The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: EGF105485
Title: TEACH (Tykerb Evaluation After CHemotherapy) study: A Randomized, Double-blind, Multicenter, Placebo-controlled Study of Adjuvant Lapatinib in Women with Early-Stage ErbB2 Overexpressing Breast Cancer
Rationale: Globally, breast cancer is the most common malignancy reported annually, and it is also the primary cause of cancer mortality in women. Approximately 20% to 40% of human breast cancers overexpress epidermal growth factor receptor 2 (HER2). Patients with HER2-positive breast cancer commonly demonstrate worse prognosis than those with HER2-negative tumors. Trastuzumab, a HER2- directed monoclonal antibody, has become part of standard therapy in the adjuvant setting together with chemotherapy. However, many thousands of women with HER2-overexpressing breast cancer have received adjuvant chemotherapy without the addition of trastuzumab because such treatment was unavailable at the time of diagnosis and treatment. Women with HER2-positive disease not treated with a HER2-directed therapy have a high risk of disease recurrence. Thus, an unmet clinical need exists in the treatment of these women. To address this unmet clinical need, Study EGF105485 was designed to determine whether treatment with oral single-agent lapatinib in women with early-stage HER2-positive breast cancer will improve disease-free survival (DFS). The study compared the efficacy and safety of lapatinib versus placebo as adjuvant treatment in women who completed their standard neoadjuvant/adjuvant chemotherapy but were not previously treated with trastuzumab and have no clinical or radiographic evidence of disease.
Phase: III
Study Period: This study was initiated on 01 August 2006 (first subject randomized) and completed on 12 July 2013. This summary includes the results of the final analysis of the primary endpoint, DFS, and efficacy and safety data up to a cut-off date of 21 September 2011 and results of the end of study analysis of the primary endpoint and efficacy and safety data up to a data cut-off date of 12 July 2013. The end of study analysis was conducted according to the protocol when the follow-up period reached a median of approximately 5 years for subjects still alive at the time of analysis.
Study Design: A Phase III, multi-center, randomized, double-blind, placebo-controlled study
Centres: A total of 397 investigative sites in 33 countries randomized subjects into this study: Argentina (8), Australia (17), Belgium (1), Brazil (6), Canada (16), Chile (3), China (7), Croatia (5), Czech Republic (3), Denmark (7), France (26), Germany (90), Greece (6), Hong Kong (3), Hungary (6), India (7), Israel (7), Italy (6), Korea (4), Latvia (3), Lithuania (3), Mexico (5), New Zealand (3), Peru (3), Philippines (4), Poland (5), Russian Federation (7), Slovakia (4), South Africa (8), Spain (18), United Kingdom (17), Ukraine (4), and United States (85)
Indication: HER2-positive primary breast cancer
Treatment: Subjects were randomized (1:1) to either lapatinib 1500 mg or placebo once daily orally for 12 months or until disease recurrence or development of a second primary cancer, unacceptable toxicity, or consent withdrawal. Randomization was stratified according to the following: • time from initial diagnosis (≤4 years versus >4 years); • hormone receptor status (ER and/or PgR positive versus ER and PgR negative); • lymph node involvement (positive versus negative).
Objectives: The primary objective of the study was to determine whether adjuvant therapy with lapatinib improves DFS in subjects with early-stage HER2-positive breast cancer.
Primary Outcome/Efficacy Variable: The primary endpoint was DFS defined as the interval between the date of randomization and the date of the first occurrence of an objective disease recurrence (including local recurrence following mastectomy, local recurrence in ipsilateral breast following lumpectomy, regional recurrence, and distant recurrence); a second primary cancer (excluding squamous or basal cell carcinoma of the skin, melanoma *in situ*, carcinoma *in situ* of the cervix, or lobular carcinoma *in situ* of the breast), contralateral breast cancer, or death from any cause without prior event (recurrence of breast cancer or second primary cancer).
Secondary Outcome/Efficacy Variable(s): Pre-defined secondary efficacy endpoints were overall survival (OS; including death from any cause); time to first recurrence (included the first recurrence of one of the following sites: local recurrence following mastectomy, local recurrence in ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, or contralateral breast cancer, including ductal carcinoma *in situ* [DCIS]); time to distant recurrence (included the first distant recurrence as an event); time to central nervous system (CNS) recurrence (included the first CNS recurrence as an event); rate of CNS recurrence; health-related quality of life (QoL) which included summary measures of physical and mental health component scores, and independent dimension scores using the Medical Outcomes Study (MOS) 36-item short-form (SF-36 v2) acute recall. QoL was measured every 6

months at Month 0, 6 and 12 (or early withdrawal visit) while on study treatment and then every 6 months for another 24 months post-study treatment.

Statistical Methods: The Intent-to-Treat (ITT) population included all randomized subjects who received at least one dose of randomized therapy (lapatinib or placebo), and was used for the analysis of study population and efficacy data. The Safety population included all randomized subjects who received at least one dose of randomized therapy (lapatinib or placebo). Subjects were summarized under the actual treatment that they received. If a subject inadvertently received both lapatinib and placebo, they were summarized under the lapatinib treatment group. This population was used for the analysis of safety data. The estimated DFS times were summarized using Kaplan-Meier survival curves, from which the 5th, 15th and 25th percentiles were calculated. Treatment arms were compared using a stratified log-rank test (stratified by time since initial diagnosis, hormone receptor status and lymph node involvement). The one-sided p-value was presented along with a supporting two-sided p-value. An estimate of hazard ratio (HR) in the lapatinib arm compared with placebo arm, was provided together with a corresponding 95% confidence interval (CI). Approximate 95% confidence limits were calculated, based on Greenwood's formula for the standard error (SE). To further explore the impact of potential prognostic factors on DFS in the lapatinib arm compared to the placebo arm, a Cox Regression analysis was performed, fitting potential prognostic covariates into the model and results were summarized using HRs and 95% CIs. The percentage of surviving subjects who were disease free at 6-monthly intervals from the time of randomization was estimated from the Kaplan-Meier curves for the primary analysis of DFS. OS was summarized using Kaplan-Meier survival curves, from which the 1st, 2nd and 5th percentiles were calculated. Treatment arms were compared using a stratified log-rank test (stratified by time since initial diagnosis, hormone receptor status and lymph node involvement). An estimate of the treatment HR based on the log-rank test was provided together with a corresponding 95% CI. The Pike Estimator was used to provide the estimate of the HR. Approximate 95% confidence limits were calculated, based on Greenwood's formula for the SE. Time to first recurrence was analyzed using competing risks methodology where deaths or second primary cancers were treated as competing risks in the Cumulative Incidence curves. Time to distant recurrence (included the first distant recurrence as an event) was analyzed in the same way as time to first recurrence including the Cumulative Incidence analysis and percentage of subjects with recurrence; however, for this analysis, local recurrences, regional recurrences, second primary cancer, contralateral breast cancer or deaths were treated as competing risks. Time to CNS recurrence (included the first CNS recurrence as an event) was analyzed in the same way as time to first recurrence including the Cumulative Incidence analysis and percentage of subjects with recurrence; however, for this analysis, local recurrences, regional recurrences, second primary cancer, other distant recurrences (not CNS), contralateral breast cancer or deaths were treated as competing risks. The rate of CNS recurrence (defined as the number and percentage of patients experiencing a CNS recurrence) was presented as the difference in percentages (lapatinib – placebo) and the 95% CI for the difference along with the Fisher's exact test. Health-related QoL was assessed through subject self-completion of the SF-36 v2; a general health related QoL metric. Scores for the eight sub-scales and the two summary indexes for physical and mental health were calculated on a 0-100 scale. Change from baseline in the SF-36 v2 scores were compared between lapatinib and placebo to test for significant statistical differences using parametric analysis of covariance, adjusting for baseline sub-scale or summary index score, treatment and country. Study population and safety data were listed and summarized.
An end of study analysis was performed when the follow-up period reached a median of approximately 5 years for subjects still alive at the time of analysis. The end of study analysis presented updated results for DFS, OS, time to CNS recurrence, and safety objectives as of the cut-off date of 12 July 2013.

Study Population: This study enrolled women aged 18 years or older with histologically or cytologically confirmed HER2-positive invasive carcinoma of the breast (T_x or T_{1-4}) at the time of the initial diagnosis. Eligible subjects had Stage I through Stage IIIc disease using the American Joint Committee on Cancer staging criteria for breast cancer (6th ed), were node positive or intermediate- or high-risk node negative, and had tumors that overexpressed HER2. Subjects also had prior cancer treatment with either lumpectomy or mastectomy, and completed all primary neoadjuvant or adjuvant chemotherapy regimens prior to study enrollment (excluding prior therapy with an ErbB1 and/or HER2 inhibitor). Subjects with any of the following were excluded: Clinical and radiologic evidence of local or regional recurrence of disease or metastatic disease at the time of study entry; metachronous invasive breast cancer (breast cancers diagnosed at different times); prior history of other breast cancer malignancies, including DCIS, concurrent anti-cancer therapy (chemotherapy, immunotherapy, and/or biologic therapy) while taking study medication; a known history of uncontrolled or symptomatic angina, arrhythmias, or chronic heart failure (CHF); a left ventricular ejection fraction by echocardiogram or multigated acquisition (MUGA) scan outside of institution's normal range; malabsorption syndrome, ulcerative colitis, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel.

Number of Subjects:	Lapatinib	Placebo
Planned, N	1500	1500

Randomized, N	1579	1582
Intent-to-Treat (ITT) Population, N	1571	1576
Primary Analysis: Data cut-off of 21 September 2011		
Treatment Status:		
Completed 12 Months of Treatment, n (%)	1071 (68)	1324 (84)
Discontinued Treatment, n (%)	500 (32)	252 (16)
Discontinued Treatment due to Adverse Event, n (%)	300 (19)	82 (5)
Discontinued Treatment due to Lost to Follow-up, n (%)	14 (<1)	4 (<1)
Discontinued Treatment due to Protocol Violation, n (%)	15 (<1)	8 (<1)
Discontinued Treatment due to Death, n (%)	2 (<1)	0
Discontinued Treatment due to Decision by Subject, n (%)	61 (4)	31 (2)
Discontinued Treatment due to Disease Recurrence, n (%)	44 (3)	68 (4)
Discontinued Treatment due to Second Primary Cancer, n (%)	5 (<1)	8 (<1)
Discontinued Treatment due to Other Reason, n (%)	59 (4)	51 (3)
Subject Disposition:		
Completed 10 Years of Follow-up or Died, n (%)	76 (5)	77 (5)
Follow-up Ongoing, n (%)	1209 (77)	1286 (82)
Discontinued Study for Reasons Other than Death, n (%)	286 (18)	213 (14)
Demographics:	Lapatinib	Placebo
Female	1571	1576
Mean Age, years (SD)	51.7 (9.89)	52.3 (9.94)
White, n (%)	1129 (72)	1132 (72)
Primary Efficacy Results: Disease-Free Survival (DFS)		
	Lapatinib (N=1571)	Placebo (N=1576)
Subjects with any recurrence of initial disease, second primary cancer, contralateral breast cancer, or death, n (%)	210 (13)	264 (17)
Number Censored, new anti-cancer agent/radiotherapy, n (%)	1 (<1)	1 (<1)
Number Censored, follow-up ongoing, n (%)	1113 (71)	1156 (73)
Number Censored, follow-up ended, n (%)	247 (16)	155 (10)
Unadjusted HR	0.83	
95% CI	(0.70, 1.00)	
Stratified log-rank one-sided p-value	0.026	
Stratified log-rank two-sided p-value	0.053	
Secondary Outcome Variable(s):		
	Lapatinib (N=1571)	Placebo (N=1576)
DFS by pre-defined subgroups		
Time since initial diagnosis, n in subgroup (n with event)		
0 to 1 year	317 (55)	330 (79)
Adjusted HR (95% CI)	0.70 (0.50, 0.99)	
>1 year to 2 years	273 (52)	278 (56)
Adjusted HR (95% CI)	1.03 (0.71, 1.51)	
>2 years to 3 years	276 (41)	260 (40)
Adjusted HR (95% CI)	1.00 (0.65, 1.55)	
>3 years to 4 years	250 (27)	264 (44)
Adjusted HR (95% CI)	0.66 (0.41, 1.07)	
>4 years	455 (35)	444 (45)
Adjusted HR (95% CI)	0.81 (0.52, 1.26)	
Lymph node involvement, n in subgroup (n with event)		
Positive	878 (146)	875 (174)
Adjusted HR (95% CI)	0.86 (0.69, 1.07)	
Negative	693 (64)	701 (90)
Adjusted HR (95% CI)	0.78 (0.57, 1.07)	
Hormone receptor status, n in subgroup (n with event)		

ER and/or PgR positive	932 (125)	927 (136)
Adjusted HR (95% CI)	0.98 (0.77, 1.25)	
ER and PR negative	639 (85)	649 (128)
Adjusted HR (95% CI)	0.68 (0.52, 0.89)	
ER status, n in subgroup (n with event)		
Positive	838 (112)	828 (126)
Adjusted HR (95% CI)	0.94 (0.73, 1.22)	
Negative	732 (98)	748 (138)
Adjusted HR (95% CI)	0.74 (0.57, 0.96)	
PgR status, n in subgroup (n with event)		
Positive	713 (98)	708 (98)
Adjusted HR (95% CI)	1.06 (0.80, 1.41)	
Negative	855 (111)	864 (166)
Adjusted HR (95% CI)	0.69 (0.54, 0.88)	
Age, n in subgroup (n with event)		
<35 years	67 (10)	56 (16)
Adjusted HR (95% CI)	0.48 (0.21, 1.10)	
35 to <50 years	573 (79)	556 (103)
Adjusted HR (95% CI)	0.74 (0.55, 0.99)	
50 to <70 years	880 (112)	885 (130)
Adjusted HR (95% CI)	0.95 (0.74, 1.22)	
≥70 years	51 (9)	79 (15)
Adjusted HR (95% CI)	0.94 (0.40, 2.21)	
Age, n in subgroup (n with event)		
<65 years	1407 (186)	1388 (234)
Adjusted HR (95% CI)	0.82 (0.68, 0.99)	
≥65 years	164 (24)	188 (30)
Adjusted HR (95% CI)	0.95 (0.56, 1.64)	
Region, n in subgroup (n with event)		
North America and Canada	253 (16)	246 (31)
Adjusted HR (95% CI)	0.47 (0.25, 0.86)	
Latin America (including Mexico)	180 (33)	205 (45)
Adjusted HR (95% CI)	0.94 (0.60, 1.48)	
Europe	698 (97)	671 (111)
Adjusted HR (95% CI)	0.90 (0.68, 1.18)	
Asia Pacific	440 (64)	454 (77)
Adjusted HR (95% CI)	0.85 (0.61, 1.18)	
Race, n in subgroup (n with event)		
White	1110 (147)	1106 (184)
Adjusted HR (95% CI)	0.83 (0.67, 1.03)	
Black	41 (8)	41 (7)
Adjusted HR (95% CI)	1.32 (0.47, 3.67)	
Asian	337 (44)	329 (52)
Adjusted HR (95% CI)	0.85 (0.57, 1.27)	
Other/missing	83 (11)	100 (21)
Adjusted HR (95% CI)	0.59 (0.28, 1.23)	
Menopausal status, n in subgroup (n with event)		
Pre-menopausal	532 (78)	489 (91)
Adjusted HR (95% CI)	0.78 (0.58, 1.06)	
Post-menopausal	1039 (132)	1087 (173)
Adjusted HR (95% CI)	0.86 (0.68, 1.08)	
Stage of disease, n in subgroup (n with event)		
Stage I	284 (24)	268 (23)
Adjusted HR (95% CI)	1.08 (0.61, 1.92)	
Stage II	896 (92)	888 (138)

Adjusted HR (95% CI)	0.67 (0.51, 0.87)	
Stage III	391 (94)	419 (103)
Adjusted HR (95% CI)	1.08 (0.81, 1.42)	
Prior neo-/adjuvant chemotherapy, n in subgroup (n with event)		
Anthracycline w/o taxane (with or w/o CMF)	906 (113)	898 (152)
Adjusted HR (95% CI)	0.78 (0.61, 0.99)	
Anthracycline with taxane (with or w/o CMF)	598 (90)	609 (103)
Adjusted HR (95% CI)	0.89 (0.67, 1.18)	
No Anthracycline	67 (7)	69 (9)
Adjusted HR (95% CI)	0.98 (0.36, 2.63)	
Concomitant bisphosphonates, n in subgroup (n with event)		
Yes	115 (12)	125 (10)
Adjusted HR (95% CI)	1.33 (0.57, 3.11)	
No	1456 (198)	1451 (254)
Adjusted HR (95% CI)	0.81 (0.67, 0.98)	
Time since last chemotherapy, n in subgroup (n with event)		
0 to <1 year	476 (85)	497 (117)
Adjusted HR (95% CI)	0.77 (0.58, 1.02)	
≥1 year	1094 (125)	1077 (147)
Adjusted HR (95% CI)	0.88 (0.69, 1.12)	
Prior or concomitant endocrine therapy (AI or SERM), n in subgroup (n with event)		
Yes	831 (100)	840 (120)
Adjusted HR (95% CI)	0.89 (0.69, 1.17)	
No	740 (110)	736 (144)
Adjusted HR (95% CI)	0.78 (0.61, 1.00)	
	Lapatinib (N=1571)	Placebo (N=1576)
Overall Survival		
Number Died (event), n (%)	92 (6)	97 (6)
Number Censored, follow-up ended, n (%)	145 (9)	118 (7)
Number Censored, withdrawn from study but follow-up for survival ongoing, n (%)	124 (8)	75 (5)
Number Censored, follow-up ongoing, n (%)	1210 (77)	1286 (82)
Time to First Recurrence		
Cumulative incidence estimate of time to first recurrence (months)		
5th percentile	15.2	10.8
10th percentile	32.0	24.6
15th percentile	NC	45.3
20th percentile	NC	55.3
Time to Distant Recurrence		
Cumulative incidence estimate of time to distant recurrence (months)		
5th percentile	20.8	15.4
10th percentile	51.2	42.4
15th percentile	NC	NC
Time to CNS Recurrence		
Cumulative incidence estimate of time to CNS recurrence (months)		
1st percentile	NC	26.9
2nd percentile	NC	51.9
5th percentile	NC	NC
Rate of CNS Recurrence		
Subjects with CNS Recurrence, n (%)	14 (7)	23 (9)
Difference in Percentages	-2.0	
95% Confidence Interval for Difference in Percentages	(-7.0, 3.3)	

Health-related QoL	Lapatinib (N=1571)	Placebo (N=1576)
Change from baseline in SF-36v2 norm-based scores for physical component summary		
Month 6, N	1092	1283
Adjusted mean (SE)	-0.78 (0.217)	-0.44 (0.211)
Difference (95% CI)	-0.33 (-0.81, 0.14)	
Month 12, N	1007	1204
Adjusted mean (SE)	-0.84 (0.251)	-0.54 (0.242)
Difference (95% CI)	-0.30 (-0.84, 0.23)	
Follow-up Month 6, N	983	1074
Adjusted mean (SE)	-0.53 (0.287)	-0.87 (0.281)
Difference (95% CI)	0.34 (-0.25, 0.92)	
Follow-up Month 12, N	940	988
Adjusted mean (SE)	-0.88 (0.290)	-0.82 (0.289)
Difference (95% CI)	-0.06 (-0.65, 0.53)	
Follow-up Month 18, N	834	889
Adjusted mean (SE)	-0.61 (0.350)	-0.89 (0.346)
Difference (95% CI)	0.27 (-0.36, 0.91)	
Follow-up Month 24, N	807	824
Adjusted mean (SE)	-0.99 (0.412)	-0.66 (0.417)
Difference (95% CI)	-0.33 (-1.00, 0.34)	
Change from baseline in SF-36v2 norm-based scores for mental component summary		
Month 6, N	1092	1283
Adjusted mean (SE)	-2.34 (0.306)	-1.74 (0.297)
Difference (95% CI)	-0.61 (-1.28, 0.07)	
Month 12, N	1007	1204
Adjusted mean (SE)	-2.74 (0.332)	-2.29 (0.322)
Difference (95% CI)	-0.45 (-1.16, 0.26)	
Follow-up Month 6, N	983	1074
Adjusted mean (SE)	-2.22 (0.368)	-1.87 (0.361)
Difference (95% CI)	-0.35 (-1.10, 0.40)	
Follow-up Month 12, N	940	988
Adjusted mean (SE)	-3.08 (0.393)	-2.76 (0.392)
Difference (95% CI)	-0.31 (-1.11, 0.49)	
Follow-up Month 18, N	834	889
Adjusted mean (SE)	-2.38 (0.480)	-2.08 (0.475)
Difference (95% CI)	-0.29 (-1.17, 0.58)	
Follow-up Month 24, N	807	824
Adjusted mean (SE)	-2.78 (0.547)	-3.05 (0.554)
Difference (95% CI)	0.28 (-0.61, 1.16)	
Change from baseline in SF-36v2 norm-based scores for physical functioning		
Month 6, N	1132	1345
Adjusted mean (SE)	-0.52 (0.235)	-0.65 (0.227)
Difference (95% CI)	0.12 (-0.39, 0.64)	
Month 12, N	1025	1234
Adjusted mean (SE)	-0.59 (0.269)	-0.91 (0.260)
Difference (95% CI)	0.32 (-0.25, 0.89)	
Follow-up Month 6, N	997	1097
Adjusted mean (SE)	-0.45 (0.296)	-0.81 (0.289)
Difference (95% CI)	0.36 (-0.24, 0.96)	
Follow-up Month 12, N	955	1013
Adjusted mean (SE)	-1.11 (0.317)	-1.40 (0.316)
Difference (95% CI)	0.29 (-0.36, 0.93)	
Follow-up Month 18, N	851	913
Adjusted mean (SE)	-0.80 (0.363)	-1.10 (0.358)

Difference (95% CI)	0.30 (-0.35, 0.96)	
Follow-up Month 24, N	818	845
Adjusted mean (SE)	-1.06 (0.438)	-1.17 (0.442)
Difference (95% CI)	0.11 (-0.59, 0.81)	
Change from baseline in SF-36v2 norm-based scores for role physical		
Month 6, N	1130	1335
Adjusted mean (SE)	-1.37 (0.276)	-0.87 (0.267)
Difference (95% CI)	-0.50 (-1.11, 0.10)	
Month 12, N	1023	1230
Adjusted mean (SE)	-1.52 (0.303)	-0.83 (0.293)
Difference (95% CI)	-0.69 (-1.34, -0.05)	
Follow-up Month 6, N	997	1094
Adjusted mean (SE)	-1.14 (0.328)	-1.45 (0.322)
Difference (95% CI)	0.31 (-0.36, 0.98)	
Follow-up Month 12, N	955	1009
Adjusted mean (SE)	-1.78 (0.344)	-1.47 (0.343)
Difference (95% CI)	-0.31 (-1.01, 0.38)	
Follow-up Month 18, N	851	909
Adjusted mean (SE)	-1.72 (0.410)	-1.68 (0.405)
Difference (95% CI)	-0.04 (-0.79, 0.70)	
Follow-up Month 24, N	818	842
Adjusted mean (SE)	-1.77 (0.486)	-1.54 (0.491)
Difference (95% CI)	-0.23 (-1.01, 0.56)	
Change from baseline in SF-36v2 norm-based scores for bodily pain		
Month 6, N	1130	1331
Adjusted mean (SE)	-1.58 (0.304)	-1.31 (0.295)
Difference (95% CI)	-0.28 (-0.94, 0.39)	
Month 12, N	1024	1229
Adjusted mean (SE)	-1.75 (0.338)	-1.62 (0.326)
Difference (95% CI)	-0.13 (-0.85, 0.58)	
Follow-up Month 6, N	995	1094
Adjusted mean (SE)	-1.13 (0.376)	-1.35 (0.368)
Difference (95% CI)	0.22 (-0.54, 0.98)	
Follow-up Month 12, N	954	1007
Adjusted mean (SE)	-1.06 (0.383)	-1.19 (0.382)
Difference (95% CI)	0.14 (-0.64, 0.91)	
Follow-up Month 18, N	847	909
Adjusted mean (SE)	-0.69 (0.461)	-1.07 (0.455)
Difference (95% CI)	0.39 (-0.45, 1.22)	
Follow-up Month 24, N	817	840
Adjusted mean (SE)	-1.69 (0.547)	-1.41 (0.553)
Difference (95% CI)	-0.28 (-1.16, 0.60)	
Change from baseline in SF-36v2 norm-based scores for general health		
Month 6, N	1124	1319
Adjusted mean (SE)	-1.01 (0.244)	-0.34 (0.236)
Difference (95% CI)	-0.67 (-1.20, -0.14)	
Month 12, N	1020	1221
Adjusted mean (SE)	-1.33 (0.275)	-0.70 (0.266)
Difference (95% CI)	-0.63 (-1.22, -0.05)	
Follow-up Month 6, N	994	1085
Adjusted mean (SE)	-1.25 (0.314)	-1.34 (0.308)
Difference (95% CI)	0.09 (-0.55, 0.73)	
Follow-up Month 12, N	951	1002
Adjusted mean (SE)	-1.93 (0.330)	-1.48 (0.329)
Difference (95% CI)	-0.45 (-1.12, 0.22)	

Follow-up Month 18, N	844	902
Adjusted mean (SE)	-1.28 (0.397)	-1.28 (0.392)
Difference (95% CI)	0.00 (-0.72, 0.72)	
Follow-up Month 24, N	813	835
Adjusted mean (SE)	-1.29 (0.471)	-1.02 (0.476)
Difference (95% CI)	-0.28 (-1.03, 0.48)	
Change from baseline in SF-36v2 norm-based scores for vitality		
Month 6, N	1126	1332
Adjusted mean (SE)	-2.30 (0.283)	-1.83 (0.274)
Difference (95% CI)	-0.47 (-1.09, 0.15)	
Month 12, N	1022	1225
Adjusted mean (SE)	-2.49 (0.309)	-1.88 (0.299)
Difference (95% CI)	-0.61 (-1.27, 0.05)	
Follow-up Month 6, N	993	1090
Adjusted mean (SE)	-1.55 (0.335)	-1.61 (0.328)
Difference (95% CI)	0.06 (-0.62, 0.74)	
Follow-up Month 12, N	953	1006
Adjusted mean (SE)	-2.45 (0.355)	-2.01 (0.354)
Difference (95% CI)	-0.43 (-1.15, 0.29)	
Follow-up Month 18, N	848	906
Adjusted mean (SE)	-1.53 (0.426)	-1.25 (0.421)
Difference (95% CI)	-0.28 (-1.05, 0.50)	
Follow-up Month 24, N	817	837
Adjusted mean (SE)	-2.03 (0.501)	-1.96 (0.507)
Difference (95% CI)	-0.08 (-0.88, 0.73)	
Change from baseline in SF-36v2 norm-based scores for social functioning		
Month 6, N	1138	1347
Adjusted mean (SE)	-2.34 (0.299)	-1.42 (0.289)
Difference (95% CI)	-0.92 (-1.57, -0.27)	
Month 12, N	1025	1234
Adjusted mean (SE)	-2.63 (0.333)	-2.05 (0.322)
Difference (95% CI)	-0.58 (-1.28, 0.13)	
Follow-up Month 6, N	997	1098
Adjusted mean (SE)	-1.80 (0.371)	-1.51 (0.363)
Difference (95% CI)	-0.30 (-1.08, 0.47)	
Follow-up Month 12, N	957	1011
Adjusted mean (SE)	-2.47 (0.383)	-2.17 (0.382)
Difference (95% CI)	-0.30 (-0.78, 0.89)	
Follow-up Month 18, N	850	912
Adjusted mean (SE)	-1.96 (0.462)	-2.01 (0.456)
Difference (95% CI)	0.06 (-0.78, 0.89)	
Follow-up Month 24, N	819	843
Adjusted mean (SE)	-2.94 (0.526)	-2.75 (0.532)
Difference (95% CI)	-0.19 (-1.04, 0.65)	
Change from baseline in SF-36v2 norm-based scores for role emotional		
Month 6, N	1124	1328
Adjusted mean (SE)	-1.80 (0.335)	-1.69 (0.325)
Difference (95% CI)	-0.12 (-0.85, 0.62)	
Month 12, N	1023	1226
Adjusted mean (SE)	-1.99 (0.357)	-1.99 (0.345)
Difference (95% CI)	0.00 (-0.76, 0.76)	
Follow-up Month 6, N	996	1091
Adjusted mean (SE)	-1.87 (0.393)	-1.88 (0.385)
Difference (95% CI)	0.01 (-0.78, 0.81)	
Follow-up Month 12, N	955	1004

Adjusted mean (SE)	-2.88 (0.425)	-2.27 (0.425)
Difference (95% CI)	-0.16 (-1.02, 0.70)	
Follow-up Month 18, N	851	905
Adjusted mean (SE)	-2.47 (0.509)	-2.50 (0.503)
Difference (95% CI)	0.04 (-0.89, 0.96)	
Follow-up Month 24, N	818	839
Adjusted mean (SE)	-2.75 (0.582)	-2.95 (0.589)
Difference (95% CI)	0.20 (-0.74, 1.14)	
Change from baseline in SF-36v2 norm-based scores for mental health		
Month 6, N	1124	1332
Adjusted mean (SE)	-1.96 (0.303)	-1.46 (0.293)
Difference (95% CI)	-0.50 (-1.16, 0.16)	
Month 12, N	1021	1225
Adjusted mean (SE)	-2.38 (0.333)	-2.11 (0.322)
Difference (95% CI)	-0.27 (-0.98, 0.43)	
Follow-up Month 6, N	993	1090
Adjusted mean (SE)	-1.92 (0.367)	-1.70 (0.360)
Difference (95% CI)	-0.22 (-0.96, 0.53)	
Follow-up Month 12, N	953	1006
Adjusted mean (SE)	-2.47 (0.390)	-2.47 (0.389)
Difference (95% CI)	0.00 (-0.79, 0.79)	
Follow-up Month 18, N	848	906
Adjusted mean (SE)	-1.91 (0.469)	-1.58 (0.464)
Difference (95% CI)	-0.33 (-1.18, 0.53)	
Follow-up Month 24, N	817	837
Adjusted mean (SE)	-2.16 (0.545)	-2.54 (0.552)
Difference (95% CI)	0.38 (-0.50, 1.26)	
End of Study Analysis: Data cut-off of 12 July 2013		
Subject Disposition:	Lapatinib (N=1571)	Placebo (N=1576)
Completed 5 Years of Follow-up or Died, n (%)	321 (20)	276 (18)
Follow-up Ongoing, n (%)	0	0
Discontinued Study for Reasons Other than Death, n (%)	1250 (80)	1300 (82)
Discontinued Study due to Sponsor Terminated Study, n (%)	866 (55)	990 (63)
Discontinued Study due to Decision by Subject, n (%)	235 (15)	167 (11)
Discontinued Study due to Lost to Follow-up, n (%)	92 (6)	90 (6)
Discontinued Study due to Investigator Decision, n (%)	36 (2)	32 (2)
Discontinued Study due to Other Reason, n (%)	13 (<1)	18 (1)
Discontinued Study due to Protocol Violation, n (%)	8 (<1)	3 (<1)
Primary Efficacy Results: DFS		
	Lapatinib (N=1571)	Placebo (N=1576)
Subjects with any recurrence of initial disease, second primary cancer, contralateral breast cancer, or death, n (%)	252 (16)	290 (18)
Number Censored, new anti-cancer agent/radiotherapy, n (%)	1 (<1)	1 (<1)
Number Censored, follow-up ended, n (%)	1318 (84)	1285 (82)
Unadjusted HR	0.91	
95% CI	(0.77, 1.08)	
Stratified log-rank one-sided p-value	0.143	
Stratified log-rank two-sided p-value	0.286	
Secondary Outcome Variable(s):		
	Lapatinib (N=1571)	Placebo (N=1576)
DFS by pre-defined subgroups		
Time since initial diagnosis, n in subgroup (n with event)		

0 to 1 year		
Adjusted HR (95% CI)	0.77 (0.56, 1.07)	
>1 year to 2 years		
Adjusted HR (95% CI)	1.05 (0.73, 1.50)	
>2 years to 3 years		
Adjusted HR (95% CI)	1.22 (0.81, 1.83)	
>3 years to 4 years		
Adjusted HR (95% CI)	0.66 (0.43, 1.03)	
>4 years		
Adjusted HR (95% CI)	0.92 (0.63, 1.36)	
Lymph node involvement, n in subgroup (n with event)		
Positive		
Adjusted HR (95% CI)	0.93 (0.76, 1.15)	
Negative		
Adjusted HR (95% CI)	0.86 (0.64, 1.15)	
Hormone receptor status, n in subgroup (n with event)		
ER and/or PgR positive		
Adjusted HR (95% CI)	1.10 (0.88, 1.37)	
ER and PgR negative		
Adjusted HR (95% CI)	0.71 (0.55, 0.93)	
	Lapatinib (N=1571)	Placebo (N=1576)
Overall Survival		
Number Died (event), n (%)	115 (7)	126 (8)
Number Censored, follow-up ended, n (%)	1456 (93)	1450 (92)

AI=aromatase inhibitor; CMF= cyclophosphamide, methotrexate and fluorouracil (5FU); NC=not calculable; SE = standard error; SERM=selective estrogen receptor modulators

All adverse events (AEs) and serious adverse events (SAEs), regardless of relationship to study treatment, were collected from the first dose of study drug to 5 days after the last dose. All SAEs assessed as related to study participation or study drug were collected from the time of consent to participate in the study through to study completion (including any follow-up period).

	Lapatinib (N=1573)	Placebo (N=1574)
Most Frequent[a] Adverse Events – On-Therapy Data cut-off of 12 July 2013	n (%)	n (%)
Subjects with any AE(s)	1450 (92)	1193 (76)
Diarrhea	958 (61)	256 (16)
Rash	923 (59)	243 (15)
Nausea	279 (18)	180 (11)
Fatigue	251 (16)	202 (13)
Dry skin	220 (14)	44 (3)
Paronychia	154 (10)	5 (<1)
Headache	140 (9)	186 (12)
Alopecia	135 (9)	25 (2)
Pruritis	130 (8)	49 (3)
Nail disorder	130 (8)	16 (1)
Asthenia	75 (5)	78 (5)
Cough	75 (5)	103 (7)
Arthralgia	70 (4)	113 (7)
Back pain	54 (3)	75 (5)

[a] defined as the 10 most frequent events in each treatment group

Serious Adverse Events - On-Therapy
Data cut-off of 12 July 2013
n (%) [n considered by the investigator to be related to study medication]

	Lapatinib (N=1573)	Placebo (N=1574)
Subjects with any SAE, n (%) -Includes both fatal and non-fatal events	99 (6)	78 (5)
	n (%) [related]	n (%) [related]
Erysipelas	8 (<1) [2]	0
Cellulitis	5 (<1) [1]	0
Pneumonia	3 (<1) [1]	2 (<1) [1]
Appendicitis	1 (<1) [0]	1 (<1) [0]
Gastroenteritis	1 (<1) [1]	1 (<1) [0]
Herpes zoster	2 (<1) [0]	0
Abscess	1 (<1) [0]	0
Breast abscess	0	1 (<1) [0]
Breast cellulitis	1 (<1) [0]	0
Bronchitis	0	1 (<1) [0]
Bronchopneumonia	1 (<1) [0]	0
Cystitis	0	1 (<1) [0]
Device-related infection	0	1 (<1) [0]
Gastroenteritis viral	1 (<1) [0]	0
Implant site cellulitis	1 (<1) [0]	0
Influenza	1 (<1) [0]	0
Lobar pneumonia	0	1 (<1) [0]
Phelonephritis	0	1 (<1) [0]
Sepsis	1 (<1) [1]	0
Sinusitis	1 (<1) [1]	0
Streptococcal sepsis	1 (<1) [1]	0
Urinary tract infection	1 (<1) [0]	0
Urosepsis	0	1 (<1) [0]
Wound infection	1 (<1) [0]	0
Breast cancer	0	2 (<1) [0]
Colon cancer	1 (<1) [0]	2 (<1) [0]
Endometrial cancer	2 (<1) [0]	1 (<1) [0]
Basal cell carcinoma	0	2 (<1) [0]
Contralateral breast cancer	1 (<1) [0]	1 (<1) [0]
Acute myeloid leukaemia	0	1 (<1) [0]
Benign breast neoplasm	1 (<1) [0]	0
Bladder papilloma	1 (<1) [0]	0
Cardiac neoplasm unspecified	1 (<1) [1]	0
Cervix carcinoma	0	1 (<1) [0]
Haemangioma of liver	1 (<1) [0]	0
Intraductal papilloma of breast	0	1 (<1) [0]
Leiomyosarcoma	0	1 (<1) [0]
Malignant melanoma in situ	1 (<1) [0]	0
Ovarian epithelial cancer	1 (<1) [0]	0
Ovarian germ cell teratoma benign	1 (<1) [0]	0
Pancreatic carcinoma metastatic	1 (<1) [0]	0
Skin cancer	1 (<1) [0]	0
Thyroid cancer	1 (<1) [0]	0
Uterine cancer	0	1 (<1) [0]
Uterine leiomyoma	1 (<1) [0]	0
Uterine leiomyosarcoma	1 (<1) [0]	0
Diarrhoea	7 (<1) [7]	0
Abdominal pain	3 (<1) [1]	0
Enteritis	1 (<1) [0]	1 (<1) [0]
Gastritis	0	2 (<1) [0]

Nausea	0	2 (<1) [0]
Vomiting	0	2 (<1) [0]
Abdominal hernia	1 (<1) [0]	0
Abdominal pain upper	1 (<1) [0]	0
Enterocolitis	1 (<1) [1]	0
Gastric ulcer	1 (<1) [1]	0
Haematochezia	1 (<1) [1]	0
Haemorrhoids	1 (<1) [0]	0
Intestinal obstruction	1 (<1) [0]	0
Intestinal perforation	1 (<1) [1]	0
Pancreatitis	0	1 (<1) [1]
Umbilical hernia	0	1 (<1) [0]
Left ventricular dysfunction	3 (<1) [3]	1 (<1) [1]
Cardiac failure	0	3 (<1) [1]
Myocardial infarction	2 (<1) [2]	0
Actue myocardial infarction	0	1 (<1) [0]
Atrial fibrillation	0	1 (<1) [0]
Atrioventricular block first degree	1 (<1) [1]	0
Myocardial ischaemia	0	1 (<1) [1]
Pericardial effusion	1 (<1) [1]	0
Tachycardia	0	1 (<1) [1]
Ejection fraction decreased	5 (<1) [4]	6 (<1) [5]
Alanine aminotransferase increased	1 (<1) [1]	0
Blood bilirubin abnormal	1 (<1) [1]	0
Transaminases increased	1 (<1) [1]	0
Ankle fracture	1 (<1) [0]	1 (<1) [0]
Accidental overdose	1 (<1) [1]	0
Chest injury	1 (<1) [0]	0
Femoral neck fracture	1 (<1) [0]	0
Foot fracture	0	1 (<1) [0]
Fracture	0	1 (<1) [0]
Humerus fracture	1 (<1) [0]	0
Muscle strain	1 (<1) [0]	0
Rib fracture	0	1 (<1) [0]
Road traffic accident	1 (<1) [0]	0
Transplant failure	1 (<1) [0]	0
Ulna fracture	0	1 (<1) [0]
Wound dehiscence	1 (<1) [0]	0
Osteoarthritis	0	2 (<1) [0]
Arthropathy	0	1 (<1) [0]
Back pain	1 (<1) [0]	0
Bone pain	0	1 (<1) [1]
Costochondritis	0	1 (<1) [0]
Intervertebral disc compression	0	1 (<1) [0]
Myalgia	0	1 (<1) [0]
Osteochondrosis	1 (<1) [0]	0
Carotid artery stenosis	1 (<1) [0]	0
Cerebellar infarction	0	1 (<1) [0]
Cerebral haemorrhage	0	1 (<1) [0]
Cerebral infarction	0	1 (<1) [0]
Cerebral ischaemia	0	1 (<1) [0]
Cerebrovascular accident	0	1 (<1) [0]
Convulsion	1 (<1) [0]	0
Headache	0	1 (<1) [0]
Paraesthesia	0	1 (<1) [0]

Syncope	1 (<1) [0]	0
Hepatotoxicity	2 (<1) [2]	0
Cholecystitis	0	1 (<1) [0]
Cholelithiasis	1 (<1) [0]	0
Cytolytic hepatitis	1 (<1) [1]	0
Hepatitis	1 (<1) [1]	0
Hepatitis toxic	1 (<1) [1]	0
Hypoglycaemia	1 (<1) [0]	2 (<1) [0]
Dehydration	0	1 (<1) [0]
Diabetes mellitus	0	1 (<1) [0]
Electrolyte imbalance	1 (<1) [1]	0
Hyperkalaemia	0	1 (<1) [0]
Hypocalcaemia	0	1 (<1) [1]
Hyponatraemia	0	1 (<1) [0]
Breast disorder	1 (<1) [0]	0
Breast mass	1 (<1) [0]	0
Menometrorrhagia	0	1 (<1) [0]
Menstrual disorder	0	1 (<1) [0]
Ovarian cyst	0	1 (<1) [0]
Ovarian enlargement	0	1 (<1) [0]
Asthenia	0	2(<1) [2]
Death	1 (<1) [0]	0
Non-cardiac chest pain	0	1 (<1) [0]
Oedema peripheral	0	1 (<1) [0]
Atelectasis	1 (<1) [1]	0
Dyspnaea exertional	0	1 (<1) [0]
Laryngeal oedema	1 (<1) [1]	0
Pulmonary embolism	0	1 (<1) [0]
Capillary leak syndrome	1 (<1) [1]	0
Femoral artery occlusion	0	1 (<1) [0]
Hypertensive crisis	0	1 (<1) [0]
Thrombosis	1 (<1) [0]	0
Depression	1 (<1) [0]	1 (<1) [0]
Suicide attempt	1 (<1) [0]	1 (<1) [0]
Suicidal ideation	1 (<1) [0]	0
Neutropenia	2 (<1) [2]	0
Drug hypersensitivity	1 (<1) [1]	0
Hypersensitivity	1 (<1) [1]	0
Rash	2 (<1) [1]	0
Vertigo	1 (<1) [0]	0
Thyroiditis subacute	0	1 (<1) [0]
Nephrolithiasis	0	1 (<1) [0]
Subjects with fatal SAEs, n (%)	4 (<1)	3 (<1)
	n (%) [related]	n (%) [related]
Bronchopneumonia	1 (<1) [0]	0
Pneumonia	1 (<1) [0]	0
Acute myeloid leukaemia	0	1 (<1) [0]
Pancreatic carcinoma metastatic	1 (<1) [0]	0
Cardiac failure	0	1 (<1) [0]
Death	1 (<1) [0]	0
Cerebrovascular accident	0	1 (<1) [0]

Conclusion:
This study showed that the analysis of the primary endpoint, DFS, did not reach the pre-specified statistical significance level and hazard ratio (0.769). At the final analysis, a total of 210 (13%) subjects in the lapatinib arm and

264 (17%) in the placebo arm had a DFS event. The Pike estimator of unadjusted HR for the risk of an event in the lapatinib arm, as compared with the placebo arm, was 0.83 (95% CI, 0.70-1.00), based on the log-rank test; p=0.026 (1-sided) p=0.053 (2-sided) value by the stratified log-rank test. At the end of study analysis, a total of 252 (16%) subjects in the lapatinib arm and 290 (18%) in the placebo arm had a DFS event. The Pike estimator of unadjusted HR for the risk of an event in the lapatinib arm, as compared with the placebo arm, was 0.91 (95% CI, 0.77-1.08), based on the log-rank test; p=0.143 (1-sided) p=0.286 (2-sided) value by the stratified log-rank test. A treatment effect in favor of lapatinib was observed in the final analysis in certain, pre-defined, subgroup analyses of DFS: subjects with hormone receptor-negative disease and those recently diagnosed (within 1 year of initial diagnosis), and this treatment effect was also observed for subjects with hormone receptor-negative disease in the end-of-study analysis. However, confirmatory statements based on statistical evidence cannot be made as these were conducted as exploratory analyses only. Lapatinib does not have a significant detrimental impact on QoL compared to placebo. Although QoL scores decreased relative to baseline for both treatment arms for all domains/summary scores for all assessments, none of the decreases reached the minimum clinically important difference commonly accepted for the SF-36. In the safety population, 92% and 76% of subjects reported AEs in the lapatinib and placebo arms, respectively. SAEs were reported by 6% and 5% of subjects in the lapatinib and placebo arms, respectively. The most frequently reported SAEs in the lapatinib-treated subjects were erysipelas, diarrhea, cellulitis, and ejection fraction decreased. There were no treatment-related deaths during the study. With a longer follow-up of approximately 5 years, the end of study efficacy and safety results are consistent with the primary results analysis.