Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial

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Summary

Background Worldwide, many patients with HER2-positive early stage breast cancer do not receive trastuzumab—the standard adjuvant treatment. We investigated the efficacy and safety of adjuvant lapatinib for patients with trastuzumab-naive HER2-positive early-stage breast cancer, started at any time after diagnosis.

Methods This study was a placebo-controlled, multicentre, randomised phase 3 trial. Women outpatients from 405 centres in 33 countries with HER2-positive early-breast cancer who had previously received adjuvant chemotherapy but not trastuzumab were randomly assigned (1:1) to receive daily lapatinib (1500 mg) or daily placebo for 12 months. Randomisation was done with a computer-generated sequence, stratified by time since diagnosis, lymph node involvement at diagnosis, and tumour hormone-receptor status. Investigators, site staff, and patients were masked to treatment assignment. The primary endpoint was disease-free survival in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00374322.

Findings Between August, 2006, and May, 2008, 3161 women were enrolled and 3147 were assigned to lapatinib (n=1571) or placebo (n=1576). After a median follow-up of 47·4 months (range 0·4–60·0) in the lapatinib group and 48·3 (0·7–61·3) in the placebo group, 210 (13%) disease-free survival events had occurred in the lapatinib group versus 264 (17%) in the placebo group (hazard ratio [HR] 0·83, 95% CI 0·70–1·00; p=0·053). Central review of HER2 status showed that only 2490 (79%) of the randomised women were HER2-positive. 157 (13%) of 1230 confirmed HER2-positive patients in the lapatinib group and in 208 (17%) of 1260 in the placebo group had a disease-free survival event (HR 0·82, 95% 0·67–1·00; p=0·04). Serious adverse events occurred in 99 (6%) of 1573 patients taking lapatinib and 77 (5%) of 1574 patients taking placebo, with higher incidences of grade 3–4 diarrhoea (97 [6%] *vs* nine [<1%]), rash (72 [5%] *vs* three [<1%]), and hepatobiliary disorders (36 [2%] *vs* one [<1%]).

Interpretation Our data show that there was no significant difference in disease-free survival between groups when analysed in the intention-to-treat population. However, exploratory analyses restricted to patients who had HER2-positive disease confirmed by central fluorescence in-situ hybridisation review suggested marginal benefit with lapatinib in terms of disease-free survival. Thus lapatinib might be an option for women with HER2-positive breast cancer who do not or cannot receive adjuvant trastuzumab.

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Introduction

Standard adjuvant treatment for HER2-positive (ERBB2-positive) breast cancers consists of chemotherapy and 1 year of intravenous trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 receptor.[1] In the absence of trastuzumab, patients with HER2-positive breast cancer have unfavourable clinical outcomes, with a relative risk for disease-free survival of 2·0 and overall survival of 2·7.[2,3] Given concurrently with chemotherapy, trastuzumab reduces the risk of death by 33–44% compared with patients with HER2-positive tumours not receiving trastuzumab, but causes asymptomatic decreases in left ventricular ejection fraction in 18% of patients and severe cardiac dysfunction in 1–4%.[4–9]

Globally, many women do not receive trastuzumab for HER2-positive primary breast cancer for either socioeconomic or logistic reasons.[10] When started as late as 2–6 years after diagnosis, adjuvant endocrine treatment improves disease-free survival.[11] An anti-HER2 treatment that could be administered either at diagnosis or later, as an alternative to trastuzumab, could be beneficial. Lapatinib—an oral, small molecule inhibitor of HER1 and HER2—is approved for use in combination with capecitabine for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab.[12,13]

Lapatinib is generally safe and well tolerated, although because it is a small molecule tyrosine-kinase inhibitor it causes frequent mild-to-moderate diarrhoea, skin rash, and transient mild increases of liver aminotransferase concentrations, as well as rare symptomatic cardiac toxic effects.[12,13] We investigated the use of adjuvant lapatinib

for patients with trastuzumab-naive HER2-positive primary breast cancer, given at any time after diagnosis and after adjuvant chemotherapy.

Methods

Study design and participants

The TEACH (Tykerb Evaluation After CHemotherapy) trial was a multicentre, phase 3, randomised, double-blind, placebo-controlled trial. Participants were hospital outpatients at 405 centres in 33 countries worldwide.

Eligibility criteria were: age 18 years or older; histologically confirmed stage I–IIIC invasive breast cancer that was HER2-positive (defined locally as 3+ by immunohistochemistry or *HER2* amplification by fluorescent in-situ hybridisation, or centrally by fluorescent in-situ hybridisation [Path Vysion HER-2 DNA Probe Kit, Abbott Molecular; HER2:CEP-17 ratio ≥2 considered amplified]); adequate locoregional and systemic treatment (appendix); Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate hepatic, renal, and bone marrow function and cardiac ejection fraction within institutional range of normal, measured by echocardiogram or multigated acquisition scans. Women were eligible for randomisation if they were disease free at any time after primary treatment and had completed adjuvant chemotherapy. For all the inclusion criteria, see appendix.

Exclusion criteria were: previous treatment with trastuzumab; clinical or radiological evidence of local or regional recurrence or metastatic disease; history of other breast cancer (including ductal carcinoma in situ); other previous malignancies (except non-melanoma skin cancer, treated in-situ cancer of the cervix, or other solid tumours with no evidence of disease for 5 years); and uncontrolled medical disorder. For all the exclusion criteria, see appendix.

The study was approved by each centres' ethics committee. Patients gave written, informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practice.

Randomisation and masking

We randomly assigned women to receive oral lapatinib (1500 mg) or placebo (in a 1:1 ratio), daily for 12 months or until disease recurrence, development of a second primary cancer, or unacceptable toxic effects.

Randomisation was done with a computer-generated sequence and was stratified. To assign a participant, the site staff entered the patient's number, time since initial diagnosis, time from completion of primary adjuvant chemotherapy, hormone receptor status (oestrogen-receptor positive, progesterone-receptor positive, or both *vs* oestrogen-receptor negative and progesterone-receptor negative), and lymph node involvement to obtain a randomisation number and treatment group assignment. Stratification factors were time since diagnosis (≤4 years or >4 years), lymph node involvement at diagnosis (negative or positive), and tumour hormone-receptor status. Investigators, clinicians, and patients were masked to the treatment assignment.

Procedures

Enrolled patients were assessed once every 3 months by clinical assessment, routine blood tests, echocardiogram, or multigated acquisition scan. All participants completed the Short Form-36 version 2 questionnaire to assess health-related quality of life at baseline and every 6 months for 24 months. Information about toxic effects was recorded. After completion of 12 months of treatment or drug withdrawal, patients were followed up once every 3 months until 2 years after diagnosis, once every 6 months until 5 years after diagnosis, and once per year thereafter. Patients had a mammogram every year throughout treatment and follow-up. Locoregional recurrence, metastatic disease, and second primary cancers were defined radiologically, pathologically, or clinically. Recurrences and second primary cancers were dated from when they were first detected. Safety was reviewed every 6 months by the independent data and safety monitoring committee.

The primary endpoint was disease-free survival, with events defined as: locoregional and distant recurrence; contralateral breast cancer (including ductal carcinoma in situ); other second primary cancer (excluding carcinoma of the skin, melanoma in situ or carcinoma in situ of the cervix); and death from any cause without a previous event (recurrence of breast cancer or second primary cancer).

Secondary endpoints were: time to first recurrence—defined as first occurrence of disease in sites defined for disease-free survival; time to distant recurrence; overall survival (including death from any cause); time to CNS recurrence; health-related quality of life; and toxic effects (toxic effects both reported by the patient and detected in chemical and haematological tests, cardiac dysfunction, and assessment of QT/QTc interval). We also assessed disease-free survival in predefined subgroups and within

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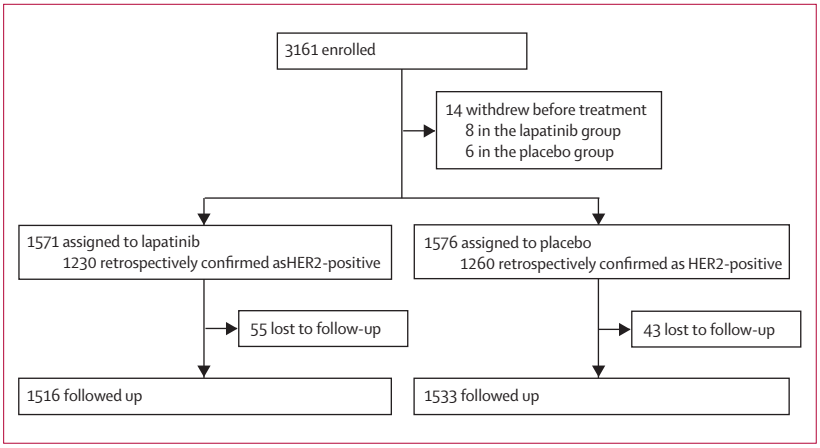

Figure 1: **Trial profile**

	Lapatinib group (n=1571)	Placebo group (n=1576)
Age		
Median (years)	51 (24–87)	52 (22–82)
<65 years	1407 (90%)	1388 (88%)
≥65 years	164 (10%)	188 (12%)
Ethnic origin*		
White	1129 (72%)	1132 (72%)
African-American or African	53 (3%)	62 (4%)
Native American or Alaskan native	65 (4%)	67 (4%)
Asian	338 (22%)	331 (21%)
Native Hawaiian or other Pacific islander	5 (<1%)	11 (<1%)
Menopausal status		
Premenopausal	532 (34%)	489 (31%)
Postmenopausal	1039 (66%)	1087 (69%)
Time since initial diagnosis		
Median (years)	2·7 (0·3–21·2)	2·7 (0·2–14·9)
≤4 years	1116 (71%)	1132 (72%)
>4 years	455 (29%)	444 (28%)
0–1 years	317 (20%)	330 (21%)
Primary tumour stage†		
T1	534 (34%)	555 (35%)
T2	797 (51%)	785 (50%)
T3	148 (9%)	143 (9%)
T4	80 (5%)	69 (4%)
Tx	12 (<1%)	23 (1%)
Axillary lymph node status‡		
Negative	692 (44%)	694 (44%)
Positive	843 (54%)	847 (54%)
Missing	35 (2%)	34 (2%)
Oestrogen or progesterone receptor status		
Positive	932 (59%)	927 (59%)
Negative	639 (41%)	649 (41%)
(Continues in next column)		
(Continued from previous column)		
HER2 status§		
Positive	1230 (78%)	1260 (80%)
Negative	218 (14%)	207 (13%)
Could not be assessed	114 (7%)	102 (6%)
Missing	9 (<1%)	7 (<1%)
Previous or concomitant endocrine treatment	753	745
Aromatase inhibitor	391 (52%)	363 (49%)
Tamoxifen or toremifene	292 (39%)	300 (40%)
Combined endocrine treatment	48 (6%)	66 (9%)
Other	22 (3%)	16 (2%)
Previous neoadjuvant or adjuvant chemotherapy		
Anthracycline without taxane	906 (58%)	898 (57%)
Anthracycline with taxane	598 (38%)	609 (39%)
No anthracycline	67 (4%)	69 (4%)
Previous radiotherapy	1132 (72%)	1116 (71%)
Reasons for not receiving neoadjuvant or adjuvant trastuzumab¶		
Not institutional practice	862 (55%)	851 (54%)
Patient preference	367 (23%)	358 (23%)
Not available	341 (22%)	366 (23%)

Data are median (range) or n (%). *Patients can be included in more than one category. †One patient in the placebo group not assessed. ‡One patient in each group not assessed. §Assessed centrally by fluorescence in-situ hybridisation. ¶One patient in each group classed as not applicable.

Table 1: **Baseline characteristics**

stratification variables to investigate the effect of treatment in known prognostic groups (eg, hormone receptor status) and in prognostically unknown subgroups (eg, time since diagnosis of <1 *vs* >1 year). The subgroups and strata were: time since initial diagnosis, lymph node involvement, hormone receptor status, oestrogen receptor status, geographic region, ethnic origin, menopausal status, stage of disease, type of previous neoadjuvant or adjuvant chemotherapy, time since the end of the last chemotherapy, and type of endocrine treatment received. For patients who had oestrogen-receptor-positive or progesterone-receptor-positive disease, we analysed treatment effect in subgroups defined by previous or concomitant endocrine treatment.

Adverse events were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). A serious event was any event that resulted in death, was life-threatening, required hospital admittance or extended current hospital admittance, resulted in disability or incapacity, resulted in congenital abnormalities or birth defects, and others, such as important medical events that might not be immediately life-threatening or result in death or admission to hospital but which might jeopardise the patient or require medical or surgical intervention to prevent one of the other outcomes listed in the definition. Additional protocol-defined criteria were: all grade 4 laboratory abnormalities; severe symptomatic congestive heart failure and cardiac death; any grade 3 signs or symptoms of pneumonitis; and alanine aminotransferase concentration more than three times the upper limit of normal and total bilirubin concentration more than twice the upper limit of normal (>35% direct bilirubin; bilirubin fractionation required).

Statistical analysis

We calculated that we would need to enrol 3000 women and have 463 disease-free survival events for 80% power (using a two sided α of 0·05) to detect a 23% (hazard ratio

[HR] 0·769) reduction in disease-free survival.[14] We assumed that yearly recurrence for patients taking placebo was 9·6%. We did an interim analysis of efficacy and futility when 309 events were reached.

The intention-to-treat population included all participants who had received at least one dose of study medication. We analysed disease-free survival and overall survival for each of the subgroups defined by the randomisation strata. We also did a post hoc analysis of the retrospectively defined population of participants whose tumours were fluorescence in-situ hybridisation positive by central *HER2* assessment.

We used a log-rank test to assess the primary endpoint in the stratified intention-to-treat population. We also did a Cox regression analysis of the primary endpoint in the intention-to-treat population with covariates of randomisation strata, age, and stage of disease. Separate Cox regression models were used to assess the effect of treatment on disease-free survival in each of the predefined strata.

Secondary endpoints of overall survival, time to first recurrence, time to distant recurrence, and time to first CNS recurrence were analysed in the intention-to-treat and the fluorescence in-situ hybridisation positive populations with a competing risk method (in which all events other than the event of interest were treated as competing risks in the cumulative incidence curves). HRs were adjusted for baseline covariates. We used Fisher's exact test to compare toxic effects between groups for descriptive purposes only. All p values are two sided. 13 preplanned analyses were done, so we used a conservative significance threshold of p=0·004. The cutoff for collection of data was Sept 26, 2011. The data were analysed on Oct 21, 2011, with Unix SAS (version 9.1.3).

This study is registered with ClinicalTrials.gov, number NCT00374322.

Role of the funding source

The sponsor contributed to the study design, study centre monitoring, management, and collection, analyses, and interpretation of data. The decision to publish was made by the authors. The corresponding author had full access to all the data and had final responsibility for the decision to submit the results for publication.

Results

The number of patients screened was not captured in the electronic database. Between August, 2006, and May, 2008, 3161 women from 33 countries were enrolled and assigned treatment (figure 1). 14 patients withdrew before treatment (nine withdrew consent, one had left ventricular ejection fraction of 53% and a lower limit of normal of 55%, one had increased alanine aminotransferase and aspartate transaminase concentrations, one was taking a prohibited drug, two because of investigator decision), and were thus excluded from the intention-to-treat population, which consisted of 1571 women in the lapatinib group and 1576 in the placebo group (figure 1). Baseline characteristics were much the same in each group (table 1). 98 patients (3%) were lost to follow-up. Loss to follow-up was not substantially different between groups (figure 1).

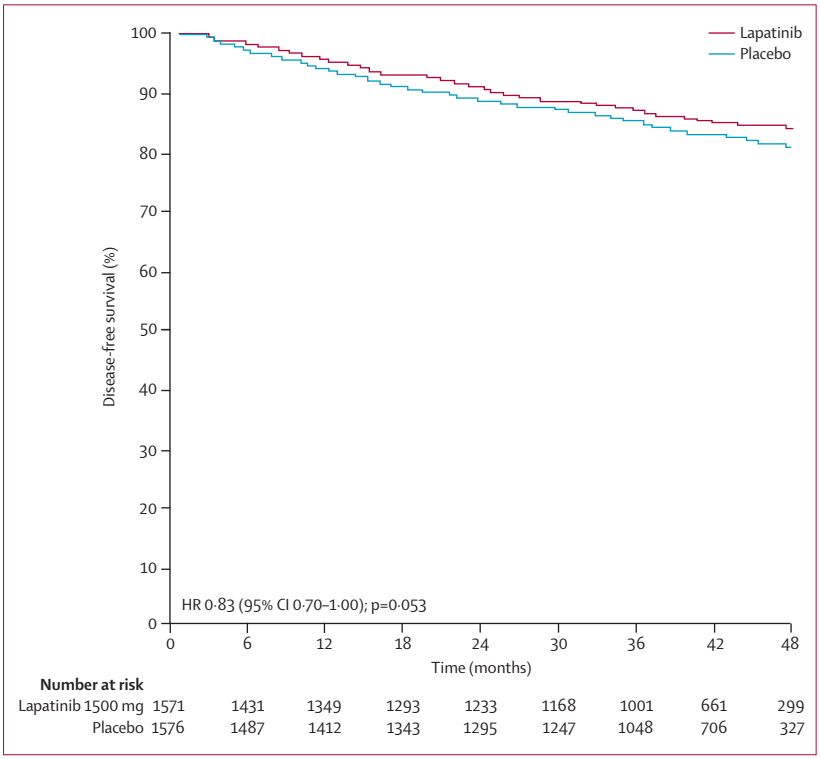

Figure 2: **Kaplan-Meier analysis of disease-free survival in the intention-to treat population**

3144 patients had HER2-positive disease as assessed by local or central laboratory. Central confirmation by fluorescence in-situ hybridisation was done for 3131 patients (some patients could not be assessed because of insufficient tissue or failure to hybridise): 2490 (80%) were positive (1230 in the lapatinib group, 1260 in the placebo group), 425 (14%) were negative, and 216 (7%) were could not be assessed (table 1). The results of central confirmation were much the same between countries (data not shown).

Median follow-up was 47·4 months (range 0·4–60·0) in the lapatinib group and 48·3 months (0·7–61·3) in the placebo group. 210 (13%) of 1571 patients in the lapatinib group had a disease-free survival event versus 264 (17%) of 1576 patients in the placebo group (HR 0·83, 95% CI 0·70–1·00; p=0·053; figure 2). The HR when adjusted for prognostic factors was 0·85 (95% CI 0·71–1·02; p=0·09).

92 (6%) patients died in the lapatinib group and 97 (6%) died in the placebo group (unadjusted HR 0·99, 95% CI 0·74–1·31; p=0·96). Of the patients in the lapatinib group, 31 (2%) had local recurrence and 30 (2%) had regional recurrence versus 46 (3%) local recurrences and 26 (2%) regional recurrences in the placebo group; less

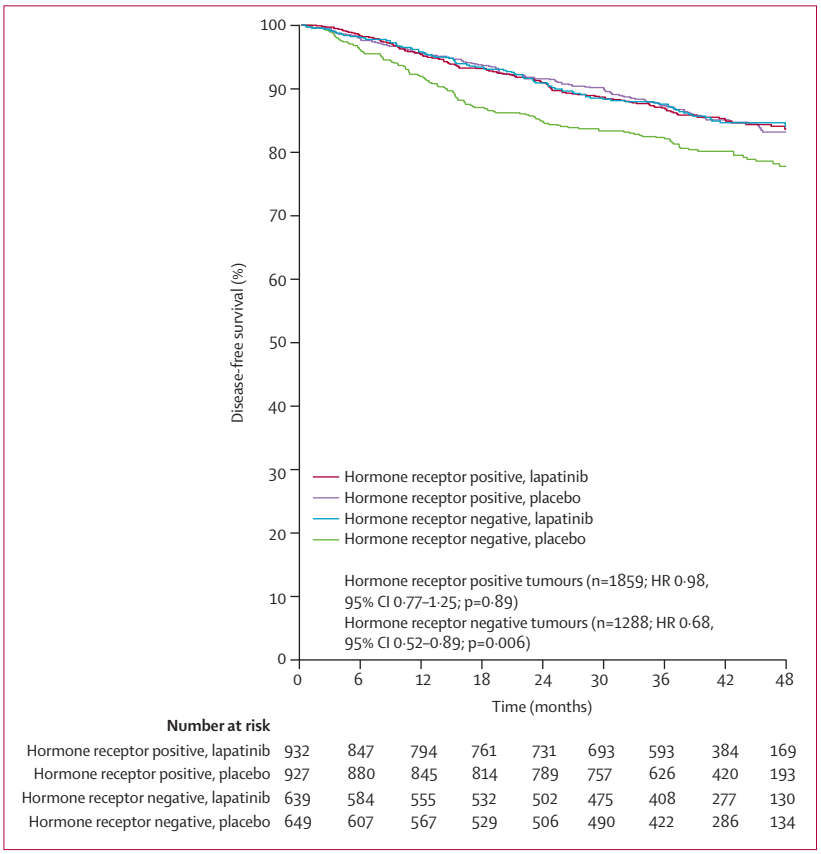

Figure 3: **Kaplan-Meier analysis of disease-free survival by treatment and hormone-receptor status in the intention-to-treat population**

than 1% in each group (n=4 for lapatinib, n=7 for placebo) had in-situ breast cancer. Distant recurrences—including in bone, liver, lung and lymph nodes—occurred in 125 (8%) patients in the lapatinib group and 156 (10%) patients in the placebo group (unadjusted HR 0·84, 95% CI 0·67–1·06; p=0·16). CNS as a site of first recurrence occurred in 13 (<1%) of patients in the lapatinib group and 21 (1%) patients in the placebo group (unadjusted HR 0·65, 95% CI 0·33–1·28; p=0·24).

Disease-free survival was better for patients with hormone-receptor-negative disease who were in the lapatinib group compared with those in the placebo group (p=0·006; figure 3); disease-free survival did not differ significantly between groups for patients with hormone-receptor-positive disease (figure 3). Additionally, for patients assigned treatment within 1 year of diagnosis, those in the lapatinib group had a greater chance of disease-free survival than did those in the placebo group (p=0·04; figure 4), whereas the groups did not differ significantly for patients assigned treatment more than 1 year after diagnosis (figure 4).

We did exploratory analyses of the 2490 patients with HER2-positive tumours confirmed centrally by fluorescence in-situ hybridisation (table 2). Disease-free survival events occurred in 157 (13%) of 1230 patients in the lapatinib group and in 208 (17%) of 1260 patients in the placebo group (table 2; HR 0·82, 95% CI 0·67–1·00; p=0·04). For patients whose *HER2* status was unconfirmed by central review, the HR was 0·92 (95% CI 0·61–1·38; p=0·94). We also analysed the secondary endpoints for patients with centrally confirmed *HER2* status. Any recurrence or occurrence of contralateral breast cancer was less likely for patients taking lapatinib than for those taking placebo (table 2; p=0·033). Distant metastasis and CNS as the site of first metastasis did not differ significantly between groups (table 2).

Table 3 shows self-reported adverse events in patients who received at least one dose of treatment. 1450 (92%) of 1573 patients who took lapatinib and 1193 (76%) of 1574 patients who took placebo reported any adverse event (p=0·003), mainly of grade 1 or 2. Diarrhoea, rash, nausea, fatigue, and hepatobiliary events were more common in the lapatinib group than in the placebo group (table 3). Overall, 99 (6%) patients taking lapatinib and 77 (5%) patients taking placebo had serious adverse events (28 [1·8%] *vs* 10 [<1%] had infections; 16 [1%] *vs* 14 [<1%] neoplasms; 17 [1%] *vs* 8 [<1%] gastrointestinal disorders; and 7 [<1%] *vs* 7 [<1%] cardiac events). Eight serious hepatobiliary events (<1%) occurred in the lapatinib group versus none in the placebo group. Occurrence of cardiac events did not differ significantly between groups (table 3). No statistically significant (p<0·05) or clinically meaningful differences existed between groups for summary quality-of-life scores relative to baseline (data not shown). No deaths were related to lapatinib treatment.

500 (32%) of 1571 patients in the lapatinib group and 252 (16%) of 1576 in the placebo group discontinued treatment before completion of 12 months. Reasons for early discontinuation included: adverse events (300 [19%] *vs* 82 [5%]), patient withdrawal (61 [4%] *vs* 31 [2%]), and disease recurrence (44 [3%] *vs* 68 [4%]). Median lapatinib adherence was 50·1 weeks (range 0·1–62·0 weeks) and 51·1 weeks (range 0·1–60·6) in the placebo group. Dose reductions were necessary for 243 (15%) of 1573 patients taking lapatinib and 40 (3%) of 1574 taking placebo.

Discussion

After 4 years, disease-free survival did not differ significantly between groups in our primary analysis. There was no significant difference in CNS recurrences and no evidence exists for a survival advantage with lapatinib treatment. Disease-free survival was better in the lapatinib group for women with hormone-receptor-negative tumours and there was a suggestion of benefit for patients who received lapatinib within a year of diagnosis, although this was not significant at prespecified limits. However, an exploratory analysis in 2490 patients with centrally confirmed HER2-positive tumours was suggestive of an improvement in disease-free survival with lapatinib (panel).

Our trial was designed to investigate whether lapatinib is beneficial in a broad patient population who had not,

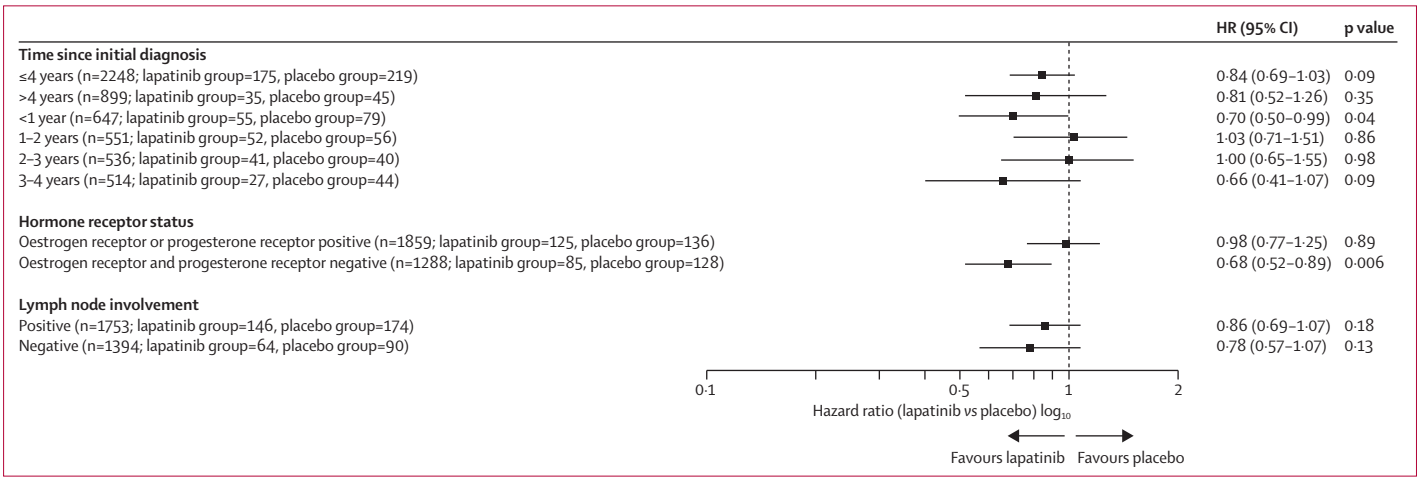

Figure 4: **Hazard ratios for disease-free survival events in subgroups in the intention-to-treat population**
HR=hazard ratio.

	ITT population				FISH+ group			
	Lapatinib group (n=1571)	Placebo group (n=1576)	HR (95% CI)	p value	Lapatinib group (n=1230)	Placebo group (n=1260)	HR (95% CI)	p value
Disease-free survival	210 (13%)	264 (17%)	0·83 (0·70–1·00)	0·053	157 (13%)	208 (17%)	0·82 (0·67–1·00)	0·04
Overall survival	92 (6%)	97 (6%)	0·99 (0·74–1·31)	0·96	79 (6%)	82 (7%)	1·02 (0·75–1·39)	0·98
Time to first recurrence	172 (11%)	220 (14%)	0·82 (0·67–1·00)	0·051	137 (11%)	183 (15%)	0·79 (0·63–0·98)	0·033
Time to distant recurrence	125 (8%)	156 (10%)	0·84 (0·67–1·06)	0·16	101 (8%)	132 (10%)	0·81 (0·62–1·04)	0·11
CNS recurrence as first recurrence	13 (<1%)	21 (1%)	0·65 (0·33–1·28)	0·24	12 (<1%)	20 (2%)	0·66 (0·33–1·34)	0·28

Data are n (%) unless otherwise stated. HRs are unadjusted. ITT=intention-to-treat. FISH+=*HER2*-positive disease confirmed centrally by fluorescence in-situ hybridisation.

Table 2: **Primary and secondary outcomes for the intention-to-treat population and for patients who had *HER2*-positive disease confirmed centrally by fluorescence in-situ hybridisation**

or could not, receive adjuvant trastuzumab. Globally, many patients with HER2-positive breast cancer do not receive standard adjuvant anti-HER2 treatment and are precluded from the proven benefit of adjuvant anti-HER2 treatment.[10] Reasons include being remote location from initial primary diagnosis or other logistic reasons, including drug unavailability or poor access to treatment because of health coverage reasons. Although we report a negative result for our primary endpoint in the intention-to-treat population, the recurrence rate of 3% versus the anticipated recurrence rate of 9·6% (appendix) suggests that we might have been studying a different population (eg, in terms of hormone-receptor status, time since diagnosis) than we had planned, and perhaps lapatinib might have had a different effect in a different population.

Patients were eligible for randomisation if they locally assessed HER2-positive disease; however, only about 80% of these patients had HER2-positive disease according to subsequent central centrally confirmed with fluorescence in-situ hybridisation, although HER2 status was not assessed centrally by immunohistochemistry. This discrepancy is similar to that in the Breast Intergroup Trial N9831, which reported a concordance of 74% in 119 paraffin-embedded breast tumour specimens, while in a retrospective combined analyses of samples from pivotal trials of adjuvant trastuzumab, a concordance of 81% was reported.[15,16] Many factors could affect these results, including the local choice of antibody, inexperience with scoring or deviation from standard immunohistochemistry techniques, assessment of non-invasive cancer components, and others. The poor concordance reported in previous trials and confirmed in our trial, which included a large population from 33 countries, is of concern. Previous trials and our study showed a significant benefit of anti-HER2 treatment in patients with centrally confirmed HER2-positive disease. High rates of false positive and false negative *HER2* results have major medical and financial consequences and quality controls for local testing or central laboratory testing need to be improved.

Some subgroups of patients have been previously reported to be more sensitive to anti-HER2 treatment than others, therefore we did exploratory analyses in these populations[9] to explore treatment benefit in subpopulations, rather than to detect heterogeneity of treatment effect. For this goal, we were more concerned with preventing type II rather than type I error. Thus, no interactions were tested before the analyses.

	Lapatinib group (n=1573)*					Placebo group (n=1574)					p value†
	Grade 1	Grade 2	Grade 3	Grade 4	Any	Grade 1	Grade 2	Grade 3	Grade 4	Any	
Abdominal pain	76 (5%)	24 (2%)	8 (<1%)	0	108 (7%)	41 (3%)	15 (<1%)	0	0	56 (4%)	1·00
Constipation	34 (2%)	4 (<1%)	0	0	38 (2%)	58 (4%)	3 (<1%)	1 (<1%)	0	62 (4%)	0·68
Diarrhoea	581 (37%)	280 (18%)	97 (6%)	0	958 (61%)	198 (13%)	48 (3%)	9 (1%)	0	256 (16%)	<0·0001
Nausea	227 (14%)	51 (3%)	1 (<1%)	0	279 (18%)	162 (10%)	16 (1%)	2 (<1%)	0	180 (11%)	0·22
Vomiting	77 (5%)	25 (2%)	2 (<1%)	0	104 (7%)	55 (3%)	16 (1%)	2 (<1%)	0	73 (5%)	0·76
Dyspepsia	82 (5%)	22 (1%)	1 (<1%)	0	106 (7%)	49 (3%)	8 (1%)	0	0	57 (4%)	0·53
Stomatitis	61 (4%)	29 (2%)	8 (<1%)	0	98 (6%)	23 (1%)	7 (<1%)	0	0	30 (2%)	0·27
Rash	557 (35%)	293 (19%)	71 (5%)	1 (<1%)	922 (59%)	203 (13%)	37 (2%)	3 (<1%)	0	243 (15%)	<0·0001
Dry skin	175 (11%)	40 (3%)	5 (<1%)	0	220 (14%)	40 (3%)	4 (<1%)	1 (<1%)	0	45 (3%)	0·01
Fatigue	188 (12%)	49 (3%)	11 (<1%)	0	251 (16%)	155 (10%)	40 (3%)	4 (<1%)	0	202 (13%)	0·68
Arthralgia	52 (3%)	15 (<1%)	2 (<1%)	0	69 (4%)	86 (5%)	24 (2%)	3 (<1%)	0	113 (7%)	0·53
Back pain	38 (2%)	15 (<1%)	1 (<1%)	0	54 (3%)	47 (3%)	25 (2%)	2 (<1%)	0	75 (5%)	0·72
Headache	105 (7%)	28 (2%)	5 (<1%)	0	140 (9%)	139 (9%)	40 (3%)	6 (<1%)	0	186 (12%)	0·64
Dizziness	49 (3%)	7 (<1%)	1 (<1%)	0	58 (4%)	46 (3%)	8 (<1%)	0	0	54 (3%)	1·0
Epistaxis	110 (7%)	7 (<1%)	0	0	118 (8%)	86 (5%)	17 (1%)	0	0	103 (7%)	0·03
Cardiac event	22 (1%)	27 (2%)	3 (<1%)	0	52 (3%)	18 (1%)	23 (1%)	9 (<1%)	0	51 (3%)	1·0
Hepatobiliary disorders‡	56 (4%)	26 (2%)	30 (2%)	6 (<1%)	118 (8%)	36 (2%)	10 (<1%)	1 (<1%)	0	47 (3%)	0·21

Data are n (%). Some events were graded as not applicable or data missing, therefore they are not included in the breakdown by grade but are included in any.* Two patients assigned to placebo received lapatinib. †Any *vs* any, calculated with Fisher's exact test. ‡Includes seven patients in the lapatinib group who meet the criteria of Hy's law (drug-related concomitant increase of alanine aminotransferase or aspartate aminotransferase concentration more than three times upper limit of normal and total bilirubin more than two times upper limit of normal).

Table 3: **Self-reported acute toxic effects (grade 1–4)**

Panel: Research in context

Systematic review

We searched Medline with the medical subject headings "breast cancer" and "anti-HER2 therapy", and/or "trastuzumab", and/or "lapatinib", and/or "adjuvant" or "metastatic" to identify studies relevant to anti-*HER2* treatment. We searched for studies published in English, between January 2000, and June 2012. We retrieved 426, of which we judged 27 to be most relevant.

Interpretation

Patients with early-stage *HER2*-positive breast cancer benefit from anti-HER2 treatment when given as up-front adjuvant treatment. Although disease-free survival did not differ significantly between lapatinib and placebo groups in the intention-to-treat population, patients whose primary tumour is *HER2*-positive by central laboratory testing should be considered for anti-*HER2* treatment even late after diagnosis.

However, our results should be viewed with caution—since a substantial risk of inflated type I error exists—and interpreted in the context of other reported clinical trial analyses of these groups. In the prespecified subgroup of patients with hormone-receptor-negative tumours, lapatinib reduced the relative risk of disease-free survival when given either soon after or delayed after adjuvant chemotherapy. By contrast, our trial showed no effect of lapatinib in patients with hormone-receptor-positive disease. The benefit of anti-HER2 treatment in the hormone-receptor-negative subgroup was also reported in a meta-analysis of up-front adjuvant trastuzumab in which the benefit for patients with hormone-receptor-positive disease was less than that for patients with hormone-receptor-negative disease, although there was no statistically positive interaction between the subsets.[9] By contrast, the report of the combined National Surgical Adjuvant Breast and Bowel Project trial B-31 and the North Central Cancer Treatment Group trial N9831, as well as the Breast Cancer International Research Group 006 report and later analysis of the HERA trial, did not find a difference in benefit between subgroups when anti-HER2 treatment was started concurrent with chemotherapy.[14,17,18] However, in all these trials endocrine treatment was used concomitantly with trastuzumab. Our results for the hormone-receptor-positive subset are consistent with neoadjuvant trials, which tested shorter exposure to anti-HER2 treatment than we did, in which fewer pathological complete responses occurred compared with hormone-receptor-negative patients.[19–22] Preclinical data suggest that cross-talk occurs between the oestrogen receptor and EGFR pathways, resulting in a stimulatory cycle that intensifies activity in both pathways.[23] In the setting of HER2-positive metastatic breast cancer, combination of anti-HER2 treatment concurrent with anti-oestrogen treatment is beneficial, suggesting a possible positive interaction.[13,24] In our study, most patients had hormone-receptor-positive tumours (59%), and 19% of hormone-receptor-positive patients did not receive concomitant endocrine treatment with lapatinib. This fact might have diminished the efficacy of lapatinib in this group and attenuated disease-free survival. Of note, patients with

hormone-receptor-negative tumours in our placebo group had a higher risk of relapse in the first 2 years than in subsequent years, while hormone-receptor-positive patients had a steady risk of relapse over the follow-up period (figure 3).

Lapatinib improved disease-free survival in patients starting treatment within 1 year of diagnosis in the intention-to-treat population. This finding could be a result of the efficacy of lapatinib in hormone-receptor-negative cancers, for which the risk of recurrence is highest in the 1–3 years after diagnosis and benefit is strongest.[25] The effect of lapatinib early in the course of the disease, given either combined or sequentially with trastuzumab, is being investigated in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial, in which the lapatinib monotherapy group was discontinued by an independent data and safety monitoring committee, who judged this group futile in terms of its non-inferiority over trastuzumab.[26]

Diarrhoea, nausea, rash, and dry skin were more common with lapatinib than with placebo. These toxic effects were generally of mild to moderate grade, and contributed to treatment discontinuations in about a fifth of patients taking lapatinib. Consistent with previous reports, hepatobiliary function disorders were uncommon (2% were grade 3–4), including increases of concentrations of liver aminotransferases, which were reversible after drug withdrawal in most patients. Quality of life did not differ significantly between groups (data not shown; we will report these findings elsewhere).

Trastuzumab plus chemotherapy remains the standard of care for women with early-stage HER2-positive breast cancer. This trial provides evidence of the effect of adjuvant lapatinib on women with HER2-positive early breast cancer, justifying ongoing assessment in other trials, which are testing combined or sequential strategies with other anti-HER2 treatments to draw more definitive conclusions. From our exploratory analyses the apparent benefit of treatment in women with hormone-receptor-negative disease and lack of benefit in women with hormone-receptor-positive disease merit further investigation and in the meantime might help clinicians worldwide when considering anti-HER2 treatment for women who have not or can not receive standard adjuvant trastuzumab.

Contributors

PEG, LSW, and DMF designed the study. PEG, IES, JO'S, BE, MK, FB, AUB, PF, MM, BM, MP-G, KIP, and DMF collected data. All authors analysed and interpreted data, wrote the report, and approved the final draft. PEG was chair of the steering committee. IES, JO'S, BE, MK, FB, AUB, PF, WG, MM, BM, MP-G, KIP, and DMF were members of the steering committee. PEG and the steering committee were responsible for approval of the study design. LSW had access to the blinded raw data.

Conflicts of interest

PEG has received speaker's honoraria from GlaxoSmithKline and Pfizer and is supported by the Avon Foundation (New York, NY, USA). MP-G's institution has received grants from GlaxoSmithKline and Roche; MP-G has received consultancy fees and honoraria from Roche. BE has received fees from GlaxoSmithKline for participating in advisory boards. KIP and IES have received honoraria and consulting fees from Roche and GlaxoSmithKline. GA and ER are employees of GlaxoSmithKline and own stocks and shares of GlaxoSmithKline. JO'S is a consultant to GlaxoSmithKline. FB is consultant to GlaxoSmithKline and has received fees from GlaxoSmithKline for participating in advisory boards. LSW is employee of GlaxoSmithKline. MK, AUB, PF, WG, MM, BM, DL, YC-G, and DMF declare that they have no conflicts of interest.

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