VOLUME 26 · NUMBER 34 · DECEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III, Double-Blind, Randomized Study Comparing Lapatinib Plus Paclitaxel With Placebo Plus Paclitaxel As First-Line Treatment for Metastatic Breast Cancer

Angelo Di Leo, Henry L. Gomez, Zeba Aziz, Zanete Zvirbule, Jose Bines, Michael C. Arbushites, Stephanie F. Guerrera, Maria Koehler, Cristina Oliva, Steven H. Stein, Lisa S. Williams, Judy Dering, Richard S. Finn, and Michael F. Press

From the "Sandro Pitigliani" Medical Oncology Unit, Prato, Italy; Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru; Allama Iqbal Medical College, Lahore, Pakistan; Riga Eastern University Hospital Latvian Oncology Centre, Rīga, Latvia; National Cancer Institute, Rio De Janeiro, Brazil; Medicine Development Center Oncology, GlaxoSmithKline, Collegeville, PA; Geffen School of Medicine at University of California, Los Angeles; and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA.

Submitted January 17, 2008; accepted July 23, 2008; published online ahead of print at www.jco.org on October 27, 2008.

Supported by GlaxoSmithKline. R.S.F. is a recipient of a National Institutes of Health Loan Repayment Program award.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Angelo Di Leo, MD, "Sandro Pitigliani" Medical Oncology Unit, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy 59100; e-mail: adileo@usl4.toscana.it.

0732-183X/08/2634-5544/$20.00

DOI: 10.1200/JCO.2008.16.2578

ABSTRACT

Purpose
Lapatinib, a dual tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR/ErbB1) and human epidermal growth factor receptor 2 (HER-2/ErbB2), is effective against HER-2–positive locally advanced or metastatic breast cancer (MBC). This phase III trial evaluated the efficacy of lapatinib in HER-2–negative and HER-2–uncharacterized MBC.

Patients and Methods
Women with MBC were randomly assigned to first-line therapy with paclitaxel 175 mg/m^2 every 3 weeks plus lapatinib 1,500 mg/d or placebo. A preplanned retrospective evaluation of HER-2 status was performed using fluorescence in situ hybridization and immunohistochemistry. The primary end point was time to progression (TTP); secondary end points were objective response rate (ORR), clinical benefit rate (CBR), event-free survival (EFS), and overall survival (OS).

Results
In the intent-to-treat population (n = 579), there were no significant differences in TTP, EFS, or OS between treatment arms, although differences in ORR and CBR were noted. In 86 HER-2–positive patients (15%), treatment with paclitaxel-lapatinib resulted in statistically significant improvements in TTP, EFS, ORR, and CBR compared with paclitaxel-placebo. No differences between treatment groups were observed for any end point in HER-2–negative patients. The most common adverse events were alopecia, rash, and diarrhea. The incidence of diarrhea and rash was significantly higher in the paclitaxel-lapatinib arm. The rate of cardiac events was low, and no difference was observed between treatment arms.

Conclusion
Patients with HER-2–negative or HER-2–untested MBC did not benefit from the addition of lapatinib to paclitaxel. However, first-line therapy with paclitaxel-lapatinib significantly improved clinical outcomes in HER-2–positive patients. Prospective evaluation of the efficacy and safety of this combination is ongoing in early and metastatic HER-2–positive breast cancer patients.

J Clin Oncol 26:5544-5552. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Aberrant activation of the human epidermal growth factor receptor (EGFR) family has been implicated in the development of metastatic breast cancer (MBC).[1] Lapatinib, an oral, small-molecule dual inhibitor of EGFR (ErbB1) and human epidermal growth factor receptor 2 (HER-2/ErbB2), demonstrated clinical activity in HER-2–positive MBC patients who previously received trastuzumab.[2] A 24% response rate was reported when therapy-naive HER-2–positive MBC patients received lapatinib monotherapy.[3] In a phase III trial in HER-2–positive MBC patients, lapatinib plus capecitabine was superior regarding time to progression (TTP) versus capecitabine alone.[4] This benefit was achieved without serious toxicities or symptomatic cardiac events, leading to the approval of lapatinib plus capecitabine for the treatment of patients with HER-2–positive MBC who were previously exposed to trastuzumab-based therapy.

Biologic rationale and clinical evidence exist to support the use of dual EGFR/HER-2–targeted agents in HER-2–positive MBC; there may be also rationale to support the potential activity of these agents in patients with breast tumors lacking HER-2 amplification. EGFR/HER-2 expression in MBC is a poor prognostic factor, and several studies suggest a

role for EGFR tyrosine kinase inhibitors in solid tumors, including MBC.[5-7] Cross-talk between different HER family receptors is associated with resistance to HER-2–targeted therapy.[8,9] This study was designed to compare the efficacy and tolerability of first-line therapy with lapatinib plus paclitaxel versus paclitaxel plus placebo in patients with MBC who were negative or untested for HER-2 overexpression.

PATIENTS AND METHODS

Patients

Women ≥ 18 years old with histologically confirmed stage III or IV breast cancer that was negative (0 or 1+ by immunohistochemistry [IHC] or fluorescence in situ hybridization [FISH] negative) or untested for HER-2 and previously untreated in the metastatic setting were eligible. Because enrollment occurred in countries where routine HER-2 testing was not common practice, it was expected that a proportion of patients would be HER-2 positive. Previous neoadjuvant/adjuvant treatment with anthracyclines and/or taxanes was permitted (cumulative doses of doxorubicin, epirubicin, and mitoxantrone < 360, 720, and 72 mg/m^2, respectively), and a disease-free interval of more than 6 months was required between the completion of taxane-based therapy and disease relapse. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 1, measurable disease per Response Evaluation Criteria in Solid Tumors or assessable disease, adequate organ function, and a cardiac ejection fraction within institutional normal range. Patients with a history of CNS metastases, uncontrolled angina, arrhythmias, congestive heart failure, or persistent peripheral neuropathy ≥ grade 2 were excluded. The institutional review board for each participating institution approved the study protocol. All patients provided written informed consent.

Study Design

This study (EGF30001) was a phase III, randomized, multicenter, double-blind, placebo-controlled trial of lapatinib and paclitaxel as first-line therapy for MBC. Patients were stratified by stage and sites of metastatic disease and randomly assigned to either oral lapatinib (1,500 mg/d once daily) with paclitaxel (175 mg/m^2 intravenously over 3 hours on day 1, every 3 weeks) or paclitaxel plus placebo once daily. Patients received therapy (paclitaxel for up to six cycles) until disease progression, withdrawal as a result of toxicity, or withdrawal of consent. Efficacy assessments were performed 9 weeks after study entry, at 12-week intervals, and at treatment end. Patients were observed for survival at 12-week intervals.

Study End Points

The primary end point was TTP. Secondary end points were objective response rate (ORR; complete or partial response confirmed ≥ 4 weeks from first response), clinical benefit rate (CBR; confirmed complete and partial response or stable disease for ≥ 24 weeks), duration of response, event-free survival (EFS), overall survival (OS), and safety.

Assessment of Adverse Events

Echocardiograms or multiple-gated acquisition scans were performed every 9 weeks. A cardiac event was defined as a symptomatic decline in left ventricular ejection fraction (LVEF) or, if asymptomatic, a ≥ 20% decrease in LVEF relative to baseline that was less than the institution's lower limit of normal. Lapatinib was discontinued in patients with symptomatic LVEF decreases. Patients with asymptomatic LVEF decreases continued therapy and had a repeat evaluation within 2 weeks. If the abnormal LVEF decrease was confirmed, lapatinib therapy was temporarily discontinued (paclitaxel treatment continued). Dose delays of less than 2 weeks and/or dose reductions were allowed for hematologic or nonhematologic (excluding cardiac) toxicities.

HER-2 Centralized Testing

Retrospective, blinded, centralized testing of all available tissue samples for HER-2 status was performed at the University of Southern California Norris Comprehensive Cancer Center (Los Angeles, CA). Using archived, paraffin-embedded breast cancer tissue, *HER2* gene amplification status was analyzed by PathVision FISH (Abbott Laboratories, Abbott Park, IL), and HER-2 protein expression status was analyzed by Dako HercepTest IHC (Dako, Carpinteria, CA).[10-12] Immunostaining was scored as 0, 1+, 2+, and 3+. The HER-2–positive population included women who were FISH positive or IHC 3+ if FISH status was unknown. The HER-2–negative population included women who were FISH nonamplified, regardless of IHC status.

Statistical Analyses

The study enrolled 580 patients to achieve 374 disease progression or death events, providing the study with 90% power (two-sided $\alpha = .05$) to detect a hazard ratio (HR) of 0.714, which corresponds to a 40% increase in median TTP in the paclitaxel-lapatinib group versus the paclitaxel-placebo group (8.4 *v* 6.0 months, respectively). The primary population was the intent-to-treat (ITT) population, which was defined as all randomly assigned patients who received ≥ one dose of study medication. Key efficacy analyses were repeated in the retrospectively defined HER-2–positive and HER-2–negative populations.

Analysis of efficacy was based on investigator evaluation of response/progression according to Response Evaluation Criteria in Solid Tumors. Confirmatory analyses were performed by independent review. The primary end point, TTP, was defined as the time from random assignment until disease progression or death resulting from breast cancer. Median TTP was calculated from cumulative incidence curves to account for competing risks methodology, where non–breast cancer deaths were considered competing risks. EFS was defined as time from random assignment until disease progression or any death. Kaplan-Meier curves were produced for all end points, and median EFS and OS were calculated from these curves. Treatment arms were compared using log-rank tests stratified by stage and site of disease. Estimates of treatment HRs based on log-rank tests and 95% CIs were calculated.

Stratified Fisher's exact tests were used to compare ORR and CBR across treatment arms. Patients with unknown or missing responses were treated as nonresponders. The incidence of AEs was compared across treatment groups for descriptive purposes and to identify possible differences in safety profiles using χ^2 methods for categoric data.

RESULTS

Study Population

This trial enrolled 580 patients between January 2004 and July 2005 (primarily from Eastern Europe and North and South America); however, one patient withdrew before treatment initiation, resulting in an ITT population of 579 patients (paclitaxel-lapatinib, n = 291; paclitaxel-placebo, n = 288; Fig 1). Patient characteristics for the ITT population were well balanced for all major baseline characteristics (Tables 1 and 2).

Delivered Therapy and Compliance

Lapatinib was well tolerated, with the mean delivered dose (1,490 mg/d; range, 1,088 to 1,941 mg/d) at 99% of the intended dose (1,500 mg/d). In addition, mean delivered doses of paclitaxel were similar in both treatment arms (172 mg/m^2; range, 82 to 187 mg/m^2 every 3 weeks in the paclitaxel-lapatinib arm; and 174 mg/m^2; range, 101 to 183 mg/m^2 every 3 weeks in the paclitaxel-placebo arm). Lapatinib was reduced to 1,250 mg/d in 18 patients (6%) and 1,000 mg/d in one patient (< 1%) for toxicity management. Paclitaxel was reduced by 20% in 19 patients (6%) and seven patients (2%) in the paclitaxel-lapatinib and paclitaxel-placebo arms, respectively, and was delayed for more than 72 hours in 165 patients (56%) and 142 patients (50%) in the paclitaxel-lapatinib and paclitaxel-placebo arms, respectively. The median duration of lapatinib treatment was 19.9 weeks, and the median duration of paclitaxel treatment was 15.1 and 16.1 weeks in the paclitaxel-lapatinib and paclitaxel-placebo arms, respectively.

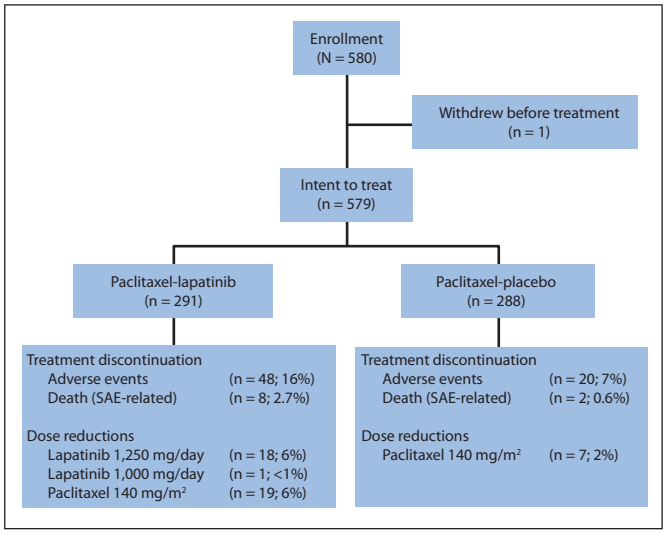

Fig 1. CONSORT diagram. SAE, serious adverse event.

Clinical Adverse Events

The most common adverse events (AEs) were alopecia, rash, diarrhea, nausea, vomiting, myalgia, and neutropenia, reflecting the known AEs of both drugs (Table 3). Rates of rash, diarrhea, mucositis, and vomiting were significantly higher in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm. AEs led to treatment discontinuation in 48 patients (16%) in the paclitaxel-lapatinib arm compared with 20 patients (7%) in the paclitaxel-placebo arm.

Six patients (2%) in each treatment group had a decrease in LVEF. Five of six patients in each group experienced an asymptomatic LVEF decrease that met protocol-defined serious AE (SAE) criteria. None of these events required a dose/schedule adjustment or resulted in treatment withdrawal or death. Decreases in LVEF were considered treatment related in three of six patients in the paclitaxel-lapatinib arm and in four of six patients in the paclitaxel-placebo arm. All events occurred more than 28 days after treatment initiation.

At least one SAE was reported in 102 patients (35%) in the paclitaxel-lapatinib arm and 63 patients (22%) in the paclitaxel-placebo arm. SAEs included neutropenia, febrile neutropenia, diarrhea, and asymptomatic LVEF decreases; however, only the incidence of diarrhea was significantly different between treatment arms (24 patients [8%] in the paclitaxel-lapatinib arm *v* two patients [< 1%] in the paclitaxel-placebo arm; $P < .0001$).

There were eight SAE-related deaths (2.7%) in the paclitaxel-lapatinib arm and two deaths (0.6%) in the paclitaxel-placebo arm. The eight fatal SAEs in the paclitaxel-lapatinib arm were a result of septic shock, septic shock and diarrhea (n = 3), cerebrovascular accident, cardiac arrest, heart failure, and pulmonary embolism. Cardiac

Table 1. Patient Characteristics in the ITT Population by Treatment Arm

Characteristic	P + L (n = 291)* No. of Patients	%	P + P (n = 288) No. of Patients	%	Total ITT Population (N = 579)* No. of Patients	%
Age, years						
Mean	51.3		52.4		51.8	
Range	23-87		25-78		23-87	
ECOG PS†						
0	164	56	161	56	325	56
1	125	43	122	43	247	43
2	0		1	< 1	1	< 1
Unknown	4	1	2	< 1	6	1
Stage of disease						
IIIB/IIIC	37	13	40	14	77	13
IV	254	87	248	86	502	87
Disease site, viscera	183	63	184	64	367	63
No. of metastatic sites						
≥ 3	161	55	168	58	329	57
2	79	27	80	28	159	27
1	51	18	39	14	90	16
0	0	0	1	< 1	1	< 1
Hormone receptor status‡						
ER positive and/or PR positive	129	44	145	50	274	47
ER negative and PR negative	100	34	97	34	197	34
Unknown	62	21	46	16	108	19
Prior adjuvant taxane	22	7	21	7	43	7
Prior adjuvant anthracycline	127	44	129	45	256	44

Abbreviations: ITT, intent to treat; P + L, paclitaxel plus lapatinib; P + P, paclitaxel plus placebo; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.

*No data were available for one patient allocated to the P + L arm because the patient was withdrawn before first dose.

†Based on the safety population (ITT: 293 patients in the P + L arm and 286 patients in the P + P arm; human epidermal growth factor receptor 2 negative: 204 patients in the P + L arm and 202 patients in the P + P arm).

‡ER/PR status based on local laboratory site data.

Table 2. Patient Characteristics by HER-2 Status and Treatment Arm

	HER-2 Positive				HER-2 Negative			
	P + L (n = 49)		P + P (n = 37)		P + L (n = 202)		P + P (n = 204)	
Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Mean	51		51		52		52	
Range	34-75		28-78		23-74		26-78	
ECOG PS*								
0	29	59	21	54	115	57	114	57
1	20	41	16	46	85	42	85	42
2	0	0	0	0	0	0	1	< 1
Unknown	0	0	0	0	4	1	2	< 1
Prior adjuvant taxane	1	2	0	0	15	7	17	8
Prior adjuvant anthracycline	22	45	16	43	85	42	99	48
Stage of disease								
III	6	12	8	22	26	13	21	10
IV	43	88	29	78	176	87	183	90
Visceral disease	34	69	19	51	125	62	138	68

Abbreviations: HER-2, human epidermal growth factor receptor 2; P + L, paclitaxel plus lapatinib; P + P, paclitaxel plus placebo; ITT, intent to treat; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.
*Based on the safety population (ITT: 293 patients in the P + L arm and 286 patients in the P + P arm; HER-2 negative: 204 patients in the P + L arm and 202 patients in the P + P arm).

arrest was a result of an arterial embolism in a patient with grade 4 obesity, hypertension, and hypercholesterolemia; heart failure was a result of suspected pulmonary embolism in a patient with grade 2 hypercholesterolemia. Neither event was considered to be drug related by the investigator. Fatal SAEs in the paclitaxel-placebo arm were a result of cerebrovascular accident and an unknown cause. The incidence of fatal events decreased sharply as the study progressed (Fig 2).

Table 3. Summary of Adverse Events Reported in ≥ 25% Patients: Safety Population

	Grade 1/2		Grade 3		Grade 4		All Grades		
Adverse Event and Treatment Group	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P*
Alopecia									.004
P + L	140	48	10	3	0	0	153	52*	
P + P	167	58	15	5	0	0	183	64*	
Rash†									< .0001
P + L	114	39	12	4	0	0	126	43	
P + P	60	21	0	0	0	0	60	21	
Diarrhea									< .0001
P + L	127	43	43	15	1	< 1	171	58	
P + P	69	24	4	1	0	0	73	26	
Nausea									NS
P + L	93	32	7	2	0	0	100	34	
P + P	83	29	2	1	0	0	85	30	
Vomiting									.01
P + L	69	23	5	2	0	0	74	25	
P + P	44	15	4	1	0	0	48	17	
Myalgia									NS
P + L	88	30	6	2	0	0	94	32	
P + P	72	25	2	1	0	0	74	26	
Neutropenia									NS
P + L	23	8	30	10	23	8	76	26	
P + P	24	8	20	7	14	5	58	20	

NOTE. The safety population was defined as all intent-to-treat patients according to actual treatment received rather than randomly assigned treatment. Two patients who were originally randomly assigned to the P + P arm received P + L; therefore, the safety population consists of 293 patients in the P + L arm and 286 patients in the P + P arm.
Abbreviations: P + L, paclitaxel + lapatinib; P + P, paclitaxel + placebo; NS, not significant.
*Grade unknown for three patients in the P + L arm and one patient in the P + P arm.
†Rash includes aggregation of the following terms: acne, rash, erythema, eczema, rash papular, dermatitis, folliculitis, and rash pustular.

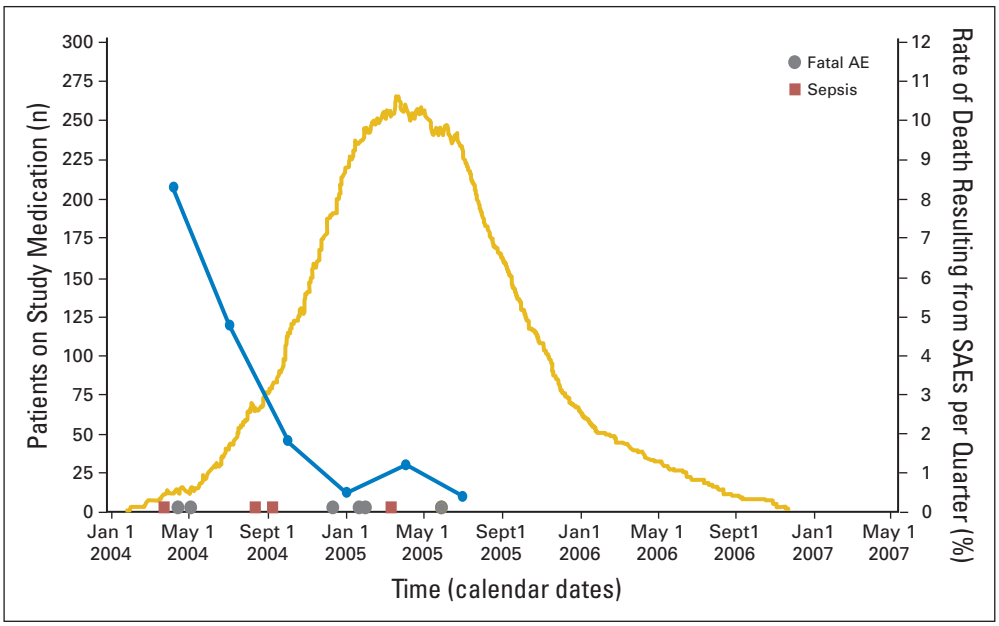

Fig 2. Fatal adverse events (AEs) by time and the number of patients on treatment. SAE, serious adverse event.

Analysis of Clinical Outcomes in the ITT Population by Treatment Arm

TTP. On the basis of investigator evaluation, median TTP was longer in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm (29 *v* 22.9 weeks, respectively); however, differences were not significant (HR = 0.87; 95% CI, 0.72 to 1.05; $P = .142$; Table 4). Similar results were reported in the independent reviewer assessment.

Response and CBR. The ORR (odds ratio = 1.7; 95% CI, 1.1 to 2.4; $P = .008$) and CBR (OR = 1.5; 95% CI, 1.0 to 2.1; $P = .025$) were significantly higher in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm (Table 4). A complete or partial response was observed in 35% of patients on the paclitaxel-lapatinib arm and 25% of patients on the paclitaxel-placebo arm.

EFS and OS. No significant differences in EFS and OS were observed. Analysis of OS was performed, although only 268 events (46%) had occurred at data lock in March 2007 (Table 4). Median OS time was higher in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm (99.1 *v* 87 weeks, respectively); however, the difference was not statistically significant.

Development of symptomatic brain metastases. In an exploratory analysis, 12 patients experienced CNS relapses (seven patients in the paclitaxel-lapatinib arm and five patients in the paclitaxel-placebo arm). The only site of disease relapse was CNS in two of seven patients in the paclitaxel-lapatinib arm and all five patients in the paclitaxel-placebo arm. The mean time to first CNS relapse was 35.3 weeks in the paclitaxel-lapatinib arm and 20.4 weeks in the paclitaxel-placebo arm.

Centralized HER-2 analysis. Archival tissue samples (slides or blocks) were collected for 531 (92%) of 579 patients. FISH results were successfully obtained for 420 patients, with 80 (19%) showing *HER2* gene amplification. IHC assays were completed for 484 patients (96% of collected samples); 278 (57%) were scored as 0, 101 (21%) were scored as 1+, 37 (8%) were scored as 2+, and 68 (14%) were scored as 3+. There was a strong association between *HER2* gene amplification by FISH and HER-2 overexpression by IHC.[13] Six patients with IHC 3+, FISH-unknown tumors were included in the HER-2–positive population; five patients with HER-2 FISH-negative and IHC 3+ tumors were not included. Patient characteristics were generally well-balanced between the HER-2–positive and HER-2–negative subsets (Table 2).

Association of HER-2 Status With Responsiveness to Lapatinib

HER-2–positive MBC. Eighty-six patients (15%) were defined as HER-2 positive (n = 49, paclitaxel-lapatinib arm; n = 37, paclitaxel-placebo arm). TTP was significantly longer in lapatinib-treated patients versus patients receiving placebo (median, 36.4 *v* 25.1 weeks, respectively; Table 4; Fig 3), with an unadjusted HR of 0.53 (95% CI, 0.31 to 0.89; $P = .005$). This suggests a 47% lower risk of progression for patients in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm. EFS was also significantly longer in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm (median, 35.1 *v* 21.9 weeks, respectively; HR = 0.52; 95% CI, 0.31 to 0.86; $P = .004$; Table 4); in addition, ORR (63.3% *v* 37.8%, respectively; $P = .023$) and CBR (69.4% *v* 40.5%, respectively; $P = .011$) were significantly higher for patients treated with paclitaxel-lapatinib versus paclitaxel-placebo (Table 4). Median OS was longer in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm; however, this difference was not statistically significant (Table 4; Fig 4). Survival data in the HER-2–positive population were not mature because only 43% of events had occurred at the time of data lock.

The limited number of CNS relapses reported in this study precludes any definitive conclusions. Only three of 12 CNS relapses occurred in centrally defined HER-2–positive patients; two of these relapses were reported in the paclitaxel-lapatinib arm.

HER-2–Negative MBC

No significant differences in ORR, CBR, TTP, EFS, or OS were observed in the paclitaxel-lapatinib arm versus the paclitaxel-placebo arm.

Table 4. Summary of Clinical Outcomes

Outcome	ITT Population		HER-2 Positive*		HER-2 Negative*	
	Paclitaxel + Lapatinib (n = 291)	Paclitaxel + Placebo (n = 288)	Paclitaxel + Lapatinib (n = 49)	Paclitaxel + Placebo (n = 37)	Paclitaxel + Lapatinib (n = 202)	Paclitaxel + Placebo (n = 204)
TTP						
Median, weeks	29	22.9	36.4	25.1	25.1	24
HR	0.87		0.53		1.05	
95% CI	0.72 to 1.05		0.31 to 0.89		0.84 to 1.32	
P	.142		.005		.662	
Response						
Response rate, %	35.1	25.3	63.3	37.8	30.2	23.5
95% CI	29.6 to 40.8	20.4 to 30.8	48.3 to 76.6	22.5 to 55.2	24.0 to 37.0	17.9 to 30.0
Odds ratio	1.7		3.0		1.4	
95% CI	1.1 to 2.4		1.1 to 8.5		0.9 to 2.3	
P	.008		.023		.128	
Complete response						
No. of patients	14	6	5	1	6	5
%	5	2	10	3	3	2
Partial response						
No. of patients	88	67	26	13	55	43
%	30	23	53	35	27	21
Stable disease						
No. of patients	97	125	9	11	68	94
%	33	43	18	30	34	46
Progressive disease						
No. of patients	65	75	7	8	50	52
%	22	26	14	22	25	25
Response unknown						
No. of patients	27	15	2	4	23	10
%	9	5	4	11	11	5
Median duration of response, weeks	28.3	27.1	32.0	24.0	27.1	36.9
Clinical benefit						
Clinical benefit rate, %	40.5	31.9	69.4	40.5	34.7	31.9
95% CI	34.9 to 46.4	26.6 to 37.7	54.6 to 81.7	24.8 to 57.9	28.1 to 41.7	25.5 to 38.7
Odds ratio	1.5		3.5		1.2	
95% CI	1.0 to 2.1		1.3 to 9.7		0.8 to 1.8	
P	.025		.011		.806	
EFS						
Median EFS, weeks	25.1	22.6	35.1	21.9	23.3	23.1
95% CI	21.9 to 32.1	21.0 to 25.4	32.4 to 45.3	20.0 to 32.9	20.9 to 27.9	21.1 to 27.9
HR	0.90		0.52		1.10	
95% CI	0.75 to 1.08		0.31 to 0.86		0.88 to 1.37	
P	.238		.004		.395	
OS						
Median OS, weeks	99.1	87	104.6	82.4	99.1	87
95% CI	84.4 to 107.6	74.6 to 108.1	75.0 to —	50.9 to —	86.4 to 110.6	74.6 to —
HR	0.86		0.74		0.89	
95% CI	0.7 to 1.1		0.4 to 1.4		0.7 to 1.2	
P	.216		.365		.438	

Abbreviations: ITT, intent to treat; HER-2, human epidermal growth factor receptor 2; TTP, time to disease progression; HR, hazard ratio; EFS, event-free survival; OS, overall survival.
*Centrally tested.

DISCUSSION

This study demonstrated that the primary activity of lapatinib in breast cancer patients is mediated through HER-2 inhibition. Other than a higher response rate (influenced by the HER-2–positive subset), no clinically relevant antitumor activity was demonstrated when lapatinib was used in the heterogeneous population of patients with advanced breast cancer with locally defined HER-2–negative or HER-2–untested tumors. Conversely, in a preplanned, blinded, subset analysis of patients with centrally defined HER-2–positive tumors, lapatinib plus paclitaxel resulted in a clinically significant 11-week increase in median TTP as well as significant increases in ORR, CBR, and EFS. Although the data are not yet mature and differences did not achieve statistical significance, median OS was longer in patients receiving lapatinib. Therefore, this combination seems to be active as first-line therapy for HER-2–positive breast cancer.

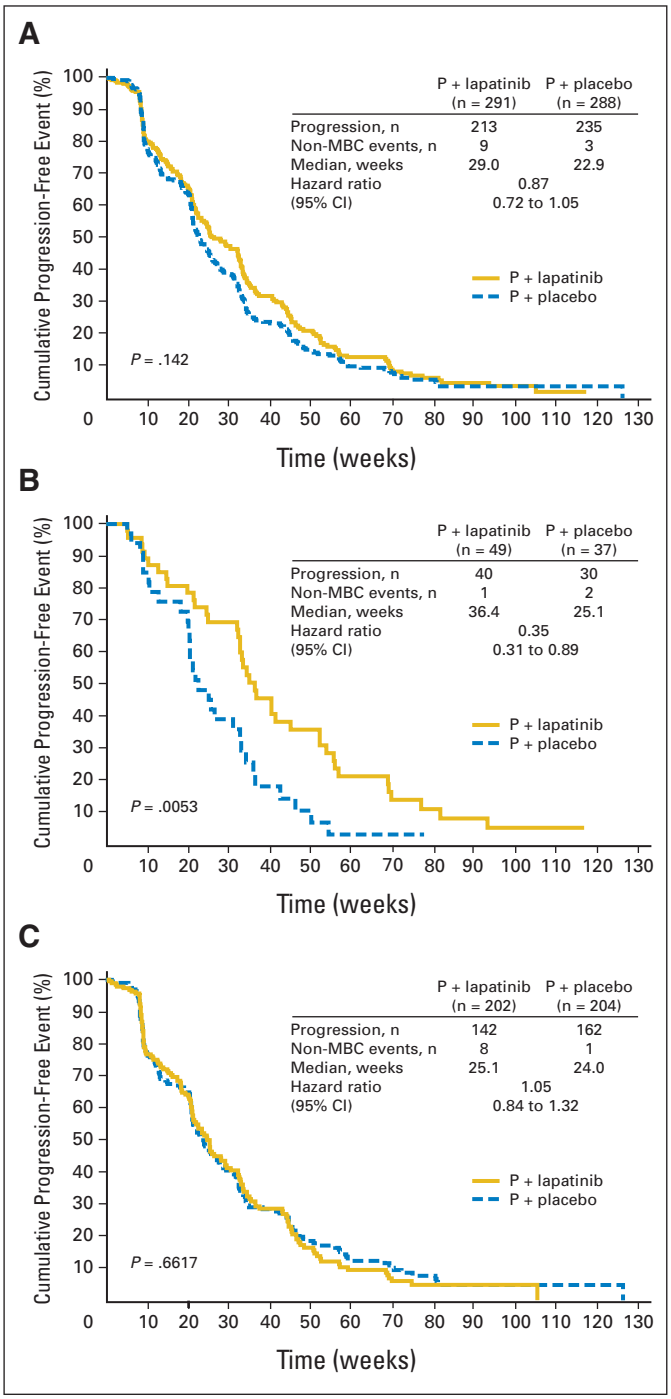

Fig 3. Kaplan-Meier estimates for time to progression. (A) Entire intent-to-treat (ITT) population. (B) Human epidermal growth factor receptor 2 (HER-2) –positive ITT population. (C) HER-2–negative ITT population. The hazard ratio refers to the comparison of paclitaxel (P) plus lapatinib versus P plus placebo. MBC, metastatic breast cancer.

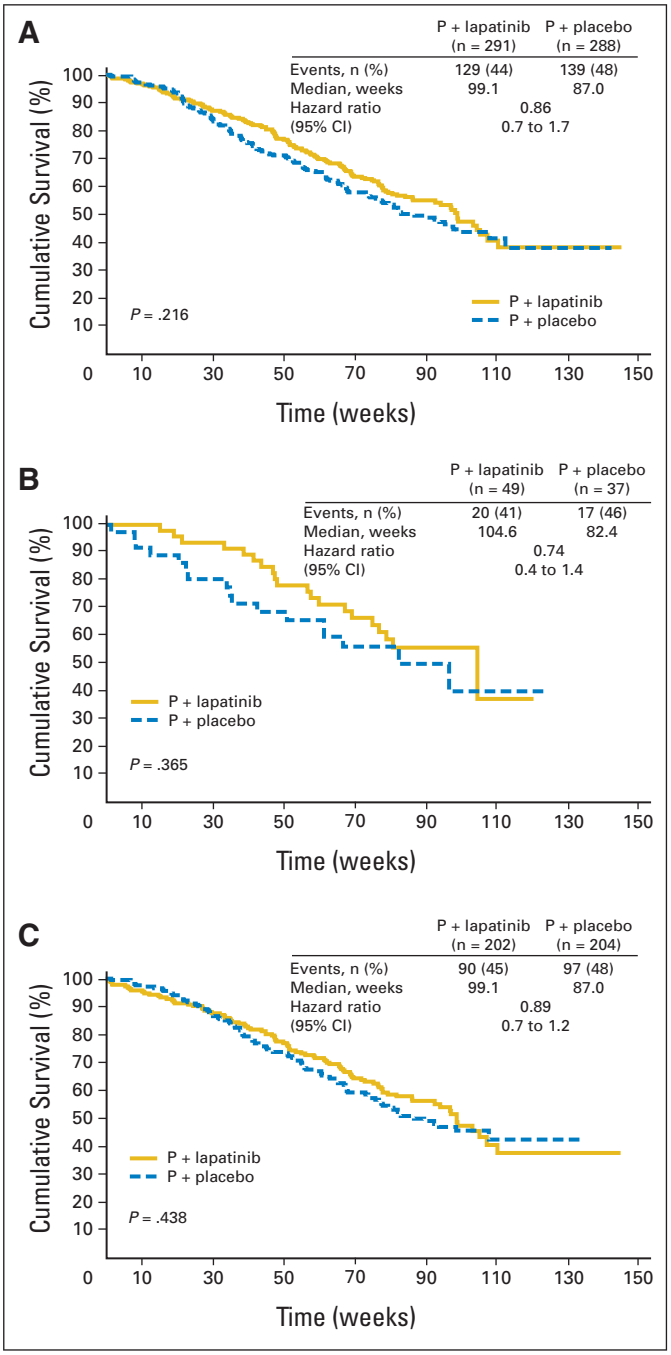

Fig 4. Kaplan-Meier estimates for overall survival. (A) Entire intent-to-treat (ITT) population. (B) Human epidermal growth factor receptor 2 (HER-2) –positive ITT population. (C) HER-2–negative ITT population. The hazard ratio refers to the comparison of paclitaxel (P) plus lapatinib versus P plus placebo.

In the present study, 80 of the 86 centrally defined HER-2–positive tumors had gene amplification conventionally detected by FISH. The remaining six tumors were defined as HER-2 positive based on an IHC score of 3+, but FISH results were not available. We considered this to be reasonable because of the relatively high probability that *HER2* amplification would be present if the FISH assay results had been available. In series where the HER-2 FISH status is known and HER-2 immunostaining is IHC 3+, the vast majority of such tumors (varying from 78% to more than 95%) are *HER2* [11,14,15]

An additional five patients had an IHC score of 3+ but lacked gene amplification by FISH and were considered HER-2 negative. We think this is appropriate based on considerable published data. Frozen tissue samples, as well as breast cancer cell lines, demonstrate a direct relationship between *HER2* gene amplification and HER-2 overexpression.[16,17] No other mechanism for HER-2 overexpression has

been demonstrated. However, a known, but variable, number of false-positive IHC 3+ results are observed when antigen retrieval is used in paraffin-embedded breast cancers with the Dako HercepTest.[11,15,18-20] Reanalysis of these same patients by an IHC assay method that does not require antigen retrieval yields an IHC result of less than 3+ in the vast majority of patients, strongly suggesting that the 3+ immunostaining was an artifact related to IHC antigen retrieval methods and not HER-2 protein overexpression.[11] Furthermore, FISH more accurately reflects the independent molecular characterization of HER-2 status than does IHC.[11,12,21,22] Therefore, all breast cancers lacking *HER2* gene amplification by FISH were considered as HER-2 negative in our analysis without regard to the IHC immunostaining status.

This trial did not demonstrate a clinically significant effect of EGFR tyrosine kinase targeting after lapatinib administration. Several phase II clinical trials have tested EGFR tyrosine kinase inhibitors in advanced breast cancer patients unselected for EGFR protein overexpression or gene abnormalities, but the results of these trials have been disappointing.[23-26]

The addition of lapatinib to paclitaxel resulted in increased grade 3 rash (4% *v* 0% for paclitaxel-placebo) and grade 3 diarrhea (15% *v* 1% for paclitaxel-placebo). No patients had drug-related cardiac complications that resulted in treatment discontinuation or death. In addition, the rate of LVEF decrease was 2% in each study arm, reinforcing the concept that lapatinib-paclitaxel is not associated with relevant cardiac problems in advanced breast cancer patients.

Lapatinib combined with paclitaxel was associated with a 2.7% incidence of fatal AEs (mainly sepsis associated with diarrhea) compared with a 0.6% incidence in the paclitaxel-placebo arm. Most of these fatal events occurred early in the accrual period and decreased sharply with time. Increased experience treating these AEs and the introduction of proactive guidelines for managing lapatinib-related diarrhea during the study likely contributed to the reduced incidence and severity of diarrhea episodes. These guidelines are a useful tool for the clinician because they contribute to a reduction in the incidence and severity of diarrhea.[27] Although investigator experience was critical in improving the safety profile, pharmacokinetic (PK) interaction may also explain the occurrence of more pronounced toxicity in the lapatinib-paclitaxel arm. Crown et al[27] and Jones et al[28] demonstrated a PK interaction between paclitaxel and lapatinib, leading to an increase of approximately 20% in the area under the concentration curve for both drugs. The manner in which this PK interaction affects the toxicity of the paclitaxel-lapatinib combination remains unclear. However, the delivered dose of paclitaxel plus lapatinib was more than 95% of the planned dose, dose reductions were 10% *v* 5% in the paclitaxel-placebo arm, and AE onset varied widely, suggesting that the PK interaction may not be clinically important.[29] Two ongoing trials (EGF105764, phase II; and EGF104535, phase III) testing the combination of lapatinib 1,500 mg/d plus paclitaxel 80 mg/m^2/wk have resulted in no diarrhea-related safety concerns in 53 enrolled patients.[27]

This phase III, randomized, double-blind, placebo-controlled clinical trial did not confirm the hypothesis that lapatinib has activity when added to paclitaxel as first-line treatment for HER-2–negative or HER-2–untested MBC. However, a planned, blinded, centralized evaluation of archival tumor samples demonstrated that lapatinib plus paclitaxel was superior to paclitaxel alone in terms of ORR, CBR, TTP, and EFS in the HER-2–positive subset. These retrospective results in a limited number of patients should be considered as hypothesis generating. Phase II and III studies of lapatinib plus taxanes are ongoing in patients with HER-2–positive MBC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Michael C. Arbushites, GlaxoSmithKline (C); Stephanie F. Guerrera, GlaxoSmithKline (C); Maria Koehler, GlaxoSmithKline (C); Cristina Oliva, GlaxoSmithKline (C); Steven H. Stein, GlaxoSmithKline (C); Lisa S. Williams, GlaxoSmithKline (C) **Consultant or Advisory Role:** Angelo Di Leo, GlaxoSmithKline (C), Roche (C); Richard S. Finn, GlaxoSmithKline (C) **Stock Ownership:** Michael C. Arbushites, GlaxoSmithKline; Stephanie F. Guerrera, GlaxoSmithKline; Maria Koehler, GlaxoSmithKline; Cristina Oliva, GlaxoSmithKline; Steven H. Stein, GlaxoSmithKline; Lisa S. Williams, GlaxoSmithKline **Honoraria:** Angelo Di Leo, GlaxoSmithKline, Roche; Richard S. Finn, GlaxoSmithKline; Michael F. Press, GlaxoSmithKline, Genentech **Research Funding:** Richard S. Finn, GlaxoSmithKline; Michael F. Press, GlaxoSmithKline, Genentech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Michael C. Arbushites, Stephanie F. Guerrera, Maria Koehler, Cristina Oliva, Steven H. Stein

Provision of study materials or patients: Angelo Di Leo, Henry L. Gomez, Zeba Aziz, Zanete Zvirbule, Jose Bines

Collection and assembly of data: Michael C. Arbushites, Stephanie F. Guerrera, Maria Koehler, Steven H. Stein, Lisa S. Williams, Judy Dering, Richard S. Finn, Michael F. Press

Data analysis and interpretation: Angelo Di Leo, Michael C. Arbushites, Stephanie F. Guerrera, Maria Koehler, Cristina Oliva, Steven H. Stein, Lisa S. Williams, Judy Dering, Richard S. Finn, Michael F. Press

Manuscript writing: Angelo Di Leo, Michael C. Arbushites, Maria Koehler, Cristina Oliva, Steven H. Stein, Lisa S. Williams, Richard S. Finn, Michael F. Press

Final approval of manuscript: Angelo Di Leo, Jose Bines, Michael C. Arbushites, Stephanie F. Guerrera, Maria Koehler, Cristina Oliva, Steven H. Stein, Lisa S. Williams, Judy Dering, Richard S. Finn, Michael F. Press

REFERENCES

1. Wang Q, Greene MI: The development of targeted therapy in the ErbB system. Am Soc Clin Oncol Ed Book 79-84, 2007

2. Blackwell KL, Kaplan EH, Franco SX, et al: A phase II, open-label, multicenter study of GW572016 in patients with trastuzumab-refractory metastatic breast cancer. J Clin Oncol 22:196, 2004 (suppl; abstr 3006)

3. Gomez HL, Chavez MA, Doval DC, et al: Results from a phase II randomized study of lapatinib as first-line treatment for patients with ErbB2-amplified locally advanced or metastatic breast cancer. Breast Cancer Res Treat 100:S68, 2006 (suppl; abstr 1090)

4. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-2743, 2006

5. Carey LA, Perou CM, Livasy CA, et al: Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295:2492-2502, 2006

6. Finn RS, Dering J, Ginther C, et al: ER+Pr– breast cancer defines a unique subtype of breast cancer that is driven by growth factor signaling and may be more likely to respond to EGFR targeted therapies. J Clin Oncol 24:6s, 2006 (suppl; abstr 514)

7. Hoadley KA, Weigman VJ, Fan C, et al: EGFR associated expression profiles vary with breast tumor subtype. BMC Genomics 8:258, 2007

8. Nahta R, Yu D, Hung MC, et al: Mechanisms of disease: Understanding resistance to HER2-targeted therapy in human breast cancer. Nat Clin Pract Oncol 3:269-280, 2006

9. Yarden Y, Sliwkowski MX: Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2:127-137, 2001

10. Mass RD, Press MF, Anderson S, et al: Evaluation of clinical outcomes according to HER2 detection by fluorescence in situ hybridization in women with metastatic breast cancer treated with trastuzumab. Clin Breast Cancer 6:240-246, 2005

11. Press MF, Sauter G, Bernstein L, et al: Diagnostic evaluation of HER-2 as a molecular target: An assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 11:6598-6607, 2005

12. Press MF, Slamon DJ, Flom KJ, et al: Evaluation of HER-2/neu gene amplification and overexpression: Comparison of frequently used assay methods in a molecularly characterized cohort of breast cancer specimens. J Clin Oncol 20:3095-3105, 2002

13. Press MF, Finn R, DiLeo A, et al: Correlation of HER2 gene amplification and immunohistochemistry (IHC) with clinical efficacy in women with metastatic breast cancer (MBC) treated with lapatinib. American Society of Clinical Oncology Breast Cancer Symposium, San Francisco, CA, September 7-8, 2007 (abstr 51)

14. Bartlett JM, Going JJ, Mallon EA, et al: Evaluating HER2 amplification and overexpression in breast cancer. J Pathol 195:422-428, 2001

15. Dybdal N, Leiberman G, Anderson S, et al: Determination of HER2 gene amplification by fluorescence in situ hybridization and concordance with the clinical trials immunohistochemical assay in women with metastatic breast cancer evaluated for treatment with trastuzumab. Breast Cancer Res Treat 93:3-11, 2005

16. Pauletti G, Godolphin W, Press MF, et al: Detection and quantitation of HER-2/neu gene amplification in human breast cancer archival material using fluorescence in situ hybridization. Oncogene 13:63-72, 1996

17. Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707-712, 1989

18. Jacobs TW, Gown AM, Yaziji H, et al: Specificity of HercepTest in determining HER-2/neu status of breast cancers using the United States Food and Drug Administration-approved scoring system. J Clin Oncol 17:1983-1987, 1999

19. Jacobs TW, Gown AM, Yaziji H, et al: Comparison of fluorescence in situ hybridization and immunohistochemistry for the evaluation of HER-2/neu in breast cancer. J Clin Oncol 17:1974-1982, 1999

20. Yaziji H, Goldstein LC, Barry TS, et al: HER-2 testing in breast cancer using parallel tissue-based methods. JAMA 291:1972-1977, 2004

21. Press MF, Bernstein L, Thomas PA, et al: HER-2/neu gene amplification characterized by fluorescence in situ hybridization: Poor prognosis in node-negative breast carcinomas. J Clin Oncol 15: 2894-2904, 1997

22. Press MF, Hung G, Godolphin W, et al: Sensitivity of HER-2/neu antibodies in archival tissue samples: Potential source of error in immunohistochemical studies of oncogene expression. Cancer Res 54:2771-2777, 1994

23. Baselga J, Albanell J, Ruiz A, et al: Phase II and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. J Clin Oncol 23:5323-5333, 2005

24. Robertson JFR, Gutteridge E, Cheung KL, et al: Gefitinib (ZD1839) is active in acquired tamoxifen (TAM)-resistant oestrogen receptor (ER)-positive and ER-negative breast cancer: Results from a phase II study. Proc Am Soc Clin Oncol 22:7, 2003 (abstr 23)

25. Tan AR, Yang X, Hewitt SM, et al: Evaluation of biologic end points and pharmacokinetics in patients with metastatic breast cancer after treatment with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor. J Clin Oncol 22:3080-3090, 2004

26. von Minckwitz G, Jonat W, Fasching P, et al: A multicentre phase II study on gefitinib in taxane- and anthracycline-pretreated metastatic breast cancer. Breast Cancer Res Treat 89:165-172, 2005

27. Crown JP, Burris HA, Jones S, et al: Safety and tolerability of lapatinib in combination with taxanes (T) in patients with breast cancer (BC). J Clin Oncol 25:38s, 2007 (suppl; abstr 1027)

28. Jones SF, Burris HA 3rd, Yardley DA, et al: Lapatinib (an oral dual kinase inhibitor) plus weekly or every 3 week paclitaxel. 27th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8-11, 2004 (abstr 1069)

29. Burris HA 3rd, Crown JP, Jones S, et al: Lapatinib in combination with taxanes: Tolerability data in 507 patients with breast cancer. 14th European Cancer Conference, Barcelona, Spain, September 23-27, 2007 (abstr 2109)

Acknowledgment

We thank participating patients, families, and investigators; Ivonne Villalobos, Angela Santiago, Roberta Guzman, Yanling Ma, and Armen Gasparyan (University of Southern California Norris Cancer Center); Perceptive Informatics; Steve Ashton, Louise Downie, and Mary-Jo Penna (GlaxoSmithKline); and ProEd Communications.

