

ORIGINAL ARTICLE

Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

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ABSTRACT

BACKGROUND

Lapatinib, a tyrosine kinase inhibitor of human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu) and epidermal growth factor receptor (EGFR), is active in combination with capecitabine in women with HER2-positive metastatic breast cancer that has progressed after trastuzumab-based therapy. In this trial, we compared lapatinib plus capecitabine with capecitabine alone in such patients.

METHODS

Women with HER2-positive, locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab were randomly assigned to receive either combination therapy (lapatinib at a dose of 1250 mg per day continuously plus capecitabine at a dose of 2000 mg per square meter of body-surface area on days 1 through 14 of a 21-day cycle) or monotherapy (capecitabine alone at a dose of 2500 mg per square meter on days 1 through 14 of a 21-day cycle). The primary end point was time to progression, based on an evaluation by independent reviewers under blinded conditions.

RESULTS

The interim analysis of time to progression met specified criteria for early reporting on the basis of superiority in the combination-therapy group. The hazard ratio for the independently assessed time to progression was 0.49 (95% confidence interval, 0.34 to 0.71; $P < 0.001$), with 49 events in the combination-therapy group and 72 events in the monotherapy group. The median time to progression was 8.4 months in the combination-therapy group as compared with 4.4 months in the monotherapy group. This improvement was achieved without an increase in serious toxic effects or symptomatic cardiac events.

CONCLUSIONS

Lapatinib plus capecitabine is superior to capecitabine alone in women with HER2-positive advanced breast cancer that has progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. (ClinicalTrials.gov number, NCT00078572.)

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N Engl J Med 2006;355:2733-43.

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METASTATIC BREAST CANCER IS THE leading cause of death from cancer among women worldwide, accounting for more than 400,000 deaths per year.¹ Women with breast cancer that overexpresses human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu) are at greater risk for disease progression and death than women whose tumors do not overexpress HER2.² Therapeutic strategies have been developed to block HER2 signaling pathways in order to improve the treatment of this cancer. Trastuzumab (Herceptin, Genentech), a recombinant, humanized, monoclonal antibody that binds to the extracellular domain of the HER2 protein, is a key component in the treatment of metastatic and early-stage HER2-positive breast cancer.³⁻⁷

Metastatic breast cancer eventually develops resistance to trastuzumab,^{8,9} and in some women, the cancer recurs after adjuvant therapy.^{6,7} For these reasons, there is a need for alternatives to block HER2 signaling. Lapatinib (Tykerb, Glaxo-SmithKline) is an orally active small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor type 1 (EGFR). In preclinical studies, lapatinib was not cross-resistant with trastuzumab.¹⁰⁻¹² The clinical activity of lapatinib in combination with capecitabine has been shown in women with HER2-positive breast cancer that progressed while they were receiving trastuzumab. The adverse-event profile of the combination therapy was similar to that of each drug individually, without relevant pharmacokinetic interactions at the recommended dose and schedule of the combination therapy (lapatinib at a dose of 1250 mg daily and capecitabine at a dose of 2000 mg per square meter of body-surface area daily on days 1 through 14 of a 21-day cycle).¹³

We conducted a phase 3, randomized, open-label study comparing lapatinib plus capecitabine with capecitabine alone in women with progressive, HER2-positive, locally advanced or metastatic breast cancer who had previously been treated with a minimum of an anthracycline, a taxane, and trastuzumab.

METHODS

PATIENTS

Eligible patients had HER2-positive, locally advanced breast cancer (a T4 primary tumor and stage IIIB or IIIC disease) or metastatic breast can-

cer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. The HER2 status was considered positive if the local institution reported grade 3+ staining intensity (on a scale of 0 to 3) by means of immunohistochemical analysis or grade 2+ staining intensity by means of immunohistochemical analysis with gene amplification on fluorescence in situ hybridization. Previous therapies had to include, but were not limited to, at least four cycles of regimens that included an anthracycline and a taxane (two cycles if the disease progressed while the woman was receiving therapy) administered concurrently or separately as adjuvant therapy or for metastatic disease. Previous treatment with trastuzumab, alone or in combination with chemotherapy for locally advanced or metastatic disease, for at least 6 weeks was required. Women previously treated with capecitabine were ineligible; previous therapy with fluorouracil was permitted. Patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), with the criteria modified to include lesions that were 15 to 19 mm in diameter as assessed by means of methods other than spiral computed tomography (CT)¹⁴; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a left ventricular ejection fraction (LVEF) within the institution's normal range; a life expectancy of at least 12 weeks; and adequate renal, hepatic, and hematologic function. Women with central nervous system (CNS) metastases were eligible if they were clinically stable for at least 3 months after the discontinuation of corticosteroid and anticonvulsant therapy. Women with preexisting heart disease or conditions that could affect gastrointestinal absorption were ineligible.

The institutional review board for each participating institution approved the study protocol. All patients gave written informed consent.

STUDY DESIGN

In this open-label study, women were randomly assigned in a 1:1 ratio to receive lapatinib plus capecitabine or capecitabine alone. Randomization in permuted blocks of six women was performed within strata defined according to disease stage and the presence or absence of visceral disease. The combination regimen consisted of lapatinib at a dose of 1250 mg daily, 1 hour before or after breakfast, on a continuous basis, and

capecitabine at a dose of 2000 mg per square meter of body-surface area in two divided doses on days 1 through 14 of a 21-day cycle. Since lapatinib is predominantly metabolized by cytochrome P-450 enzymes (CYP3A4), medications that inhibit or induce CYP3A4 were prohibited (Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Capecitabine monotherapy was administered at a dose of 2500 mg per square meter of body-surface area in two divided doses on days 1 through 14 of a 21-day cycle.

Standard recommendations for capecitabine dosage modifications were followed for the management of adverse events.¹⁵ Lapatinib was withheld for up to 14 days for grade 2 hematologic toxicity or any grade 3 or 4 toxicity. Lapatinib was permanently discontinued if grade 3 or 4 interstitial pneumonitis or cardiac dysfunction occurred. It was also permanently discontinued if improvement (a change to grade 0 or 1) did not occur within 14 days. After recovery from grade 2 hematologic toxicity or grade 3 toxicity, lapatinib was to be resumed at a dose of 1250 mg daily, although the site investigators could reduce the dose to 1000 mg daily after grade 3 toxicity if doing so was thought to be in the woman's interest. Resumption of lapatinib administration after grade 4 toxicity was optional but required a dose reduction to 1000 mg daily.

Women were assessed every 6 weeks for the first 24 weeks, then every 12 weeks while they were receiving the study treatment. Women without progressive disease for whom the study treatment was withdrawn were assessed every 12 weeks until the commencement of alternative anticancer treatment, disease progression, or death. Efficacy was defined according to RECIST criteria, modified to include lesions that were 15 to 19 mm in diameter as assessed by methods other than spiral CT.¹⁴ Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 3.0), which grades events as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). Treatment continued until the investigator identified disease progression or unacceptable toxic effects.

The primary end point was the time to progression, defined as the time from randomization to disease progression or death due to breast can-

cer. Secondary end points were progression-free survival, defined as the time from randomization to disease progression or death due to any cause; overall survival; the overall response rate; the rate of clinical benefit, defined as a complete response, partial response, or stable disease for at least 6 months; and safety.

For analyses of the time to progression, progression-free survival, the overall response rate, and the clinical benefit rate, copies of serial radiographs and photographs of visible lesions used for efficacy determinations were collected for independent assessment under blinded conditions. Supportive analyses of these end points were conducted with the use of investigator-reported assessments.

CARDIAC EVALUATION

Evaluation of the LVEF by means of echocardiography or multiple gated acquisition scanning was performed at the time of the efficacy assessments with the use of the same technique for the duration of the study. A cardiac event was defined as a decline in the LVEF that was symptomatic, regardless of the degree of decline or was asymptomatic but with a relative decrease of 20% or more from baseline to a level below the institution's lower limit of the normal range. Lapatinib was discontinued in patients with symptomatic cardiac events (CTCAE grade 3 or 4). For asymptomatic events, lapatinib was withheld and could be resumed at a dose of 1000 mg per day if the LVEF 2 to 3 weeks later was at or above the institution's lower limit of the normal range.

STATISTICAL ANALYSIS

We calculated that a total of 266 time-to-progression events would be required to achieve a statistical power of 90%, with a two-sided, 5% type I error, to detect a 50% increase in the median time to progression (from an estimated 3 months in the group receiving capecitabine alone to 4.5 months in the group receiving lapatinib plus capecitabine). An analysis of overall survival was to be performed after 457 deaths had occurred, giving a statistical power of 80% to detect a 30% increase in median survival (from 8 months in the monotherapy group to 10.4 months in the combination-therapy group). To meet both of these requirements, an enrollment of 528 women was planned.

The intention-to-treat population, comprising all women who underwent randomization, was

used for the analyses of efficacy data. Log-rank tests stratified according to the stage of disease and the presence or absence of visceral disease were used to analyze time-to-event end points, and Fisher's exact tests were used for tumor-response rates. To account for the risk of death that was not related to breast cancer, cumulative incidence curves were used to summarize the time to progression. Kaplan–Meier curves were used to summarize progression-free survival and overall survival.

An independent data and safety monitoring committee reviewed the safety and efficacy data. A planned interim analysis of disease progression was to be conducted after approximately 133 independently assessed events. The date of the data lock to initiate the independent review and interim analysis was to be determined by the number of events reported by the investigators. To adjust for differences between the assessments by the independent reviewers and the investigators' assessments, the date for the interim-analysis data lock was set to allow investigator-reported events to be approximately 10% higher than 133. The final analysis would occur after 266 independently assessed disease-progression events had occurred. For patients in whom progressive disease was not confirmed by independent review or who did not die, the time to progression was censored at the date of the last independent assessment and before the initiation of alternative anticancer therapy. Reporting of the data would be considered at the time of the interim analysis if the *P* value from a stratified log-rank test for the time to progression was below a prespecified level. One-sided O'Brien–Fleming boundaries¹⁶ at a 2.5% significance level were to be used to assess the superiority or futility of combination therapy as compared with that of capecitabine alone. The study would continue until the final analysis if a stopping boundary was not crossed at the interim analysis.

The study was funded and conducted by Glaxo-SmithKline. It was designed by two of the authors, who are employees of the sponsor, with input from participating academic investigators. The interim analyses were conducted by an independent statistician and presented to the data and safety monitoring committee without disclosure to the academic investigators or the sponsor. After the committee's recommendation to close accrual and report the results, complete analyses

were supervised by an employee of the sponsor and reviewed along with the raw data by both academic investigators and employees of the sponsor. The authors vouch for the completeness and accuracy of the results. All of the authors reviewed the results of the analyses and contributed to the writing of the manuscript.

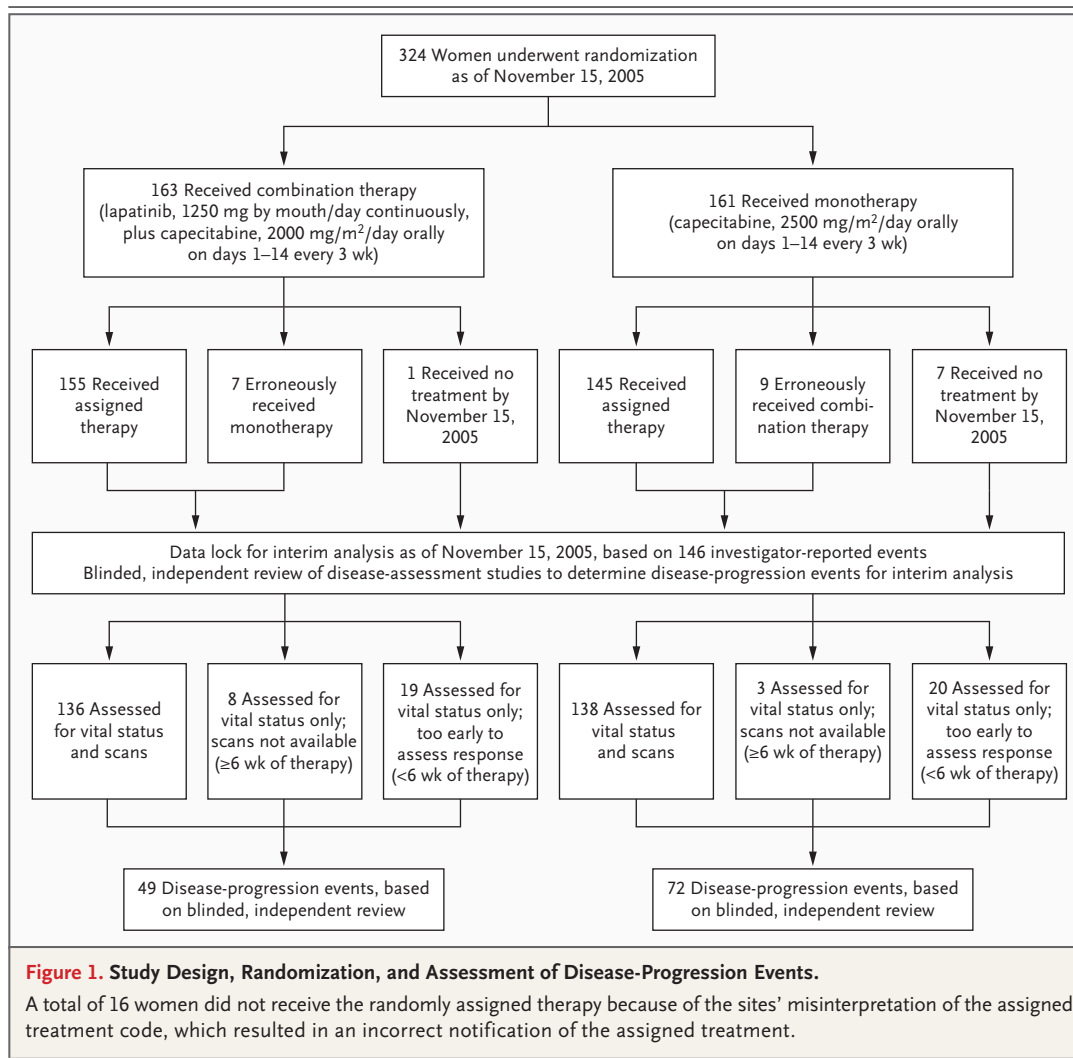
RESULTS

Enrollment began on March 29, 2004, and on the basis of investigator-reported disease-progression events, November 15, 2005, was chosen for the data lock. As of this latter date, 146 disease-progression events had been reported in 324 patients. Vital status and disease assessments for 274 patients were available for independent evaluation, which documented 114 disease-progression events. The first assessments for response had yet to be performed for 39 women who had been receiving therapy for less than 6 weeks. The assessments of 11 women were unavailable. Corresponding one-sided O'Brien–Fleming boundaries were calculated on the basis of 114 disease-progression events for the log-rank test; the superiority boundary was $P \leq 0.0014$ and the futility boundary was $P \geq 0.4516$. After a review on March 20, 2006, the data and safety monitoring committee recommended reporting the study results, notifying women of the results, and offering lapatinib with capecitabine to women in the monotherapy group. To ensure that all relevant data up to the November 15, 2005, cutoff date were included, a data-validation process was conducted, and the analyses were repeated. We report the results of these analyses.

PATIENT POPULATION

Figure 1 shows the numbers of women who received the assigned study treatment, the numbers for whom assessment data were available, and the numbers of disease-progression events. Seven unreported deaths due to breast cancer occurred before the data lock and were not included in the review by the monitoring committee. With these deaths included, 121 independently assessed disease-progression events had occurred by the time of the data lock. These events form the basis of the analyses presented here.

The baseline characteristics of the women were similar in the two treatment groups (Table 1). Most of the women (96%) had metastatic disease,



97% had received an anthracycline, and 97% had received a taxane. Trastuzumab had been administered to 97% of women (as treatment for metastatic disease in 91% and only as adjuvant or neoadjuvant treatment in 5%). The median time from discontinuation of trastuzumab to randomization was 5.3 weeks in the combination-therapy group and 6.0 weeks in the monotherapy group. The median duration of previous treatment with trastuzumab was 42 weeks in the combination-therapy group and 44 weeks in the monotherapy group.

DELIVERED THERAPY AND COMPLIANCE WITH DISEASE ASSESSMENT SCHEDULE

A total of 155 of 163 women in the combination-therapy group (95%) and 145 of 161 women in the monotherapy group (90%) received the randomly

assigned treatment. The median daily doses of administered capecitabine per cycle were 2000 mg per square meter of body-surface area in the combination-therapy group and 2377 mg per square meter in the monotherapy group. The median daily dose of lapatinib in the combination-therapy group was 1250 mg. Compliance with the timing of the assessment schedule was similar in the two groups (Fig. 1 of the Supplementary Appendix).

INTERIM ANALYSIS OF DISEASE-PROGRESSION EVENTS

On March 20, 2006, the data and safety monitoring committee reviewed the interim analysis based on 114 disease-progression events. Forty-five disease-progression events occurred in the combination-therapy group and 69 occurred in the monotherapy group (hazard ratio for disease pro-

Table 1. Baseline Characteristics of the 324 Women Included in the Analysis.		
Characteristic	Lapatinib plus Capecitabine (N=163)	Capecitabine Alone (N=161)
Age — yr		
Median	54	51
Range	26–80	28–83
ECOG performance status — no. (%)		
0	96 (59)	89 (55)
1	61 (37)	68 (42)
Unknown	6 (4)	4 (2)
Hormone receptor status — no. (%)		
Positive for estrogen receptor, progesterone receptor, or both	78 (48)	75 (47)
Negative for both estrogen receptor and progesterone receptor	80 (49)	80 (50)
Unknown	5 (3)	6 (4)
Stage of disease — no. (%)		
IIIB or IIIC	7 (4)	7 (4)
Metastatic	156 (96)	154 (96)
No. of advanced or metastatic sites — no. (%)		
≥3	79 (48)	80 (50)
2	53 (33)	46 (29)
1	31 (19)	35 (22)
Advanced or metastatic sites — no. (%)		
Visceral only	27 (17)	28 (17)
Visceral and nonvisceral	98 (60)	96 (60)
Nonvisceral only	38 (23)	37 (23)
Previous therapy — no. (%)		
Anthracyclines	158 (97)	156 (97)
Taxanes	159 (98)	156 (97)
Fluorouracil	83 (51)	92 (57)
Vinorelbine	71 (44)	70 (43)
Trastuzumab	157 (96)	156 (97)
As adjuvant therapy	7 (4)	9 (6)
As neoadjuvant therapy	0	1 (<1)
For metastatic disease	150 (96)	146 (94)
Duration of trastuzumab therapy — wk		
Median	42	44
Range	3–296	5–329
Duration of trastuzumab therapy — no. (%)		
<6 wk	2 (1)	2 (1)
6–12 wk	19 (12)	11 (7)
>12 wk	136 (87)	143 (92)
Time from discontinuation of trastuzumab therapy to randomization — no. (%)		
<4 wk	49 (31)	40 (26)
4–8 wk	49 (31)	54 (35)
>8 wk	59 (38)	60 (38)
Unknown	0	2 (1)

Figure 2. Cumulative Incidence of Disease Progression or Death from Breast Cancer According to the Assessment of the Independent Review Committee (Panel A), Kaplan–Meier Estimates of Overall Survival (Panel B), and Cumulative Incidence of Disease Progression or Death from Breast Cancer According to the Site Investigators' Assessments (Panel C).

gression, 0.51; 95% confidence interval [CI], 0.35 to 0.74; $P < 0.001$). The one-sided P value of 0.00016 ensured that the superiority boundary ($P = 0.0014$), recalculated for 114 events, was crossed.

PRIMARY END-POINT ANALYSIS AFTER DATA VALIDATION

After the data validation, the analyses were repeated on the basis of the 121 disease-progression events assessed by the independent reviewers. Progressive disease accounted for 101 of the events; 20 were breast cancer–related deaths. Forty-nine disease-progression events occurred in the combination-therapy group, and 72 occurred in the monotherapy group (hazard ratio, 0.49; 95% CI, 0.34 to 0.71; $P < 0.001$) (Fig. 2A). The one-sided P value of 0.00004 showed that the superiority boundary that was recalculated for 121 events ($P = 0.0019$) had also been crossed. The median time to progression was 8.4 months with combination therapy and 4.4 months with monotherapy. A Cox regression model indicated that the only significant effect on time to progression was the treatment assignment. Although the assumption of proportional hazards was not met, the model indicated that the average hazard ratio for the combination therapy as compared with capecitabine alone was 0.47 (95% CI, 0.32 to 0.68; $P < 0.001$).

SECONDARY END POINTS

The overall response rate was 22% (95% CI, 16 to 29) in the combination-therapy group and 14% (95% CI, 9 to 21) in the monotherapy group ($P = 0.09$). The corresponding clinical-benefit rates were 27% for the combination-therapy group and 18% for the monotherapy group (Table 2). Forty-nine events (disease progression or death from any cause) occurred in the combination-therapy group, and 76 occurred in the monotherapy group (hazard ratio for disease progression or death from any cause in the combination-therapy group, 0.47; 95% CI, 0.33 to 0.67; $P < 0.001$). Thirty-six deaths occurred in the combination-therapy group,

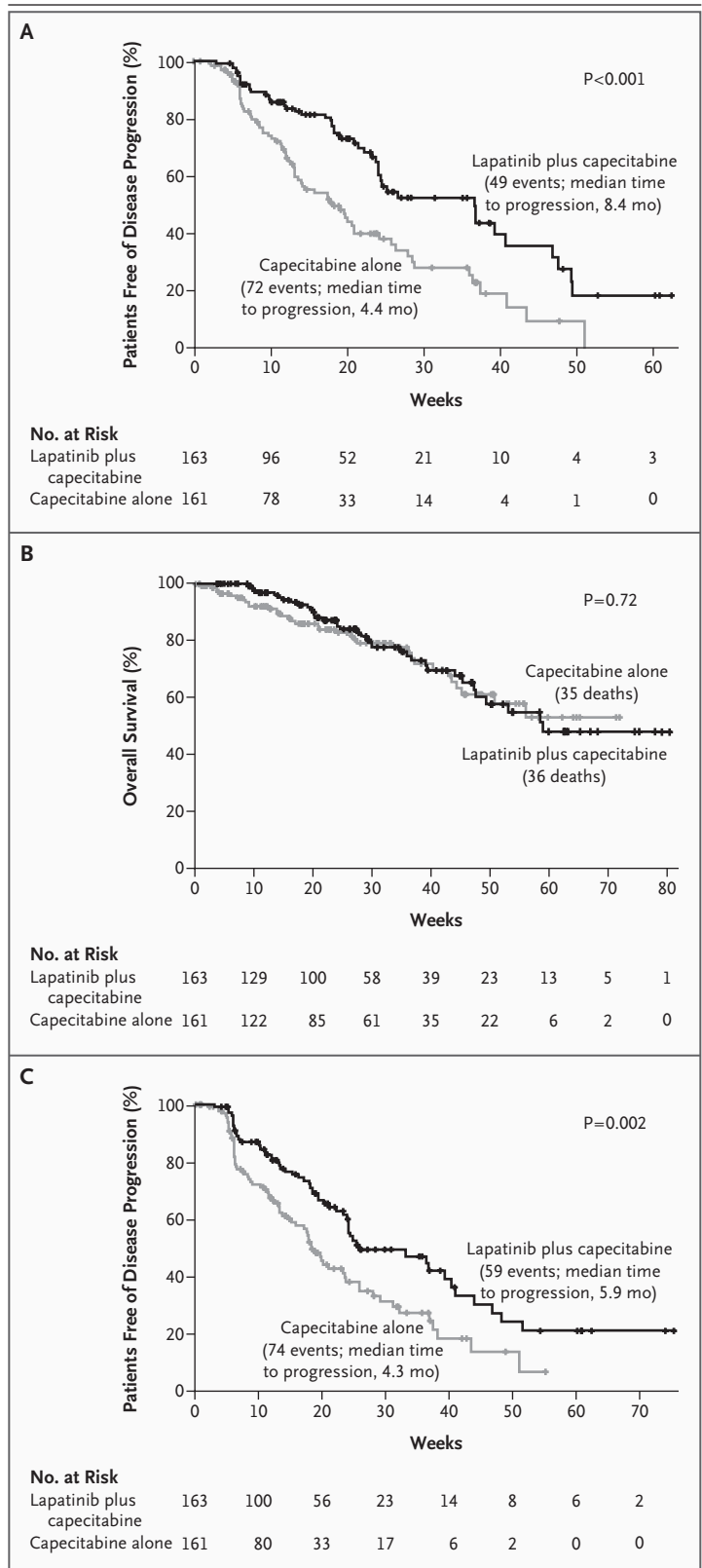


Table 2. Efficacy End Points in the Intention-to-Treat Population.*

End Point	Lapatinib plus Capecitabine (N=163)	Capecitabine Alone (N=161)	Hazard Ratio (95% CI)	P Value
Median time to progression — mo	8.4	4.4	0.49 (0.34–0.71)	<0.001†
Median progression-free survival — mo	8.4	4.1	0.47 (0.33–0.67)	<0.001†
Overall response — % (95% CI)	22 (16–29)	14 (9–21)		0.09‡
Complete response — no. (%)	1 (<1)	0 (0)		
Partial response — no. (%)	35 (21)	23 (14)		
Clinical benefit — no. (%)	44 (27)	29 (18)		
Death — no. (%)	36 (22)	35 (22)		

* End points are based on evaluation by the independent review committee under blinded conditions.

† The P value was calculated with the log-rank test.

‡ The P value was calculated with Fisher's exact test.

and 35 occurred in the monotherapy group (hazard ratio, 0.92; 95% CI, 0.58 to 1.46; $P=0.72$) (Fig. 2B).

CNS AS THE SITE OF FIRST PROGRESSION

In the monotherapy group, 11 women had progressive CNS metastases, as compared with 4 women in the combination-therapy group. This difference was not statistically significant ($P=0.10$ by Fisher's exact test).

SUPPORTIVE ANALYSES

An analysis of the investigator-assessed time to progression, based on the date of disease progression or death due to breast cancer, was conducted for the first 133 of the 146 reported disease-progression events. The subsequent 13 events were censored for this analysis. Investigators reported 59 disease-progression events in the combination-therapy group and 74 in the monotherapy group (hazard ratio for disease progression in the combination-therapy group, 0.59; 95% CI, 0.42 to 0.84; $P=0.002$) (Fig. 2C). The median time to progression was 5.9 months in the combination-therapy group and 4.3 months in the monotherapy group. Investigator-assessed response rates were 29% (95% CI, 23 to 37) in the combination-therapy group and 17% (95% CI, 11 to 24) in the monotherapy group ($P=0.01$).

Table 2 of the Supplementary Appendix shows a 75% concordance between the assessments of time to progression that were made by the independent reviewers and the assessments made by the investigators. The primary reasons for differences were alternative interpretations of lesions and selection of different lesions by reviewers. In

a sensitivity analysis with the use of the earliest disease-progression event assessed by the investigator or by the independent reviewers, there were 167 events: 74 in the combination-therapy group and 93 in the monotherapy group (hazard ratio for progression, 0.59; 95% CI, 0.43 to 0.80; $P<0.001$).

ADVERSE EVENTS

Table 3 shows adverse events through November 15, 2005, according to the treatment received. The most common adverse events were diarrhea, the hand-foot syndrome, nausea, vomiting, fatigue, and rash that was distinct from the hand-foot syndrome. Most adverse events were grade 1, 2, or 3. Grade 4 diarrhea occurred in two women in the combination-therapy group (1%). One case each of grade 4 fatigue, headache, and dizziness was reported in the monotherapy group. Diarrhea, dyspepsia, and rash occurred more often in the group of women who received combination therapy. Five women had a fatal adverse event: two in the combination-therapy group and three in the monotherapy group. The death of one woman in the monotherapy group, who had diarrhea, vomiting, and small-bowel obstruction, was deemed by the investigator to be related to drug toxicity. Adverse events led to discontinuation of treatment in 22 women in the combination-therapy group (13%) and in 18 women in the monotherapy group (12%).

CARDIAC SAFETY

Asymptomatic cardiac events were identified in four women in the combination-therapy group and in one woman in the monotherapy group. All

Table 3. Adverse Events.

Event	Lapatinib plus Capecitabine (N = 164)					Capecitabine Alone (N = 152)					P Value*
	Grade 1	Grade 2	Grade 3	Grade 4†	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4†	Any Grade	
	<i>number of events (percent)</i>										
Diarrhea	44 (27)	33 (20)	19 (12)	2 (1)	98 (60)	21 (14)	22 (14)	17 (11)	0	60 (39)	<0.001
Nausea	48 (29)	21 (13)	3 (2)	0	72 (44)	42 (28)	18 (12)	3 (2)	0	64 (42)‡	0.83
Vomiting	30 (18)	10 (6)	3 (2)	0	43 (26)	22 (14)	11 (7)	3 (2)	0	37 (24)‡	0.80
Stomatitis	17 (10)	7 (4)	0	0	24 (15)	12 (8)	5 (3)	1 (<1)	0	18 (12)	0.57
Abdominal pain	13 (8)	10 (6)	2 (1)	0	25 (15)	17 (11)	13 (9)	2 (1)	0	32 (21)	0.23
Constipation	14 (9)	2 (1)	0	0	16 (10)	13 (9)	3 (2)	1 (<1)	0	17 (11)	0.82
Dyspepsia	13 (8)	5 (3)	0	0	18 (11)	4 (3)	1 (<1)	0	0	5 (3)	0.014
Hand-foot syndrome	16 (10)	52 (32)	12 (7)	0	80 (49)	19 (12)	39 (26)	16 (11)	0	74 (49)	1.00
Rash	32 (20)	11 (7)	2 (1)	0	45 (27)	14 (9)	7 (5)	2 (1)	0	23 (15)	0.011
Dry skin	18 (11)	0	0	0	18 (11)	6 (4)	2 (1)	0	0	8 (5)	0.10
Fatigue	16 (10)	10 (6)	3 (2)	0	29 (18)	17 (11)	18 (12)	5 (3)	1 (<1)	41 (27)	0.06
Mucosal inflammation	11 (7)	7 (4)	0	0	18 (11)	7 (5)	9 (6)	3 (2)	0	19 (12)	0.80
Asthenia	6 (4)	4 (2)	0	0	10 (6)	7 (5)	8 (5)	3 (2)	0	18 (12)	0.11
Headache	9 (5)	6 (4)	0	0	15 (9)	13 (9)	4 (3)	1 (<1)	1 (<1)	20 (13)†	0.34
Pain in extremity	13 (8)	6 (4)	1 (<1)	0	21 (13)†	9 (6)	2 (1)	1 (<1)	0	13 (9)†	0.30
Back pain	9 (5)	6 (4)	2 (1)	0	17 (10)	5 (3)	3 (2)	1 (<1)	0	9 (6)	0.22
Anorexia	18 (11)	6 (4)	1 (<1)	0	25 (15)	21 (14)	8 (5)	1 (<1)	0	30 (20)	0.37
Dyspnea	8 (5)	5 (3)	5 (3)	0	18 (11)	4 (3)	3 (2)	3 (2)	0	10 (7)	0.24

* P values were calculated with Fisher's exact test for differences in toxicities of any grade.

† A total of 13 grade 4 adverse events occurred among 10 (6%) of the patients receiving lapatinib plus capecitabine, and 16 grade 4 adverse events occurred among 11 (7%) of the patients receiving capecitabine alone. These differences are not significant.

‡ The number includes one event with an unknown grade.

of these events in the combination-therapy group were considered to be related to treatment, and all women had an LVEF value that was at or above the lower limit of the normal range on subsequent assessment. Prinzmetal's angina developed in one of the four women. It resolved when the study treatment was permanently discontinued, but there was a subsequent drop in the LVEF. An asymptomatic cardiac event occurred in one of the four women after tumor progression, and in the remaining two women, treatment with lapatinib was resumed at a dose of 1000 mg daily without recurrence of a cardiac event. The cardiac event in the monotherapy group was deemed to be unrelated to treatment and did not resolve. There were no symptomatic cardiac events, and lapatinib was not discontinued because of a decrease in the LVEF. There were no differences in the mean LVEF values between the two groups at scheduled assessments (Figure 2 of the Supplementary Appendix).

DISCUSSION

This phase 3, randomized study compared lapatinib plus capecitabine with capecitabine alone in women with advanced, progressive HER2-positive breast cancer who had received multiple previous treatments. The interim analysis showed that the addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression. The early reporting boundary for superiority was crossed. The median time to progression was 8.4 months in the combination-therapy group and 4.4 months in the monotherapy group. On the basis of the efficacy analysis and the absence of concern about safety, the data and safety monitoring committee recommended terminating enrollment and reporting the results.

To minimize ascertainment bias, the determination of the primary end point (time to progression) was based on an assessment of disease status by independent reviewers under blinded

conditions. This design is consistent with the guidelines of the Food and Drug Administration.¹⁷ The independent reviewers identified different and fewer disease-progression events than did the investigators, but the rates of discordance were similar for the two treatment groups, and despite the differences, there was a consistent, statistically significant reduction in disease-progression events with lapatinib plus capecitabine. The sensitivity analysis provides support for the strength of the findings.

As compared with capecitabine alone, lapatinib plus capecitabine was not associated with an increase in either serious toxic effects or rates of discontinuation related to adverse events. There were no withdrawals from treatment due to declines in LVEF, no cases of congestive heart failure, and no decreases in the mean LVEF values in the group receiving lapatinib. There was a bias, because we selected women for this study who had normal cardiac function after they had received therapies that included trastuzumab. Also, since the duration of observation was limited, the possibility of late events cannot be excluded. Nevertheless, the low incidence of adverse cardiac effects of lapatinib is reassuring.

The development of CNS metastases is an important clinical problem occurring in approximately one third of women with metastatic breast cancer who receive trastuzumab.^{18,19} Although CNS disease developed in a small number of women during this study, it occurred in fewer

women in the combination-therapy group than in the monotherapy group (4 vs. 11); the difference was not statistically significant.

This trial shows that lapatinib, a small-molecule, tyrosine kinase inhibitor that blocks downstream signaling pathways of HER2 and EGFR through inhibition of the autophosphorylation sites on the receptors,^{10,12,20} has clinical activity in HER2-positive breast cancer. The results provide support for the use of lapatinib and capecitabine in women with progression of HER2-positive breast cancer after treatment with trastuzumab. The findings also warrant evaluation of the role of lapatinib, which has a mechanism of action distinct from that of trastuzumab, earlier in the treatment of HER2-positive breast cancer.

Supported by GlaxoSmithKline.

Dr. Geyer reports receiving consulting fees from GlaxoSmithKline; Dr. Pienkowski, consulting fees from Roche; Dr. Kaufman, consulting and lecture fees from GlaxoSmithKline; and Dr. Crown, consulting, lecture fees, and grant support from GlaxoSmithKline. Mr. Forster and Drs. Berger, Oliva, Rubin, and Stein are employees of GlaxoSmithKline. Mr. Forster and Drs. Berger and Stein report holding equity stock in GlaxoSmithKline. Dr. Cameron reports receiving consulting and lecture fees from GlaxoSmithKline and Roche and grant support from Roche. Confidentiality agreements between academic authors of this report and the sponsor did not extend to the data collected and analyzed in this trial. No other potential conflict of interest relevant to this article was reported.

We thank the women who participated in this study; the members of the independent data and safety monitoring committee; Beth Newstat, Melanie Bailey-Tippetts, and Steve Ashton from GlaxoSmithKline; and the Phillips Group for technical assistance in the preparation of the manuscript.

APPENDIX

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