threatening toxicity in a 4-week study in dogs (data on file).

The mean steady-state exposure of the doses at which two patients achieved PR were above the minimum efficacious dose exposure (431 ng$\times$h/ml) in nude mice. In addition, the mean steady-state exposure at the therapeutic dose of 240 mg was ~2.6-fold higher than the minimum efficacious dose exposure. However, there was no clear correlation between the dose or exposure and the severity of major AEs (i.e. diarrhea, fatigue, nausea or abdominal pain) because of the small number of patients in this study.

Irreversible inhibition of the EGFR kinase is desirable because such inhibition can occur in the presence of ATP within the cell and can only be overcome by new synthesis of EGFR. Several ATP-competitive EGFR tyrosine kinase inhibitors have been developed and investigated in clinical trials for the treatment of cancer. First-generation irreversible inhibitors include agents such as pelitinib (EKB-569). A US Phase I study showed no major antitumor responses at the MTD of pelitinib (25), although two patients in a Japanese Phase 1 study with advanced non-small cell lung cancer with EGFR mutations and acquired gefitinib resistance showed radiographic tumor regression (26). However, as pelitinib showed limited activity in Her2-dependent tumor models, the development of irreversible inhibitors with improved activity toward Her2-expressing tumors continued (16). It was discovered that attaching a large lipophilic group to the molecule resulted in improved potency for Her2 kinase inhibition (16). Thus, the structure of the second-generation irreversible pan-Her inhibitor neratinib is similar to the structure of pelitinib, but with this different aniline headpiece. The binding model for neratinib at the ATP site of Her2 indicates that the aniline portion of the molecule fits into a long lipophilic pocket. The nature and placement of these groups most likely gives neratinib its improved Her2 activity compared with pelitinib.

In conclusion, the MTD of oral neratinib was determined to be 240 mg once daily in Japanese patients with advanced solid tumors. Neratinib 240 mg was safe and well tolerated, and demonstrated encouraging antitumor activity in this patient population. We therefore recommend that this dose is used for subsequent studies in Japanese patients. The results of this Phase 1 study are consistent with those observed in white patients and warrant further investigation of neratinib in Japanese patients with solid tumors.

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Conflict of interest statement

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ORIGINAL ARTICLE

Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2

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Abstract
Background The addition of mTOR inhibitor everolimus (EVE) to exemestane (EXE) was evaluated in an international, phase 3 study (BOLERO-2) in patients with hormone-receptor-positive (HR^+) breast cancer refractory to letrozole or anastrozole. The safety and efficacy of anticancer treatments may be influenced by ethnicity (Sekine et al. in Br J Cancer 99:1757–62, 2008). Safety and efficacy results from Asian versus non-Asian patients in BOLERO-2 are reported.

Methods Patients were randomized (2:1) to 10 mg/day EVE + EXE or placebo (PBO) + EXE. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, response rate, clinical benefit rate, and safety.

Results Of 143 Asian patients, 98 received EVE + EXE and 45 received PBO + EXE. Treatment with EVE + EXE significantly improved median PFS versus PBO + EXE among Asian patients by 38 % (HR = 0.62; 95 % CI, 0.41–0.94). Median PFS was also improved among non-Asian patients by 59 % (HR = 0.41; 95 % CI, 0.33–0.50). Median PFS duration among EVE-treated Asian patients was 8.48 versus 4.14 months for PBO + EXE, and 7.33 versus 2.83 months, respectively, in non-Asian patients. The most common grade 3/4 adverse

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events (stomatitis, anemia, elevated liver enzymes, hyperglycemia, and dyspnea) occurred at similar frequencies in Asian and non-Asian patients. Grade 1/2 interstitial lung disease occurred more frequently in Asian patients. Quality of life was similar between treatment arms in Asian patients.

Conclusion Adding EVE to EXE provided substantial clinical benefit in both Asian and non-Asian patients with similar safety profiles. This combination represents an improvement in the management of postmenopausal women with $HR^+/HER2^-$ advanced breast cancer progressing on nonsteroidal aromatase inhibitors, regardless of ethnicity.

Keywords Advanced breast cancer · Endocrine resistance · Everolimus · Exemestane · Progression-free survival

Introduction

Worldwide, breast cancer is the most common malignancy in women and one of the leading causes of cancer deaths [1–3]. Incidence of breast cancer in Asia is increasing [3]. In Asia, as in Western countries, treatment approaches for breast cancer typically follow National Comprehensive Cancer Network [4] and St. Gallen guidelines. For postmenopausal patients with hormone-receptor-positive (HR^+) advanced breast cancer, aromatase inhibitors (steroidal or nonsteroidal) are the standard initial treatment [4]. Even so, most patients are unresponsive to initial treatment or acquire resistance. Other treatment options include estrogen receptor (ER) antagonists (e.g., tamoxifen) and ER downregulators (e.g., fulvestrant). These treatment options provide limited clinical benefit once endocrine resistance develops (especially after aromatase inhibitor therapy), and survival is poor [5]. New treatment options that can offer patients with advanced breast cancer the hope of overcoming resistance and that can prolong the time of effectiveness of endocrine therapy and delay chemotherapy are needed.

Hyperactivation of the mammalian target of rapamycin (mTOR) pathway is associated with breast cancer progression and with the development of endocrine resistance [6]. Aberrations in phosphatidylinositol 3-kinase (PI3K)/mTOR pathway protein expression are also associated with poor prognosis in HR^+ breast cancer [7]. However, in vitro and in vivo data indicate that mTOR inhibitors can inhibit cell proliferation and restore sensitivity to fulvestrant, letrozole, and tamoxifen [8–11].

Everolimus (Afinitor®, Novartis) is an orally active mTOR inhibitor. It is approved for the treatment of patients with progressive neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, and subependymal giant cell astrocytoma associated with tuberous sclerosis [12]. Recently, everolimus (EVE) was also approved in combination with exemestane (EXE) for use in the USA and the 27 European Union member states, plus Iceland and Norway, and in Mexico, Argentina, and other Latin American countries, for the treatment of postmenopausal patients with HR^+ breast cancer whose disease has progressed during or after nonsteroidal aromatase inhibitor therapy. This approval was based on outcomes from BOLERO-2. In this phase 3 study, EVE + EXE improved progression-free survival (PFS) compared with EXE + placebo (PBO; median PFS = 7.8 months vs 3.2 months, respectively; hazard ratio [HR] = 0.45; $P < 0.0001$) [12].

Variations in the pharmacodynamics and pharmacokinetics of anticancer agents can be attributed in part to ethnic differences, potentially resulting in alterations of their safety and efficacy profiles [13]. In fact, some studies of targeted therapies have shown that variability in safety and efficacy is associated with patient ethnicity [14]. To ensure an optimal treatment response is balanced with a manageable safety profile, the potential inter-ethnic differences in anticancer drug effects should be considered [13]. Treatment for lung cancer using the epidermal growth factor inhibitor gefitinib, for example, is more effective in Asian patients than in patients of other ethnicities [15].

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The incidence of interstitial lung disease (ILD) is also more prevalent in Asian patients treated with gefitinib monotherapy than in those of other ethnicities [15]. ILD is one of the relatively common, serious adverse events (AEs) associated with molecular targeted anticancer therapies, and treatment with EVE has been associated with ILD [16, 17]. Thus, it is important to compare the frequency of AEs, including ILD, induced by EVE in both Asian and non-Asian patients.

To determine whether patient ethnicity has an effect on the efficacy and safety of EVE + EXE, we performed an analysis in Asian versus non-Asian patients with HR^+ advanced breast cancer in BOLERO-2 after a median follow-up of 18 months.

Patients and methods

The BOLERO-2 study is an international, phase 3, multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov identifier NCT00863655). The protocol and results for the entire study have been reported [16, 18]. Post hoc analyses of the data from Asian patients (who selected Asian as their race at randomization) and non-Asian patients included in BOLERO-2 are reported herein.

Patients

Patients were postmenopausal women with metastatic or locally advanced, estrogen receptor-positive (ER^+) human epidermal growth factor receptor-2 nonamplified ($HER2^-$) breast cancer that had recurred or progressed during or after letrozole or anastrozole therapy as described previously [16]. This study was conducted in accordance with the Declaration of Helsinki, in agreement with the institutional review board at each participating center, in accordance with Good Clinical Practice and applicable local regulations. Every patient provided written informed consent.

Study design

Patients were randomized (2:1) to EVE (10 mg/day) + EXE (25 mg/day) or PBO + EXE (25 mg/day). Randomization was stratified according to sensitivity to endocrine therapy and the presence of visceral metastasis. Treatment continued until disease progression, intolerable toxicity, or withdrawal of consent. During the study, dose reductions or interruptions were allowed to manage AEs. Crossover from the PBO arm to the EVE arm was not allowed.

Study endpoints

The primary endpoint was PFS, defined as the time from randomization to the first documentation of disease progression (as assessed by the local investigator according to Response Evaluation Criteria in Solid Tumors [RECIST] [19] or, in the case of nonmeasurable disease, unequivocal progression or appearance of new lesions) or death from any cause. The key secondary endpoint was overall survival. Other secondary endpoints included overall response rate (ORR), clinical benefit rate (CBR), and time to overall response and duration of overall response according to RECIST [19].

Efficacy and safety assessments

An independent data monitoring committee (IDMC) was responsible for monitoring safety and pharmacokinetic data as well as reviewing efficacy results at the interim and final analyses. Tumor evaluation based on computed tomography or magnetic resonance imaging was performed at baseline (within 6 weeks before randomization) and every 6 weeks thereafter until disease progression and initiation of further anticancer therapy. Objective tumor response and disease progression were assessed per RECIST version 1.0 [19]. AEs were assessed at each study visit and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [20].

Patient-reported outcomes

Quality of life (QOL) was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30; Version 3.0, 2001), a reliable and valid questionnaire developed to assess the quality of life of cancer patients [21, 22]. This self-administered questionnaire is composed of 30 items arranged into a number of functional and symptom subscales as well as a global health status (GHS)/global QOL subscale, which was the primary QOL variable of interest for BOLERO-2.

Statistical analyses

Progression-free survival was based on the intent-to-treat analysis, according to the randomized treatment group and stratification. Distribution of PFS was estimated using the Kaplan–Meier method, and the HRs and corresponding 95 % confidence intervals (CIs) were estimated using the Cox proportional hazard model. In addition, the protocol-specified time to definitive deterioration (TTD) in the EORTC QLQ-C30 GHS score (defined as a 5 % decrease in QOL relative to baseline, with no subsequent increase above this threshold) was calculated in the Asian subset using Kaplan–Meier estimates and was described using medians and 95 % CIs. The TTD was compared between EVE + EXE and PBO + EXE using a log-rank test.

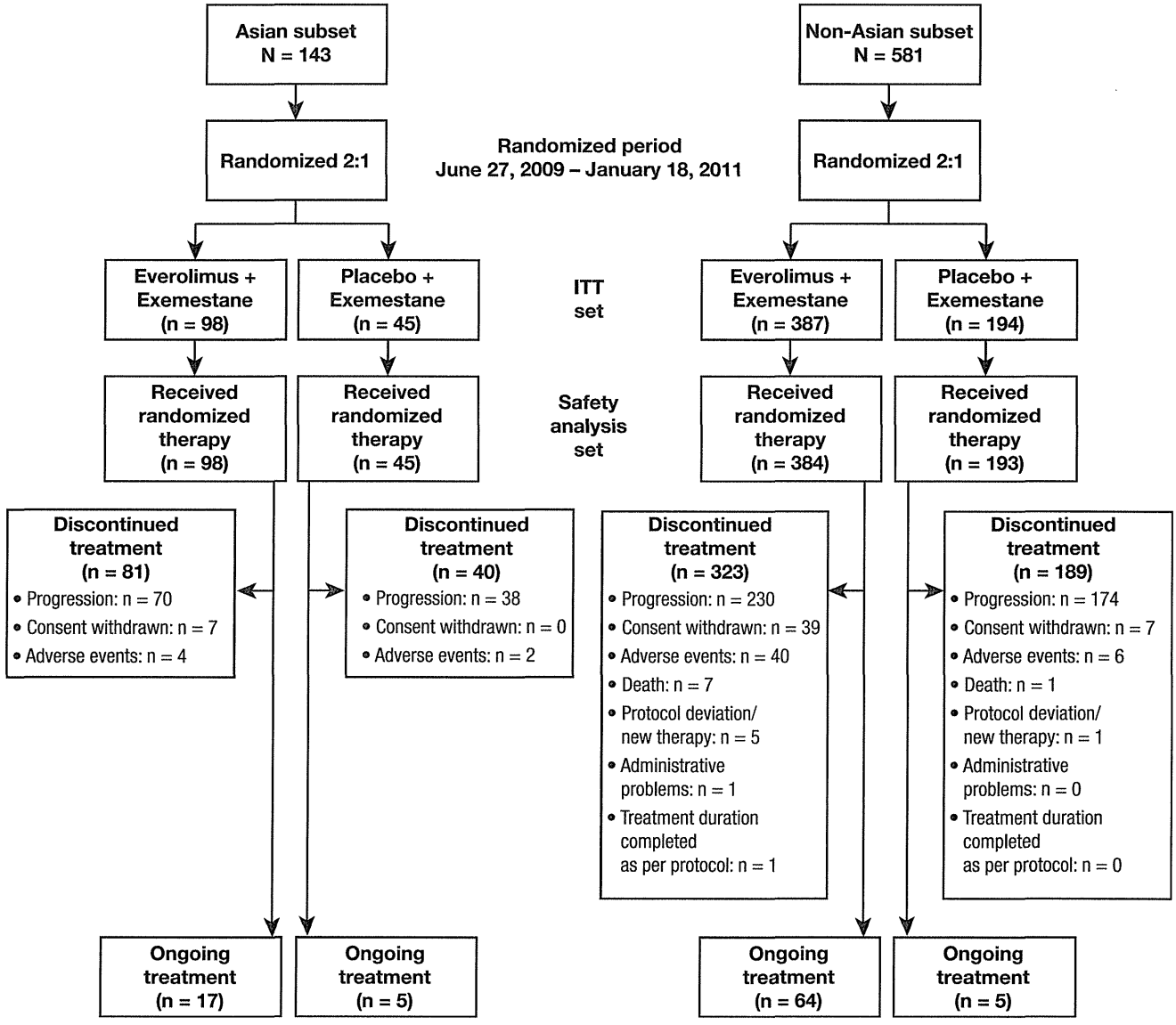

Fig. 1 CONSORT flowchart. *ITT* intention-to-treat. Ongoing treatment refers to those patients at time of cutoff for this analysis. Note that disease progression events in this figure are those that resulted in treatment discontinuation

Results

Patient characteristics

Median follow-up was 18 months at the time of this analysis (cutoff date 15 December 2011). Of the 724 patients in BOLERO-2, 143 were Asian, with 106 (74.1 %) of Japanese origin. There were 98 Asian patients in the EVE + EXE arm and 45 in the PBO + EXE arm (Fig. 1).

Patient and disease characteristics at baseline among the Asian and non-Asian patients were generally comparable, although the Asian patients were younger and a greater proportion had good performance status (Table 1). Among the Asian population, there were more patients in the EVE + EXE arm who had at least 3 sites of metastases compared with the PBO + EXE arm. In the PBO + EXE arm, Asian patients had less visceral disease than non-Asian patients. Prior treatments at study entry were mostly similar between Asian and non-Asian patients. However, more non-Asian patients in the EVE + EXE arm received chemotherapy in the metastatic setting than Asian patients (Table 1).

The median durations of exposure to treatment were longer in Asian patients than in non-Asian patients. Among Asian patients, median exposure to EVE was 27.6 weeks, whereas median exposure to EXE was 32.6 weeks in the EVE + EXE arm and 18.0 weeks in the PBO + EXE arm. Among non-Asian patients, median exposure to EVE was 23.7 weeks; median exposure to EXE was 28.1 weeks in the EVE + EXE arm and 13.9 weeks in the PBO + EXE arm (Table 2).

Table 1 Demographics of Asian versus Non-Asian population

Baseline demographics	Asian		Non-Asian	
	Everolimus + exemestane ($n = 98$)	Placebo + exemestane ($n = 45$)	Everolimus + exemestane ($n = 387$)	Placebo + exemestane ($n = 194$)
Age, years				
Mean (SD)	59.9 (7.2)	58.6 (8.2)	63.1 (10.9)	61.8 (10.0)
Median (range)	59.5 (40.0–79.0)	60.0 (28.0–72.0)	63.0 (34.0–93.0)	61.0 (38.0–90.0)
Age group, %				
<65 years	77.6	82.2	55.3	62.9
≥65 years	22.4	17.8	44.7	37.1
Ethnicity, %				
Chinese	5.1	0	0	0
Japanese	72.4	77.8	0	0
Mixed	1.0	0	2.1	3.1
Hispanic/Latino	0	0	7.2	5.2
Indian (subcontinent)	0	0	0.3	0
Other	21.4	22.2	90.4	91.8
Number of metastatic sites, %[a]				
1	33.7	33.3	31.5	25.3
2	22.4	33.3	32.6	35.6
≥3	42.8	33.3	35.7	39.2
ECOG performance status, %				
0	82.7	86.7	54.8	53.1
1	15.3	13.3	41.1	40.2
2	0	0	2.3	3.6
Time between initial diagnosis and 1st recurrence/metastasis, %				
<3 months	13.3	11.1	22.2	20.1
3 to <6 months	0	0	1.3	2.6
≥6 months	80.6	80.0	69.3	71.6
Missing	6.1	8.9	7.2	5.7
Metastatic cancer sites, %				
CNS[b]	2.0	0	1.0	0
Visceral (excluding CNS)[c]	59.2	53.3	58.1	60.8
Lung	34.7	31.1	28.2	33.5
Liver	31.6	22.2	33.9	32.5
Lung and liver	9.2	4.4	9.0	12.4
Bone	69.4	51.1	78.3	83.5
Bone only	20.4	11.1	22.0	21.1
Other	56.1	73.3	49.1	53.6
Previous chemotherapy, %				
Adjuvant/neoadjuvant only	60.2	48.9	39.5	37.6
Metastatic only	6.1	11.1	15.8	9.3
Both	10.2	15.6	12.4	16.0
Number of previous chemotherapy lines in advanced setting, %				
1	16.3	26.7	28.2	23.7
2	0	0	0	0

Data from 15 December 2011 safety update cutpoint

CNS central nervous system, *ECOG* Eastern Cooperative Oncology Group, *SD* standard deviation

[a] One patient each in the Asian and non-Asian subgroups had missing information

[b] CNS includes spinal cord, brain and meninges

[c] Visceral includes lung, liver, pleural, pleural effusions, peritoneum, and ascites

The percentages of patients who required EVE dose reductions or interruptions were similar between the Asian and non-Asian patients (71.4 vs. 65.6 %), as were the percentages of Asian and non-Asian patients who required EXE dose reductions or interruptions while receiving EVE + EXE (22.4 vs. 24.2 %), respectively. In contrast, Asian patients receiving PBO + EXE required more EXE dose reductions or interruptions than non-Asian patients (26.7 vs. 8.3 %), respectively. Most of these dose reductions or interruptions were the result of an AE (data not shown). At the time of cutoff, 15.4 % of Asian patients and 11.9 % of non-Asian patients were ongoing with study treatment (Fig. 1). Among Asian patients, 82.7 % discontinued EVE + EXE treatment and 88.9 % discontinued PBO + EXE treatment, whereas 83.5 and 97.4 % of non-Asian patients discontinued EVE + EXE and PBO + EXE treatment, respectively (Fig. 1). Most of the patients who discontinued treatment did so because of disease progression.

Efficacy

The combination of EVE and EXE reduced the risk of disease progression by 38 % among Asian patients compared with PBO + EXE (HR = 0.62; 95 % CI, 0.41–0.94; Fig. 2). At the cutoff date, 17.3 % of Asian patients in the EVE + EXE arm and 11.1 % of patients in the PBO + EXE arm were progression free and remained on treatment, whereas 71.4 % of Asian patients in the EVE + EXE arm and 84.4 % of patients in the PBO + EXE arm had disease progression (Fig. 1). Median PFS per local investigator assessment among Asian patients in BOLERO-2 was 8.48 months for EVE + EXE versus 4.14 months for PBO + EXE (Fig. 2).

Japanese patients comprised the largest subset within the Asian subgroup, and nearly 15 % of the overall BOLERO-2 patient population. Therefore, additional analyses specific to the Japanese subset were feasible, and indicated that treatment with EVE + EXE significantly improved median PFS versus PBO + EXE by 42 % (HR = 0.58) in these patients. The median PFS results also favored the combination of everolimus and exemestane in European and North American patients (Fig. 3).

There were no complete responses (CRs) recorded for either the EVE + EXE or the PBO + EXE arm. No partial responses (PRs) were observed with PBO + EXE in the Asian subset, compared with 19 PRs (19.4 %) in the EVE + EXE arm based on local investigator assessment. Overall, Asian patients had greater CBR and ORR in the EVE + EXE arm than in the PBO + EXE arm (CBR, 58.2 vs. 28.9 %; ORR, 19.4 % vs. 0, respectively; Table 3).

For non-Asian patients, the median PFS per investigator assessment in the 2 arms was 7.33 months and 2.83 months, respectively (HR = 0.41; 95 % CI, 0.33–0.50; Table 3, Fig. 2). Based on local investigator assessment, there were 3 CRs and 39 PRs (10.1 %) among non-Asian patients in the EVE + EXE arm versus no CRs and 4 PRs in the PBO + EXE arm. The CBR and ORR for non-Asian patients were 49.6 and 10.9 % in the combination arm versus 25.8 and 2.1 % in the PBO + EXE arm, respectively (Table 3).

Safety

Across the entire study, the most common treatment-emergent AEs in the EVE + EXE arm included stomatitis and rash; these were also the most common AEs among both Asian and non-Asian patients (Table 4) [15]. Some AEs were reported in a higher percentage of Asian patients compared with the non-Asian patients. These included stomatitis, rash, dysgeusia, pneumonitis, nail disorder, increased LDH, nasopharyngitis, and ILD. Specifically, the rates of grade 1 and 2 dysgeusia were higher in Asian versus non-Asian patients in the EVE + EXE arm (30.6 vs. 19.8 %) but comparable in the PBO + EXE arm (6.7 vs. 5.7 %). The incidence of nasopharyngitis was similar across treatment arms, but much higher in Asian than non-Asian patients in both the EVE + EXE (22.4 vs. 7.0 %) and PBO + EXE (20.0 vs. 6.2 %) arms; all events were grades 1 or 2 (Table 4). Pneumonitis, which was reported only in the EVE + EXE arm, was higher in Asian patients than in non-Asian patients in the EVE + EXE arm (23.5 vs. 14.1 %, respectively). However, the frequency of grade 3 and 4 pneumonitis was

Table 2 Duration of exposure to study treatment

	Asian patients				Non-Asian patients			
	Everolimus + exemestane (n = 98)		Placebo + exemestane (n = 45)		Everolimus + exemestane (n = 384)		Placebo + exemestane (n = 193)	
	Everolimus	Exemestane	Placebo	Exemestane	Everolimus	Exemestane	Placebo	Exemestane
Duration (weeks)								
Median	27.6	32.6	18.0	18.0	23.7	28.1	13.1	13.9
Range	2.0–123.3	2.0–123.3	2.0–101.0	4.0–101.0	1.0–109.4	1.0–109.4	1.0–82.0	1.0–82.0

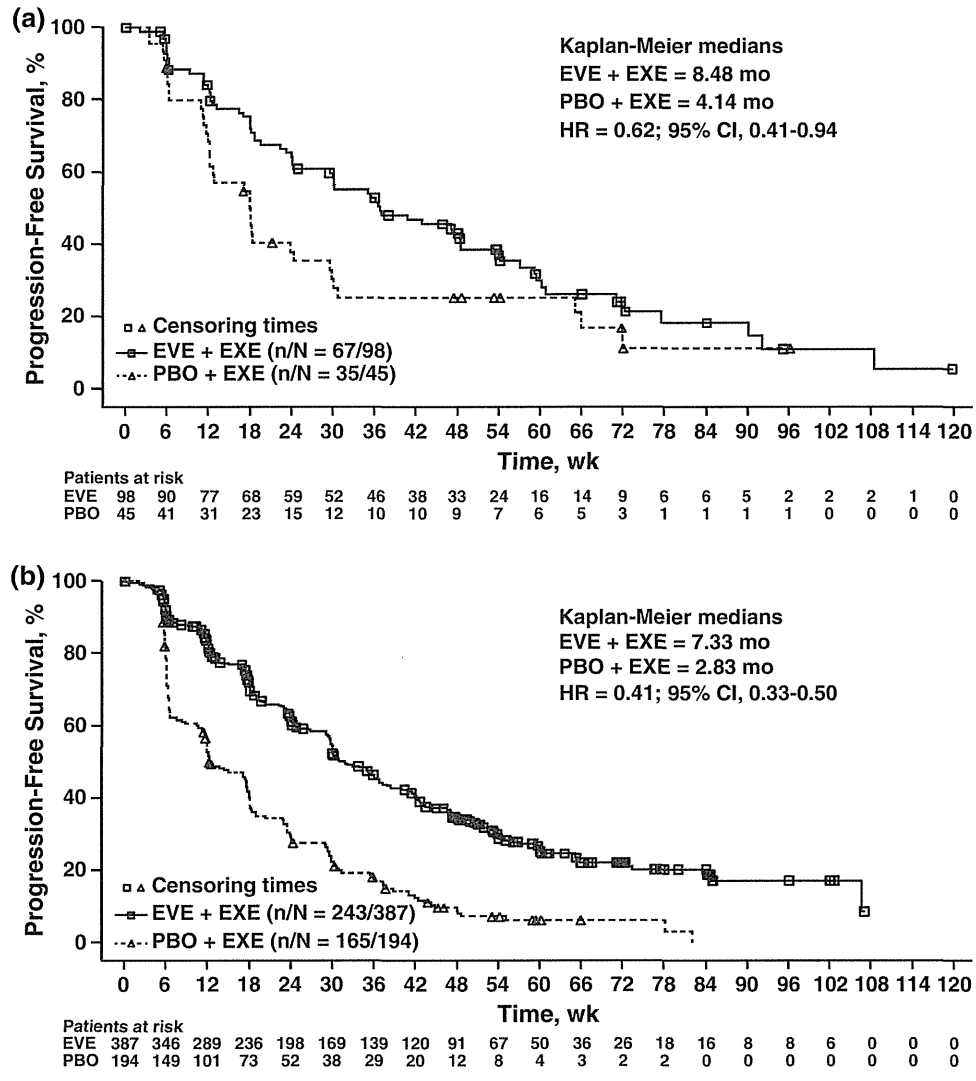

Fig. 2 Kaplan–Meier analyses of progression-free survival in **a** Asian and **b** non-Asian patients with advanced breast cancer. *CI* confidence interval, *EVE* everolimus, *EXE* exemestane, *HR* hazard ratio, *PBO* placebo

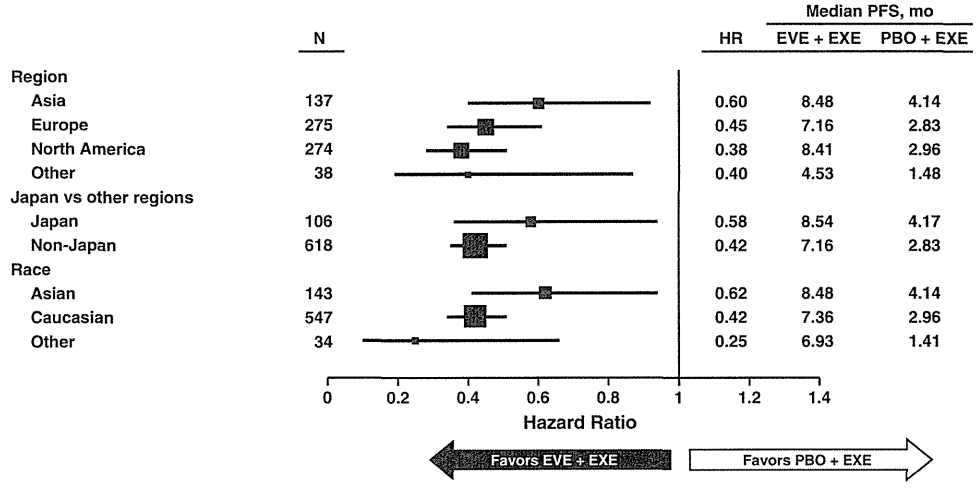

Fig. 3 Forest plot of progression-free survival subgroup analysis by region and ethnicity. Subsets were prespecified in the analysis plan. Data from 18-months' median follow-up. *EVE* everolimus, *EXE* exemestane, *HR* hazard ratio, *PBO* placebo, *PFS* progression-free survival

lower in Asian patients compared with non-Asian patients (2.0 vs. 3.6 %, respectively). In contrast, hot flushes were comparable in incidence between Asian and non-Asian patients. They were, however, less frequent in Asian and non-Asian patients in the EVE + EXE arm (6.1 and 5.5 %) than in the PBO + EXE arm (13.3 and 14.5 %) (Table 4).

Table 3 Best response

	Asian		Non-Asian	
	Everolimus + exemestane ($n = 98$)	Placebo + exemestane ($n = 45$)	Everolimus + exemestane ($n = 387$)	Placebo + exemestane ($n = 194$)
Best overall response, %				
Complete	0	0	<1	0
Partial	19	0	10	2
Stable disease	66	78	73	55
Progressive disease	11	20	10	36
Unknown	3	2	7	8
Objective response rate, %[a]	19	0	11	2
Clinical benefit rate, %[b]	58	29	50	26

[a] Complete and partial responses

[b] Complete and partial responses plus stable disease ≥24 weeks

Notably, the incidence of grade 3 and 4 AEs among patients who received EVE + EXE was generally similar or lower in Asian patients compared with non-Asian patients (Table 4). The only exceptions were increased aspartate aminotransferase (AST) levels and cough. The most common grade 3 and 4 AEs (≥5 %) for both Asian and non-Asian patients in the EVE + EXE treatment group included stomatitis (8.2 vs. 7.8 %), anemia (7.1 vs. 7.6 %), increased AST levels (6.1 vs. 2.9 %), hyperglycemia (4.1 vs. 6.0 %), and dyspnea (3.1 vs. 5.7 %), respectively. There were very few grade 4 AEs reported, regardless of treatment arm or ethnicity subset, and none were reported in at least 5 % of the patients studied (Table 4).

Quality of life in Asian patients

Treatment with EVE + EXE did not affect TTD in EORTC QLQ-C30 GHS compared with PBO + EXE in Asian patients. At the protocol-defined threshold of 5 % decrease from baseline, the median TTD was 8.4 months (95 % CI, 6.9–11.1 months) in the EVE + EXE arm compared with 5.6 months (95 % CI, 2.9–15.2 months) in the PBO + EXE arm (HR = 0.79; 97.5 % CI, 0.44–1.44; Fig. 4).

Discussion

Although women with HR^+ breast cancer often respond to multiple lines of endocrine therapy, most ultimately progress. When patients with HR^+ advanced breast cancer progress despite nonsteroidal aromatase inhibitors, the current treatment paradigm includes EXE followed by tamoxifen, toremifene, or fulvestrant [4]. This paradigm is followed in Asia as well as in Western countries. Once patients progress on initial endocrine therapy, the available treatment options offer limited clinical benefit and poor survival [5]. New treatment options are needed that can offer patients with advanced breast cancer the hope of overcoming resistance, prolong the time for which endocrine therapy is effective, and delay chemotherapy.

In the phase 3 BOLERO-2 study, the addition of EVE to EXE increased median PFS by 4.6 months [12]. These results suggest that inhibition of cross-talk pathways (PI3K/mTOR) may help improve outcomes in this patient population. Nearly 20 % of the 724 patients in this study were Asian, providing an opportunity to determine the efficacy and safety of EVE in this important subgroup.

Ethnic differences can account for variations in both the pharmacokinetics and pharmacodynamics of anticancer agents, potentially resulting in alterations of the safety and efficacy profiles of these agents [13]. For example, docetaxel, like gefitinib [15], has demonstrated enhanced efficacy in Asian versus Caucasian patients [13]. This was accompanied, however, by higher incidence of febrile neutropenia requiring hospitalization [13]. CYP2D6 genetic polymorphisms have been shown to affect the conversion of tamoxifen to its most active metabolite, endoxifen. As a result, the efficacy of tamoxifen might vary according to the distribution of these genetic polymorphisms among various ethnic populations [13]. The distribution of genetic polymorphisms affecting CYP2D6 activity is different between Asian and non-Asian patients. Thus, it is hypothesized that the efficacy of tamoxifen may also be different between these patient populations [13]. To ensure optimal treatment response and understand the safety profile, it is important to consider the potential inter-ethnic differences in anticancer drug effects [13].

We have demonstrated in this report that the efficacy of EVE is consistent between the Asian and non-Asian subgroups. Combining EVE with EXE more than doubled the median PFS versus EXE with PBO, from 4.14 to 8.48 months for Asians and from 2.83 to 7.33 months for