

Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer

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A B S T R A C T

Purpose

Cross-talk between human epidermal growth factor receptors and hormone receptor pathways may cause endocrine resistance in breast cancer. This trial evaluated the effect of adding lapatinib, a dual tyrosine kinase inhibitor blocking epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2), to the aromatase inhibitor letrozole as first-line treatment of hormone receptor (HR)–positive metastatic breast cancer (MBC).

Patients and Methods

Postmenopausal women with HR-positive MBC were randomly assigned to daily letrozole (2.5 mg orally) plus lapatinib (1,500 mg orally) or letrozole and placebo. The primary end point was progression-free survival (PFS) in the HER2-positive population.

Results

In HR-positive, HER2-positive patients ($n = 219$), addition of lapatinib to letrozole significantly reduced the risk of disease progression versus letrozole-placebo (hazard ratio [HR] = 0.71; 95% CI, 0.53 to 0.96; $P = .019$); median PFS was 8.2 v 3.0 months, respectively. Clinical benefit (responsive or stable disease ≥ 6 months) was significantly greater for lapatinib-letrozole versus letrozole-placebo (48% v 29%, respectively; odds ratio [OR] = 0.4; 95% CI, 0.2 to 0.8; $P = .003$). Patients with centrally confirmed HR-positive, HER2-negative tumors ($n = 952$) had no improvement in PFS. A preplanned Cox regression analysis identified prior antiestrogen therapy as a significant factor in the HER2-negative population; a nonsignificant trend toward prolonged PFS for lapatinib-letrozole was seen in patients who experienced relapse less than 6 months since prior tamoxifen discontinuation (HR = 0.78; 95% CI, 0.57 to 1.07; $P = .117$). Grade 3 or 4 adverse events were more common in the lapatinib-letrozole arm versus letrozole-placebo arm (diarrhea, 10% v 1%; rash, 1% v 0%, respectively), but they were manageable.

Conclusion

This trial demonstrated that a combined targeted strategy with letrozole and lapatinib significantly enhances PFS and clinical benefit rates in patients with MBC that coexpresses HR and HER2.

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INTRODUCTION

Despite recent advances in the treatment of hormone receptor (HR)–positive metastatic breast cancer (MBC), resistance to endocrine therapies limits their success. Cross-talk between pathways involving the epidermal growth factor family of receptors—ErbB1 (epidermal growth factor receptor [EGFR]) and ErbB2 (human epidermal growth factor receptor 2 [HER2])—and the estrogen receptor (ER) has been implicated in resistance to endocrine therapy.¹⁻⁵ This has created a rationale for using

targeted agents against EGFR pathways in combination with endocrine manipulation to overcome endocrine resistance.

Overexpression of HER2 confers resistance to established endocrine therapies,^{2,6-8} and a randomized trial in HR-positive, HER2-positive MBC reported that trastuzumab combined with the aromatase inhibitor (AI) anastrozole doubled the median progression-free survival (PFS) compared with anastrozole alone from 2.4 to 4.8 months.⁹ Experimental models have shown that hormone-sensitive ER-positive breast cancer cells

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that initially lack EGFR or HER2 develop acquired resistance over time with enhanced expression of receptors involved in cross-talk with ER.¹⁰⁻¹⁴ Two randomized trials in HR-positive MBC suggested that the EGFR tyrosine kinase inhibitor (TKI) gefitinib may improve PFS when added to endocrine therapy.^{15,16} Thus, for patients with HR-positive, HER2-positive tumors, a strategy of combined therapy might enhance endocrine effectiveness, whereas it could delay disease progression for those with HR-positive, HER2-negative tumors at risk of early relapse.

Lapatinib, a potent, orally active, dual TKI against EGFR and HER2, has demonstrated activity in both trastuzumab-naïve and pretreated HER2-positive MBC.¹⁷⁻²⁵ Synergy between lapatinib and tamoxifen occurs in models of endocrine resistance.^{26,27} A phase I study confirmed that letrozole and lapatinib could be coadministered at their recommended doses without pharmacokinetic interac-

tion.²⁸ This phase III trial compared the combination of letrozole plus lapatinib with letrozole plus placebo as first-line treatment of patients with HR-positive MBC, including a population with known HER2-positive tumors.

PATIENTS AND METHODS

Patients

Eligible patients were postmenopausal women with histologically confirmed stage IIIB/IIIC or IV ER-positive and/or progesterone receptor (PgR)–positive invasive breast cancer. No prior therapy for advanced or metastatic disease was allowed. Prior neoadjuvant/adjuvant antiestrogen therapy was allowed, as was adjuvant AI and/or trastuzumab, provided it was completed more than 1 year before study entry. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, normal organ function, and a

Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	HER2 Positive				ITT			
	Letrozole + Placebo (n = 108)		Letrozole + Lapatinib (n = 111)		Letrozole + Placebo (n = 644)		Letrozole + Lapatinib (n = 642)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years*								
Median	59		60		63		62	
Range	45-87		44-85		35-95		31-94	
ECOG performance status*								
0	51	47	59	53	349	54	370	58
≥ 1	57	53	51	46	286	44	268	42
Hormone receptor status*								
ER/PgR positive	69	64	74	67	414	64	420	65
ER positive/PgR negative	20	19	19	17	90	14	91	14
Disease stage								
IIIB or IIIC	7	6	5	5	30	5	25	4
IV	101	94	106	95	613	95	616	96
No. of metastatic sites*								
Median	2		2		2		2	
Range	1-7		1-7		0-7		0-7	
Disease stage								
Bone only	18	17	16	14	85	13	94	15
Visceral or soft tissue	90	83	95	86	559	87	548	85
Liver	37	34	33	30	171	27	146	23
Lung	40	37	43	39	242	38	248	39
Lymph node	43	40	57	51	304	47	312	49
Soft tissue	31	29	35	32	218	34	212	33
Other	18	17	19	17	127	20	125	19
Previous therapy								
Endocrine*	62	57	60	54	317	49	313	49
Tamoxifen or toremifene only	60	56	59	53	302	47	300	47
Aromatase inhibitor only	1	< 1	1	< 1	3	< 1	5	< 1
Chemotherapy*	51	47	61	55	280	43	281	44
Anthracycline only	38	35	41	37	172	27	171	27
Anthracyclines and taxanes	9	8	9	8	41	6	42	7
Other	4	4	11	10	66	10	68	11
Biologic therapy (any)	1	< 1	1	< 1	1	< 1	2	< 1
Interval since prior adjuvant antiestrogen therapy*								
≥ 6 months or no prior therapy	67	62	73	66	487	76	501	78
< 6 months	41	38	38	34	157	24	141	22

Abbreviations: HER2, human epidermal growth factor receptor 2; ITT, intent to treat; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.

*Indicates prespecified baseline prognostic factors used in predefined stepwise Cox regression model. Additional factors included treatment, disease-free interval, and serum HER2 (extracellular domain) at baseline.

left ventricular ejection fraction (LVEF) within the institutional range of normal. Patients with extensive symptomatic visceral disease were excluded. Availability of archived tumor tissue was required for subsequent biomarker analyses. All patients provided signed informed consent, and the protocol was approved by institutional review boards. This study was funded by GlaxoSmithKline (Research Triangle Park, NC) and conducted in accordance with good clinical practice and all applicable regulatory requirements, including the 1996 version of the Declaration of Helsinki.

Study Design

This was a randomized, double-blind, controlled, parallel-group, multicenter, phase III study. Patients were stratified by sites of disease (soft tissue/visceral or bone-only disease) and prior adjuvant antiestrogen therapy (< 6 months since discontinuation or \geq 6 months since discontinuation or no prior endocrine therapy). The combination regimen consisted of lapatinib 1,500 mg orally and letrozole 2.5 mg orally daily. The control arm consisted of letrozole 2.5 mg daily with matching lapatinib placebo pill. Therapy on both arms was administered daily until disease progression or withdrawal from study. The protocol did not permit crossover of treatment at the time of progression.

Women were assessed before each 4-week course of therapy, every 12 weeks starting at week 108, and at study conclusion or withdrawal. All patients were observed for survival information. Randomized therapy was permanently discontinued for unacceptable toxicity assessed according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0) or for the development of grade 3 or 4 interstitial pneumonitis, hepatotoxicity, or cardiac dysfunction. Cardiac evaluations were performed at 8-week intervals before week 108 and at 12-week intervals thereafter. Recommendations for dose modifications and toxicity management were provided in accordance with US Food and Drug Administration–approved lapatinib prescribing information.²⁹

The primary end point was investigator-assessed PFS, defined as time from random assignment until the earliest date of disease progression or death as a result of any cause in the HER2-positive population. Secondary end points included overall response rate (ORR); clinical benefit rate (CBR), which was defined as complete response, partial response, or stable disease for \geq 6 months; overall survival (OS); safety; and PFS for the intent-to-treat (ITT) HR-positive population. Disease progression and response evaluations were determined according to Response Evaluation Criteria in Solid Tumors (RECIST).³⁰ Measurable disease was not required. The ITT population included all randomly assigned patients regardless of whether they received study medication. The HER2-positive population included all randomly assigned patients who had documented HER2 positivity in a commercial laboratory³¹ in primary or metastatic sites defined as either fluorescence in situ hybridization positive, 3+ staining intensity by immunohistochemistry, or 2+ by immunohistochemistry and fluorescence in situ hybridization positive. The safety population included all patients who received at least one dose of randomized therapy.

Statistical Analysis

Two sample size calculations were performed. A total of 1,280 HR-positive patients were required to ensure that 218 patients with HER2-positive tumors were enrolled to obtain 173 events with 80% power to detect a hazard ratio (HR) of 0.645 ($\alpha = .05$). Additionally, 612 events were needed in the ITT population to provide 90% power to detect an HR of 0.769. To ensure that the overall type I α error rate was preserved, a closed hierarchical testing procedure was used, whereby PFS was initially tested in the HER2-positive population at an α level of .05. Testing was performed in the ITT population at an α level of .05 only if statistical significance was achieved in the HER2-positive population. An Independent Data Monitoring Committee convened on an ongoing basis to monitor safety data. PFS and OS were summarized using the Kaplan-Meier method and compared between treatment arms using a stratified log-rank test, stratifying for site of disease and prior adjuvant antiestrogen therapy. The date of documented disease progression was defined as the date of either radiologic or symptomatic disease progression. To further explore the impact of well-known prespecified baseline prognostic factors (Table 1) on PFS and OS, a predefined stepwise Cox regression model was used.

RESULTS

Patient Population

Between December 9, 2003 and December 29, 2006, 1,286 patients with HR-positive MBC were randomly assigned to receive letrozole plus lapatinib ($n = 642$) or letrozole plus placebo ($n = 644$); of these, 17% of patients in each arm had tumors centrally confirmed in a commercial laboratory as HER2 positive ($n = 111$ and $n = 108$, respectively). The safety population consisted of 1,278 patients. Figure 1 outlines all treatment populations.

Baseline patient and disease characteristics were well balanced between treatment arms for both the HER2-positive and ITT HR-positive populations (Table 1). Only three patients received prior adjuvant trastuzumab therapy.

Clinical Efficacy

After a median follow-up time of 1.8 years, median PFS for patients in the HER2-positive population increased from 3.0 months for letrozole-placebo to 8.2 months for letrozole-lapatinib, demonstrating a significant reduction in the risk of progression for the combination (HR = 0.71; 95% CI, 0.53 to 0.96; $P = .019$; Fig 2A). In the HER2-positive population, the ORR was significantly improved from 15% to 28% for patients treated with letrozole-lapatinib (odds ratio [OR] = 0.4; 95% CI, 0.2 to 0.9; $P = .021$). Including patients with stable disease for \geq 6 months, the CBR was likewise significantly improved (29% to 48%; OR = 0.4; 95% CI, 0.2 to 0.8; $P = .003$; Fig 2B). With less than 50% of OS events yet recorded, the median OS in the HER2-positive population was 32.3 months in the letrozole-placebo arm compared with 33.3 months in the combination arm (HR = 0.74; 95% CI, 0.5 to 1.1; $P = .113$; Fig 2C).

The significant result for PFS in the HER2-positive population allowed for analysis of the ITT HR-positive population by hierarchical testing. After a median follow-up of 2 years, median PFS increased from 10.8 months with letrozole-placebo to 11.9 months with the combination (HR = 0.86; 95% CI, 0.76 to 0.98; $P = .026$; Fig 3A), and there was no statistical difference in ORR or CBR between treatment arms (Fig 3B). In the 952 patients with centrally confirmed HER2-negative tumors, there was no improvement in PFS (HR = 0.90; 95% CI, 0.77 to 1.05; $P = .188$).

The stepwise Cox regression analysis for PFS adjusting for known baseline prognostic factors confirmed the benefit of combination therapy in the HER2-positive population (HR = 0.65; 95% CI, 0.47 to 0.89; $P = .008$). After retaining treatment and stratification factors, age (younger), performance status (0), and baseline serum soluble HER2 extracellular domain (measured by quantitative enzyme-linked immunosorbent assay) were identified as being significant. In the HER2-negative population, there was also an impact of combination therapy on PFS, and in addition to the significant baseline factors mentioned earlier, the number of metastatic sites (< three sites) and prior adjuvant antiestrogen stratification were identified as being significant in the HER2-negative population.

In view of this finding and the relevance of prior tamoxifen exposure in the HER2-negative population on endocrine resistance, an exploratory analysis of predefined prior antiestrogen therapy stratification was performed. In the \geq 6 months since discontinuation/none group ($n = 752$), 33% of patients had received prior adjuvant

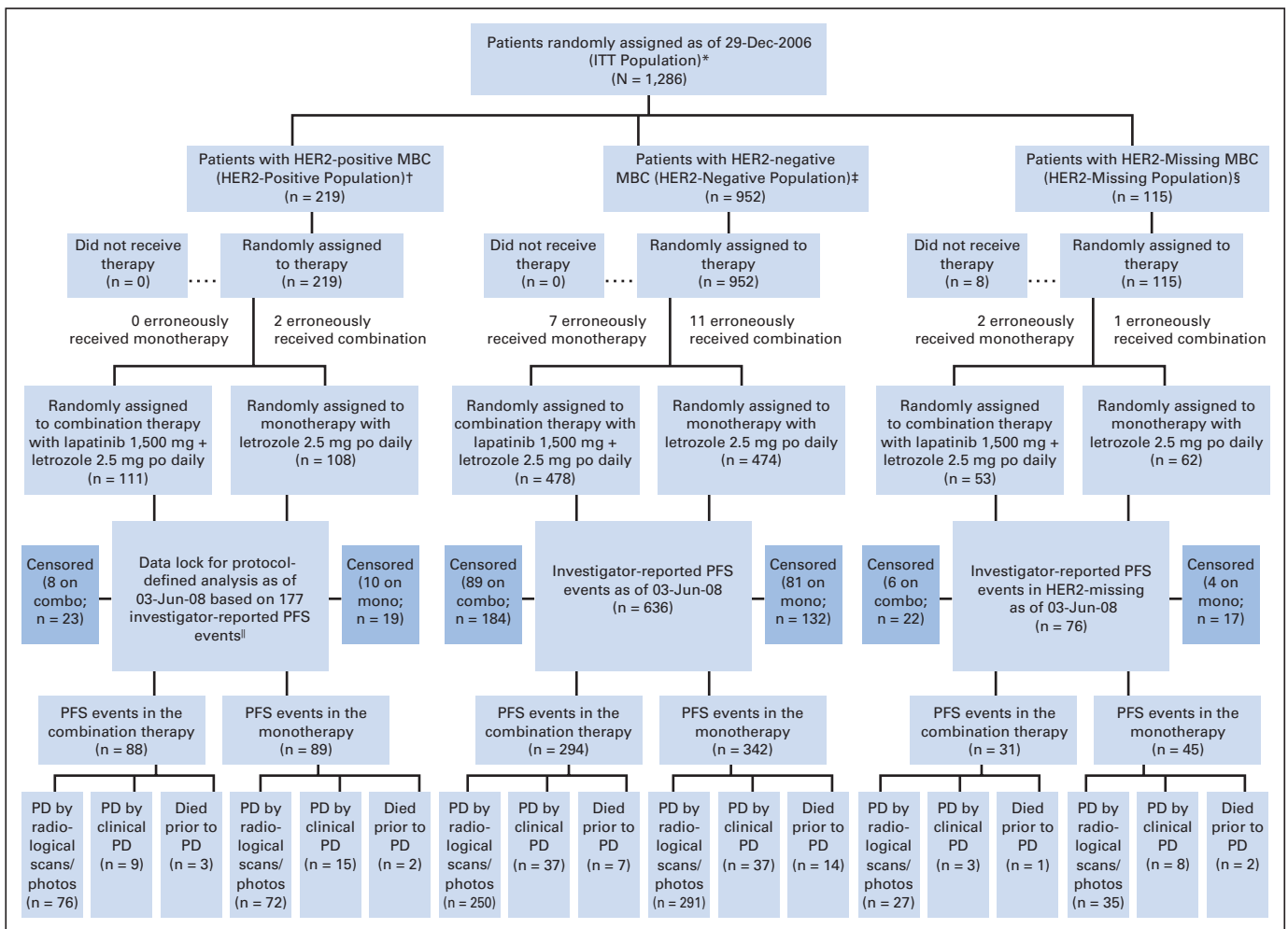


Fig 1. Study design, populations, random assignment, and assessment of events. (*) In the intent-to-treat (ITT) population, 1,088 patients discontinued treatment—64% for progression, 5% for consent withdrawal, 10% for an adverse event, 1% for a protocol violation, < 1% for death, < 1% lost to follow-up, and 3% for other reasons (including but not limited to radiation, surgery, scans misread/misinterpreted, and investigator discretion). (†) In the human epidermal growth factor receptor 2 (HER2) –positive population, 201 patients discontinued treatment—76% for progression, 6% for consent withdrawal, 5% for an adverse event, 1% for a protocol violation, < 1% for death, and 3% for other reasons. (‡) In the HER2-negative population, 782 patients discontinued treatment—11% as a result of an adverse event, 4% as a result of consent withdrawal, < 1% as a result of loss to follow-up, 1% as a result of protocol violation, 62% as a result of progression, < 1% as a result of death, and 3% as a result of other reasons. (§) In the population with HER2 status unknown, 105 patients discontinued treatment—64% for progressive disease, 10% for consent withdrawal, 10% for an adverse event, < 1% for protocol violation, < 1% lost to follow-up, < 1% for death, and 5% for other reasons. (¶) The protocol-defined primary and secondary study analyses were to commence once approximately 173 events (disease progression or deaths on study) had occurred in the HER2-positive population. MBC, metastatic breast cancer; po, orally; combo, combination therapy; mono, monotherapy; PFS, progression-free survival; PD, progressive disease.

tamoxifen (median duration, 5.0 years); median time since discontinuation was 3.5 years. The remaining 67% of patients had no prior exposure to hormone therapy. The HR for PFS in this group was 0.94 (95% CI, 0.79 to 1.13; $P = .522$; Fig 4A). The overall CBR was similar between the letrozole-lapatinib and letrozole-placebo arms (62% v 64%, respectively) within the ≥ 6 months since discontinuation/none group, regardless of PgR status (Fig 4B). In the less than 6 months since discontinuation group ($n = 200$), the median duration of prior adjuvant tamoxifen was 2.8 years; median time since discontinuation was only 1 month. By contrast, the HR in this group was 0.78 (95% CI, 0.57 to 1.07; $P = .117$; Fig 5A), with an increase in median PFS from 3.1 to 8.3 months favoring the combination. A numerically higher CBR was found in the letrozole-lapatinib arm versus letrozole-placebo arm (44% v 32%, respectively; OR = 0.6; 95% CI, 0.3 to 1.1; $P = .112$; Fig 5B), and analysis based on PgR (positive or negative) status showed a

consistent numerical difference in favor of the combination arm, especially for those with PgR-negative tumors, with five (36%) of 14 patients having clinical benefit in the letrozole-lapatinib arm versus two (15%) of 13 patients treated with letrozole alone (Fig 5B). However, by logistic regression analysis, no interaction between treatment group and PgR status was seen.

Safety

Patients received treatment for a median of 40 weeks in the letrozole-lapatinib arm and 38 weeks in the letrozole-placebo arm, with compliance (pill count agreement of > 80%) of more than 95% in both arms. The most common adverse events were diarrhea, rash, nausea, arthralgia, and fatigue (majority were grade 1 or 2), with a higher incidence in the combination arm for diarrhea and rash (Table 2). Of the 60 patients (10%) who had grade 3 or 4 diarrhea in the

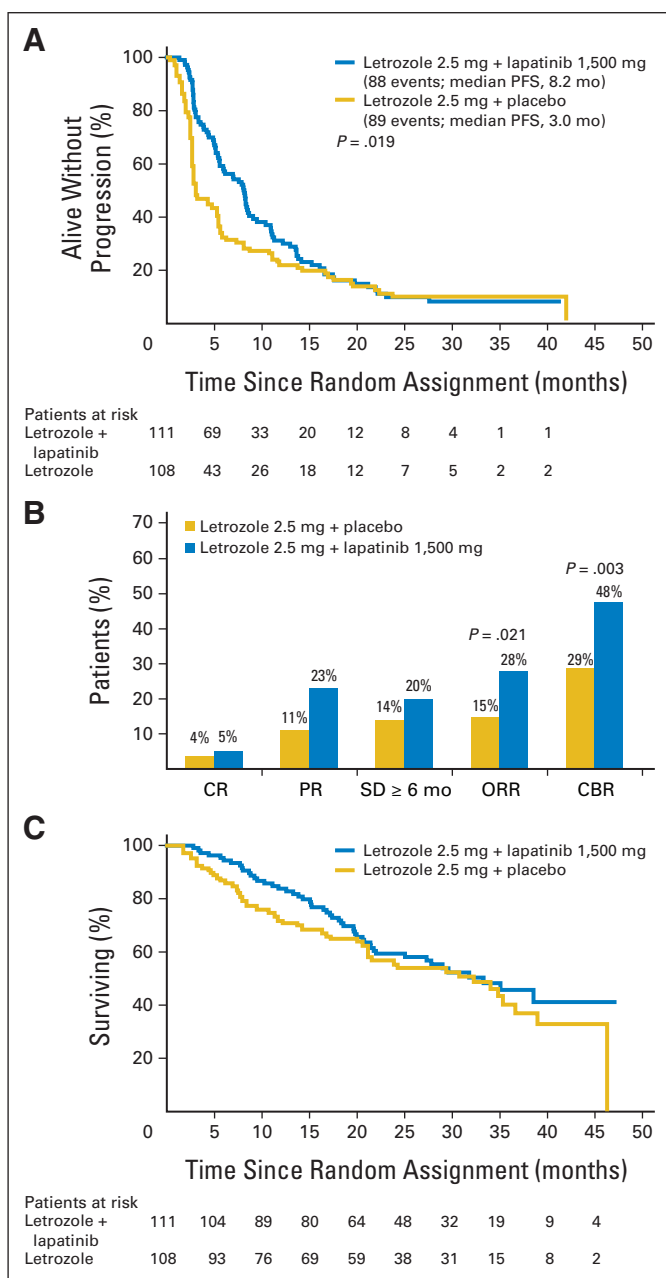


Fig 2. Clinical efficacy in human epidermal growth factor receptor 2–positive population. (A) Kaplan-Meier estimates of progression-free survival (PFS), (B) response rates and clinical benefit rates (CBR), and (C) Kaplan-Meier estimates of overall survival. CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate.

combination arm, 15% required discontinuation. For the remainder, diarrhea was managed by dose reduction (19%), dose interruption (36%), or supportive intervention without treatment dose adjustments (31%). Treatment-related LVEF decline and elevation of liver function transaminases were infrequent. Seven patients had a symptomatic LVEF decline—two patients (0.3%) on letrozole-placebo and five patients (0.8%) on lapatinib-letrazole. One patient on the letrozole-placebo arm was thought to have had drug-induced liver injury (ALT/AST $> 3\times$ upper limit of normal, total bilirubin $\geq 1.5\times$ upper limit of normal, and alkaline phosphatase $< 2\times$ upper limit of

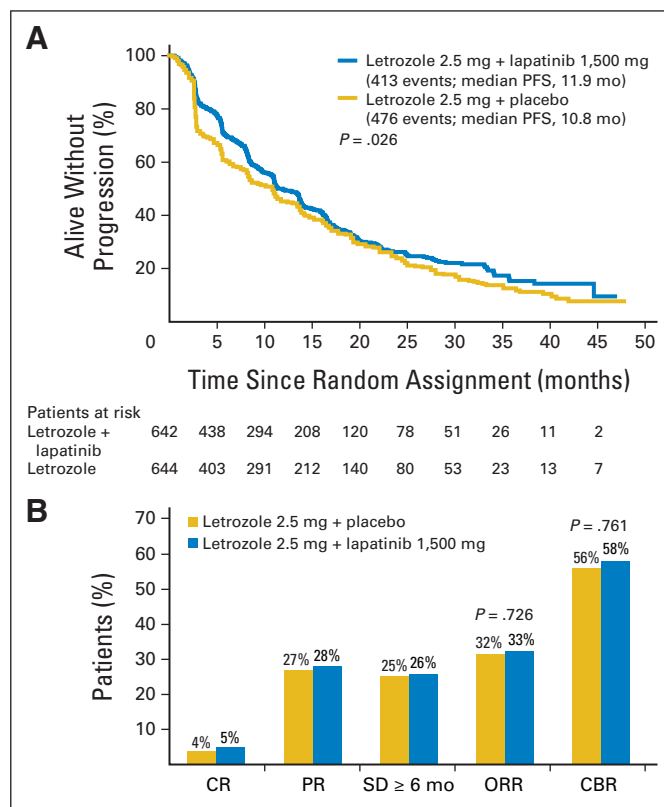


Fig 3. Clinical efficacy in intent-to-treat population. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) response rates and clinical benefit rates (CBR). CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate.

normal) compared with eight patients on the combination arm. Two of the eight women on the combination arm and the patient in the letrozole-placebo arm required drug discontinuation, with resolution of liver function tests thereafter; the other six patients resolved laboratory abnormalities without drug discontinuation. Any serious adverse event related to study drug occurred in 8% of patients receiving the combination compared with 4% of patients receiving letrozole-placebo. There were a total of 16 fatalities related to serious adverse events (eight deaths in each arm), of which only three were deemed related to study drug (one in letrozole-lapatinib arm [hepatobiliary] and two in letrozole-placebo arm [one cardiac, one dyspnea]). No new or unexpected safety signals for either drug were identified.

DISCUSSION

Coexpression of HER2 in HR-positive breast cancer confers relative endocrine resistance, and preclinical models have used targeted strategies to enhance efficacy of either tamoxifen or estrogen deprivation.^{13,14,32-34} The Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer (TANDEM) trial evaluated anastrozole with or without the addition of trastuzumab in HR-positive, HER2-positive MBC ($n = 208$)⁹ and showed that the combined approach had a significant benefit for PFS. Our study demonstrated that in a similar HR-positive, HER2-positive population ($n = 219$), the combination of letrozole and lapatinib significantly prolonged PFS

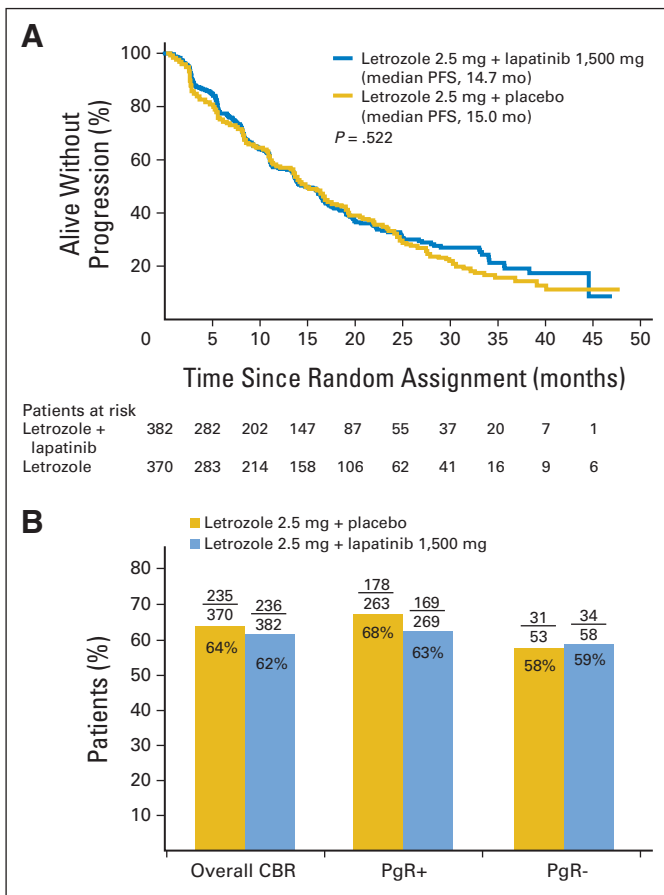


Fig 4. Clinical efficacy in the human epidermal growth factor receptor 2-negative population predefined subgroup with an interval of ≥ 6 months since discontinuation of prior adjuvant tamoxifen or no prior adjuvant tamoxifen. (A) Kaplan-Meier estimates of progression-free survival (PFS) and (B) response and clinical benefit rates (CBR). Progesterone receptor (PgR) status was measured only in known estrogen receptor-positive patients.

compared with letrozole alone (median PFS, 8.2 v 3.0 months respectively), representing a statistically significant 29% reduction in the risk of disease progression. Consistent with these findings, a superior CBR (48% with letrozole-lapatinib v 29% with letrozole alone) and trend toward improvement in OS were also seen. This trial demonstrated that for HR-positive, HER2-positive patients with MBC, the combination of letrozole and lapatinib is superior to an AI plus placebo.

Importantly, the population of women with HER2-positive MBC treated in the studies discussed earlier differ significantly from patients enrolled onto two randomized trials of first-line taxane-based chemotherapy with or without trastuzumab that showed a survival advantage with the addition of targeted therapy.^{35,36} In the endocrine studies, all patients with HER2-positive MBC had HR-positive disease compared with only 40% to 60% of patients in the chemotherapy studies; also, patients in the endocrine studies were older (median age, 60 v 53 to 55 years, respectively) and had a lower incidence of visceral metastases. Although each of the four trials confirmed a benefit with the addition of a targeted therapy over endocrine or chemotherapy alone, these differences in populations preclude direct comparisons. Our study supports letrozole-lapatinib as a possible therapeutic approach to control HR-positive, HER2-positive MBC in appropriate

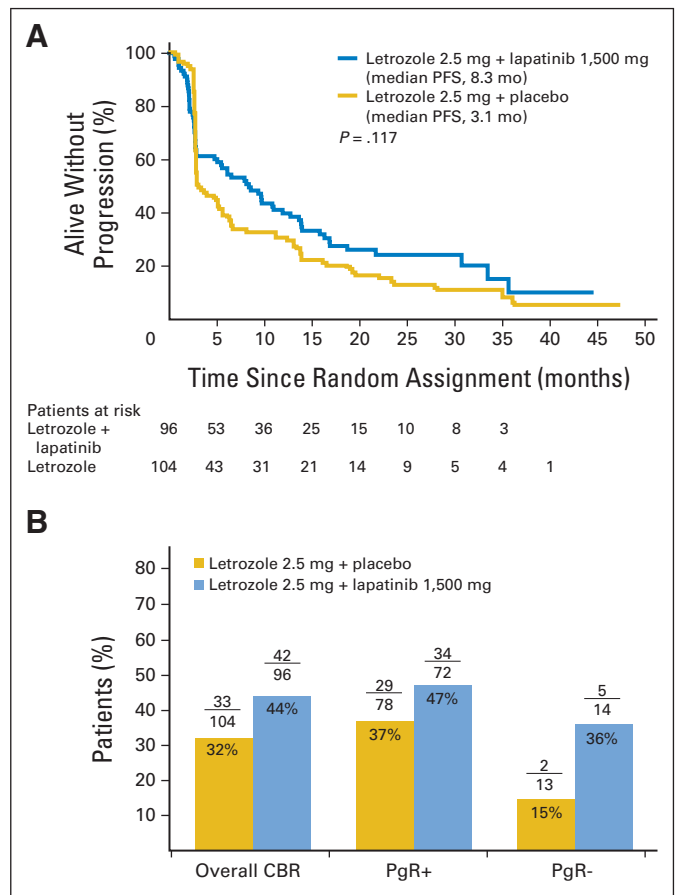


Fig 5. Clinical efficacy in the human epidermal growth factor receptor 2-negative population predefined subgroup with an interval of less than 6 months since discontinuation of prior adjuvant tamoxifen. (A) Kaplan-Meier estimates of progression-free survival (PFS) and (B) response and clinical benefit rates (CBR). Progesterone receptor (PgR) status was measured only in known estrogen receptor-positive patients.

patients for a significant period of time before chemotherapy and trastuzumab are required.

In HR-positive breast carcinomas that are initially HER2 negative, EGFR and HER2 pathways may become upregulated on development of endocrine resistance, and a combined growth factor receptor- and endocrine-targeted approach could delay acquired resistance.^{37,38} Clinically, for patients who relapse during adjuvant therapy with tamoxifen-resistant MBC where growth factor receptors may have become upregulated, dual targeted therapy could enhance the objective response rate compared with AIs alone. Alternatively, in hormone-sensitive MBC without prior tamoxifen exposure, combined therapy could delay the emergence of acquired resistance over time by preventing upregulation of growth factor receptors. Osborne et al¹⁵ demonstrated a trend toward improved PFS for the addition of the EGFR TKI gefitinib to tamoxifen versus tamoxifen alone in patients who were either endocrine naïve or more than 12 months since completion of prior adjuvant endocrine therapy (median PFS, 10.9 v 8.8 months, respectively; HR = 0.84; 95% CI, 0.59 to 1.18; P = .31); in a small subset of patients with known HER2-positive tumors (n = 37), an improvement in PFS was also seen (median PFS, 6.7 v 5.8 months, respectively; HR = 0.54; 95% CI, 0.25 to 1.15; P = .11). In 93 HR-positive MBC patients, Cristofanilli et al¹⁶ reported prolongation of

Table 2. Adverse Events

Adverse Event	Letrozole + Placebo (n = 624)								Letrozole + Lapatinib (n = 654)							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Diarrhea*	91	15	27	4	6	< 1	0	0	210	32	147	22	58	9	2	< 1
Rash*	68	11	15	2	0	0	0	0	186	28	100	15	7	1	0	0
Nausea*	85	14	40	6	4	< 1	0	0	141	22	53	8	6	< 1	0	0
Arthralgia	100	16	37	6	8	1	0	0	81	12	39	6	7	1	0	0
Fatigue	63	10	42	7	3	< 1	0	0	77	12	47	7	10	2	0	0
Back pain	41	7	42	7	13	2	1	< 1	50	8	42	6	12	2	0	0
Vomiting*	42	7	21	3	4	< 1	1	< 1	63	10	38	6	7	1	1	< 1
Headache	52	8	28	4	3	< 1	0	0	63	10	26	4	2	< 1	0	0
Cough	73	12	15	2	2	< 1	0	0	59	9	19	3	2	< 1	0	0
Hot flush*	65	10	27	4	0	0	0	0	54	8	12	2	3	< 1	0	0
Asthenia	45	7	19	3	5	< 1	0	0	55	8	20	3	5	< 1	0	0
Pain in extremity	42	7	24	4	5	< 1	0	0	39	6	25	4	2	< 1	0	0
Dyspnea	36	6	27	4	7	1	2	< 1	31	5	27	4	5	< 1	1	< 1
Pruritus*	43	7	11	2	1	< 1	0	0	54	8	23	4	2	< 1	0	0
Alopecia*	44	7	1	< 1	0	0	0	0	82	13	2	< 1	1	< 1	0	0
Constipation	48	8	17	3	2	< 1	0	0	54	8	6	< 1	0	0	0	0
Anorexia	34	5	18	3	2	< 1	0	0	51	8	16	2	5	< 1	0	0
Dry skin	25	4	2	< 1	0	0	0	0	71	11	15	2	1	< 1	0	0
Epistaxis	7	1	3	< 1	1	< 1	0	0	63	10	6	< 1	1	< 1	0	0
Nail disorder	5	< 1	1	< 1	0	0	0	0	60	9	11	2	1	< 1	0	0

*A statistically significant ($P < .05$) effect was observed between treatment groups for the total incidence of these adverse events.

PFS with the addition of gefitinib to anastrozole compared with anastrozole alone (median PFS, 14.6 v 8.2 months, respectively; HR = 0.55; 95% CI, 0.32 to 0.94). In both trials, no information was provided on the number of patients who were totally endocrine naïve or had received prior tamoxifen, which could be an important predictor for benefit from combined therapy in delaying time to progression of disease.

In this study, 952 patients with HR-positive MBC were confirmed centrally as having original HER2-negative primary breast cancer. In addition, the protocol predefined a stratification based on prior adjuvant antiestrogen exposure. In the 752 patients with ≥ 6 months since discontinuation of antiestrogen therapy or no prior antiestrogen therapy, two thirds had no prior endocrine therapy, and one third had taken tamoxifen for a median of 5 years, with at least 3 years since discontinuation. Essentially, this represents a hormone-sensitive population. The efficacy data show that in the endocrine-sensitive population, there was no significant improvement in PFS or CBR for the combination (Fig 4). In contrast, the 200 patients who experienced relapse less than 6 months since discontinuation had all received tamoxifen for a median of 2.9 years and entered the study with a median of less than 1 month since discontinuation. These patients would be considered clinically relatively tamoxifen resistant, and in this group, a statistically nonsignificant trend toward improvement in both PFS and CBR was seen (Fig 5). These data in the HER2-negative population suggest that there is no benefit for the addition of an EGFR/HER2-targeted therapy to an AI in an HR-positive, HER2-negative, endocrine-sensitive or -naïve MBC population but suggest there could be possible benefit for patients who experience relapse early during adjuvant tamoxifen therapy (consistent with preclinical models where growth factor activity is enhanced in association with endocrine resistance).^{10,34,37,38} Lack of PgR expres-

sion has been suggested as a surrogate for enhanced growth factor receptor activity in ER-positive breast cancer,^{39,40} and although a trend in favor of clinical benefit from the combination was observed in tamoxifen-resistant patients with PgR-negative tumors, the numbers in this subset are too small to draw definitive conclusions, and overall, no substantial benefit in favor of PgR-negative tumors was seen in this trial. Primary tumors have been collected from more than 80% of patients enrolled onto the trial; further biomarker studies in tamoxifen-treated patients are clearly warranted to identify a tumor phenotype that may predict relapse and subsequent benefit from combined letrozole and lapatinib.

The inability of lapatinib to delay progression with letrozole in the endocrine-sensitive, HR-positive, HER2-negative population is in contrast to the preclinical^{37,38} and clinical^{15,16} data reported with the EGFR TKI gefitinib. One potential explanation is that tamoxifen may induce different endocrine resistance pathways to aromatase inhibition. Specifically, tamoxifen has been demonstrated in preclinical models to enhance upregulation of EGFR and HER2.^{11,38} Consequently, gefitinib may synergize well with tamoxifen in endocrine-sensitive disease to delay EGFR/HER2 activation. In contrast, aromatase inhibition may induce different resistance pathways to tamoxifen and, when combined with an EGFR/HER2 inhibitor in endocrine-sensitive disease, may fail to provide added benefit. The initial benefit seen with gefitinib plus anastrozole in a small phase II study¹⁶ was not observed in a second randomized phase II trial with the combination.⁴¹ Our study showed that lapatinib plus letrozole failed to delay endocrine resistance in more than 750 patients with endocrine-sensitive, EGFR/HER2-negative disease. Indeed, this lack of benefit in hormone-sensitive breast cancer was demonstrated preclinically by the failure of trastuzumab and letrozole when combined

from the outset to delay endocrine resistance in HR-positive xenografts, albeit that combined therapy was effective at the time resistance to letrozole had developed.⁴²

In summary, this trial confirmed that for patients with known HR-positive, HER2-positive MBC, a combined targeted therapy approach is superior to endocrine therapy alone. The letrozole-lapatinib combination was well tolerated and produced a clinically meaningful improvement in several efficacy end points. As such, combination therapy with lapatinib and letrozole could be considered an effective treatment option for patients with known HR-positive, HER2-positive MBC.

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