Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO), a randomised, open-label, multicentre, phase 3 trial: survival outcomes and their association with pathological complete response

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Summary

Background: We investigated whether the increase in pathological complete response (pCR) rates with neoadjuvant combination of lapatinib and trastuzumab in addition to weekly paclitaxel would translate into improved survival outcomes in HER2-positive early breast cancer (EBC) patients.

Methods: This multicentre, randomised, open-label, phase III trial enrolled 455 women with HER2-positive EBC. Given treatments were: oral lapatinib, intravenous trastuzumab, or their combination for 6 weeks (biological window), followed by an additional 12 weeks of the assigned anti-HER2 therapy in combination with weekly paclitaxel (80 mg/m²). Definitive surgery was performed 4 weeks after the last dose of paclitaxel. After surgery, women received 3 cycles of intravenous 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by 34 weeks of the same assigned neoadjuvant anti-HER2 therapy. The primary endpoint was pCR which was reported by Baselga et al (Lancet 2012). Secondary endpoints included event-free (EFS) and overall survival (OS). EFS and OS were reported in the intention-to-treat population. Associations between pCR and EFS or OS were reported using landmark analysis. This trial is registered with ClinicalTrials.gov, NCT00553358 and it is in follow-up phase.

Findings: 154 women received lapatinib, 149 trastuzumab and 152 the combination of lapatinib and trastuzumab. At a median clinical follow-up of 3·77 years (95% CI 3·72-3·98), the3-year EFS was numerically higher for women treated with lapatinib and trastuzumab compared with trastuzumab [84% (95% CI 77%-89%) vs. 76% (95% CI 68%-82%); HR 0·78; 95% CI 0·47-1·28; p=0·33] in the whole population. In the landmark analysis, we observed better EFS [HR

0·38; 95% CI 0·22-0·63; p=0·0003] and OS [HR 0·35; 95% CI 0·15-0·70; p=0·005] for women with pCR compared to those without pCR. Women treated with the combination of lapatinib plus trastuzumab had better EFS with pCR than without pCR [HR 0·32; 95% CI 0·12-0·74; p=0·012]. Adverse events were consistent with known safety profile of lapatinib and/or trastuzumab.

Interpretation: The observed correlation between pCR and improved EFS with dual HER2 blockade has implications for clinical care and reinforces the validity of neoadjuvant HER2 therapies while setting the stage for studies aimed at improving the outcome for patients that do not achieve a pCR.

Funding: GlaxoSmithKline

Introduction:

Overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) occurs in approximately 15% of breast cancers and is associated with poor prognosis (1). Anti-HER2 drugs such as trastuzumab (monoclonal antibody; Herceptin, Genentech, California, CA, USA) and lapatinib (tyrosine kinase inhibitor; Tykerb, GlaxoSmithKline, Brentford, UK) are widely used for the treatment of HER2-positive breast cancer, with the former being approved for use in the metastatic and adjuvant settings while the latter for the metastatic setting only (2-6). A previous report of the NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) phase III, randomized trial showed that dual anti-HER2 blockade with lapatinib and trastuzumab combined with weekly paclitaxel significantly increased the rate of pathological complete response (pCR) compared to trastuzumab and weekly paclitaxel (51·3% vs.

29·5% respectively; p= 0·0001) (7). In a recent meta-analysis funded by the US Food and Drug Administration (FDA) involving 11·955 patients, reaching pCR after neoadjuvant therapy was significantly associated with better event-free survival (EFS) and overall survival (OS), particularly in the HER2-positive population (N= 1·989) irrespective of hormone receptor status (Hazard Ratio (HR) 0·39 for EFS and HR 0·34 for OS) (8).

As previously reported, the primary objective was to compare the rate of pCR as defined by the NSABP guidelines (absence of residual invasive disease in the breast) (7). Secondary objectives pre-specified in the NeoALTTO protocol were to evaluate the effect of treatment on EFS and OS as well as the association between achieving locoregional pCR (ypT0/is ypN0) and survival outcomes. We report results at a median follow up of 3·77 years in 455 women with HER2-positive EBC enrolled in the NeoALTTO trial.

Methods

Study design and patients:

The NeoALTTO trial (Breast International Group 1-06) was previously reported in detail (7). In summary, 455 women were randomised between January 5, 2008 and May 27, 2010 to one of the three parallel treatment groups: oral lapatinib, intravenous trastuzumab, or lapatinib plus trastuzumab. Treatment details are provided in the procedure section. Key eligibility included histologically confirmed HER2-positive EBC defined as immunohistochemistry (IHC) 3+ with >30% of invasive cells or Fluorescence InSitu Hybridization (FISH) ratio >2.2 as per guidelines (9). HER2 status was assessed locally (after laboratory accreditation) or centrally (Vall D'Hebron Institute of Oncology,

Barcelona). Hormone receptor was locally tested and considered positive or negative as per local guidelines. Women had to have a tumour greater than 2 cm and adequate baseline hepatic, renal, cardiac and bone marrow function. Left ventricular ejection fraction (LVEF) at baseline had to be 50% or more. Women with bilateral, inflammatory or metastatic breast cancer were not eligible (7).

The ethics committee and relevant health authorities at each participating institution approved the study protocol. All participating women gave written informed consent prior to study entry.

Randomisation and masking:

This section was extensively reported in the first publication, which focused on the primary endpoint of pathological complete response (pCR) (7).

Procedures:

Neoadjuvant treatments and doses are summarized in Table 1. Women received oral lapatinib, intravenous trastuzumab, or lapatinib plus trastuzumab for 6 weeks (biological window), followed by an additional 12 weeks of the assigned anti-HER2 therapy plus weekly paclitaxel. Definitive surgery was performed 4 weeks after the last dose of paclitaxel. Chemotherapy was given to all women within 6 weeks of definitive surgery and consisted of 3 cycles of FEC (5-fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2) given intravenously every 3 weeks. After chemotherapy, all women received the same assigned neoadjuvant anti-HER2 therapy for an additional 34 weeks to complete a total duration of 52 weeks (1 year) of anti-HER2 therapy. Radiotherapy given concomitantly with anti-HER2 drugs was mandatory in

Table 1. Treatment groups in the NeoALTTO trial (N=455)

	Lapatinib (N= 154)	**Trastuzumab (N= 149)**	**Lapatinib plus Trastuzumab (N= 152)**
Neoadjuvant phase			
Anti-HER2 drugs: first six weeks administered without paclitaxel (biological window)	1500 mg daily (orally) for 18 weeks	4 mg/kg loading dose followed by 2 mg/kg IV for 18 weeks (weekly)	1000 mg daily (orally) for 18 weeks* + 4 mg/kg loading dose followed by 2 mg/kg IV for 18 weeks (weekly)
Paclitaxel	80 mg/m2 IV weekly x 12 weeks		
Adjuvant phase			
FEC	5-fluorouracil 500 mg/m² + epirubicin 100 mg/m² + cyclophosphamide 500 mg/m² given IV every 3 weeks for a total of 3 cycles		
Anti-HER2 drugs	1500 mg daily (orally) for 34 weeks	8 mg/kg loading dose followed by 6 mg/kg IV for 34 weeks (every 3 weeks)	1000 mg daily (orally) for 34 weeks + 8 mg/kg loading dose followed by 6 mg/kg IV for 34 weeks (every 3 weeks)

Abbreviations: IV: intravenous

Note: * An amendment was introduced to reduce the dose of lapatinib to 750 mg daily when paclitaxel was added in order to reduce the incidence of diarrhoea (amendment 2 October 2008); 54 of 152 women received treatment at reduced dose due to the fast accrual of the trial.

women treated with breast conserving surgery and was given according to local guidelines in case of mastectomy and started 4 weeks after completion of FEC. Endocrine therapy was prescribed for women with hormone receptor positive tumours as per local policy for a minimum duration of 5 years.

LVEF was measured with either echocardiography or multiple gate acquisition scan at baseline, at week 6 after randomization, before surgery, at weeks 1, 13, 25 and 34 of targeted adjuvant therapy and in the post-treatment follow-up at months 12, 18, 24, 36, 48 and 60, and then yearly up to year 10. A primary cardiac event was defined as cardiac death or congestive heart failure NYHA Class III or IV. A secondary cardiac event was defined as an asymptomatic (NYHA I) or mildly symptomatic (NYHA II) significant drop in LVEF, confirmed by a second LVEF assessment within approximately 3 weeks. A significant LVEF drop was defined as an absolute decrease of more than 10 points below baseline LVEF and to below 50%.

Outcomes

The primary endpoint was pCR which was reported in 2012 and was defined as the absence of invasive tumour cells in the breast at the time of surgery (7). Secondary endpoints included locoregional pCR, disease-free and overall survival, safety and tolerability. An amendment released in May 2013 replaced disease-free survival with EFS to align with the FDA recommendations. Accordingly, EFS was defined as the time from randomization to first EFS event. For women who underwent breast cancer surgery, EFS events were defined as post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For women who did not undergo breast cancer surgery, EFS events

were death during clinical follow-up or non-completion of any neoadjuvant investigational product due to disease progression. OS was defined as the time from randomization to death from any cause. The NeoALTTO trial was powered to detect treatment differences with respect to pCR rate, but is underpowered to detect moderate treatment differences with respect to EFS and OS. Thus, both analyses (EFS/OS) are intended to be descriptive. Locoregional pCR (ypT0/is ypN0), referred to as pCR, was defined as the absence of invasive cancer in breast and ipsilateral axillary lymph nodes at post-neoadjuvant surgery. This definition was published in 2012 and introduced to the protocol in amendment 3 for consistency with FDA recommendations (7). These changes in survival outcome definitions were implemented after trial completion, but before any survival analysis was performed. We did not analyze DFS or OS as per original definition.

Statistical Analysis:

The trial was powered to detect differences between treatment groups with respect to pCR rate. Assessment of EFS and OS outcomes is therefore descriptive, and p-values are presented as measures of variability and not for inferential purposes. These were pre-planned analysis even if the number of expected events is low (10, 11). Differences in EFS and OS between the trastuzumab group and each of the lapatinib-containing groups are described using hazard ratios and 95% confidence intervals with p-values from two-sided stratified log-rank tests, implemented as Wald tests from the Cox models (12). Tests of proportionality were performed. All 455 patients (i.e. the ITT population) were included in these analyses.

Associations between pCR and EFS/OS were examined using landmark analyses (13,14). pCR is a „categorizing" event known after study entry and therefore analyses of „outcome" events according to pCR are potentially subject to guarantee time bias (GTB). The landmark analysis controls for GTB. A 30-week landmark time was selected as it would be sufficiently long for primary breast cancer surgery to be performed and not too long to eliminate the occurrence of EFS events. Date of surgery is patient dependent and thus not as free of GTB as the landmark approach for analyses in this report designed to assess the EFS and OS outcomes comparing patients who did or did not achieve pCR,

For EFS/OS, the 30-week landmark population included only women who were still in clinical (survival) follow-up and were event-free (alive) at 30 weeks after randomization (web appendix 1A and 1B). Patients were allocated to two groups according to their pCR status recorded up to week 30 from randomization, and these groups were compared with respect to EFS/OS. Two-sided stratified log-rank tests of EFS/OS were implemented as Wald tests from the Cox model (12) with pCR status and assigned treatment arm fitted as covariates and the stratification factors entered as strata variables (Web appendix 2). Of note, the number of patients with missing pCR status is low and so these patients were excluded from the landmark analysis.

Supplemental analyses were also performed where pCR status was included as a time dependent covariate in Cox proportional hazards models of EFS and OS from randomization in all women in the ITT population whose pCR status was known. These models were adjusted for the assigned treatment group, tumour size and other stratification variables.

All analyses of EFS and OS were repeated separately for the hormone receptor positive and negative cohorts. Differences in characteristics of these two cohorts were summarized using Fisher exact tests.

Incidence rates and exact 95% confidence intervals (15) were calculated for the primary cardiac endpoint and any cardiac endpoint for each treatment group separately. Incidence rates in the lapatinib-containing groups were compared with the incidence rates in the trastuzumab group using unstratified binomial pairwise comparisons.

Analyses were done with SAS (version 9·3)

This trial is registered with ClinicalTrials.gov, NCT00553358.

Role of the funding source:

GlaxoSmithKline, the manufacturer of lapatinib, distributed the study drugs and provided financial support to the trial, but imposed no restrictions on the investigators with respect to study design, data collection, data analysis, data interpretation, and writing of this manuscript. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

The first manuscript draft was written by two authors (Evandro de Azambuja and José Baselga) and the study statisticians (Andrew P. Holmes and Eileen Holmes). All authors reviewed and approved the manuscript prior to submission.

Results:

Figures 1A and 1B show the trial profile. As previously reported, 154 women were assigned to the lapatinib group, 149 to the trastuzumab group and 152 to

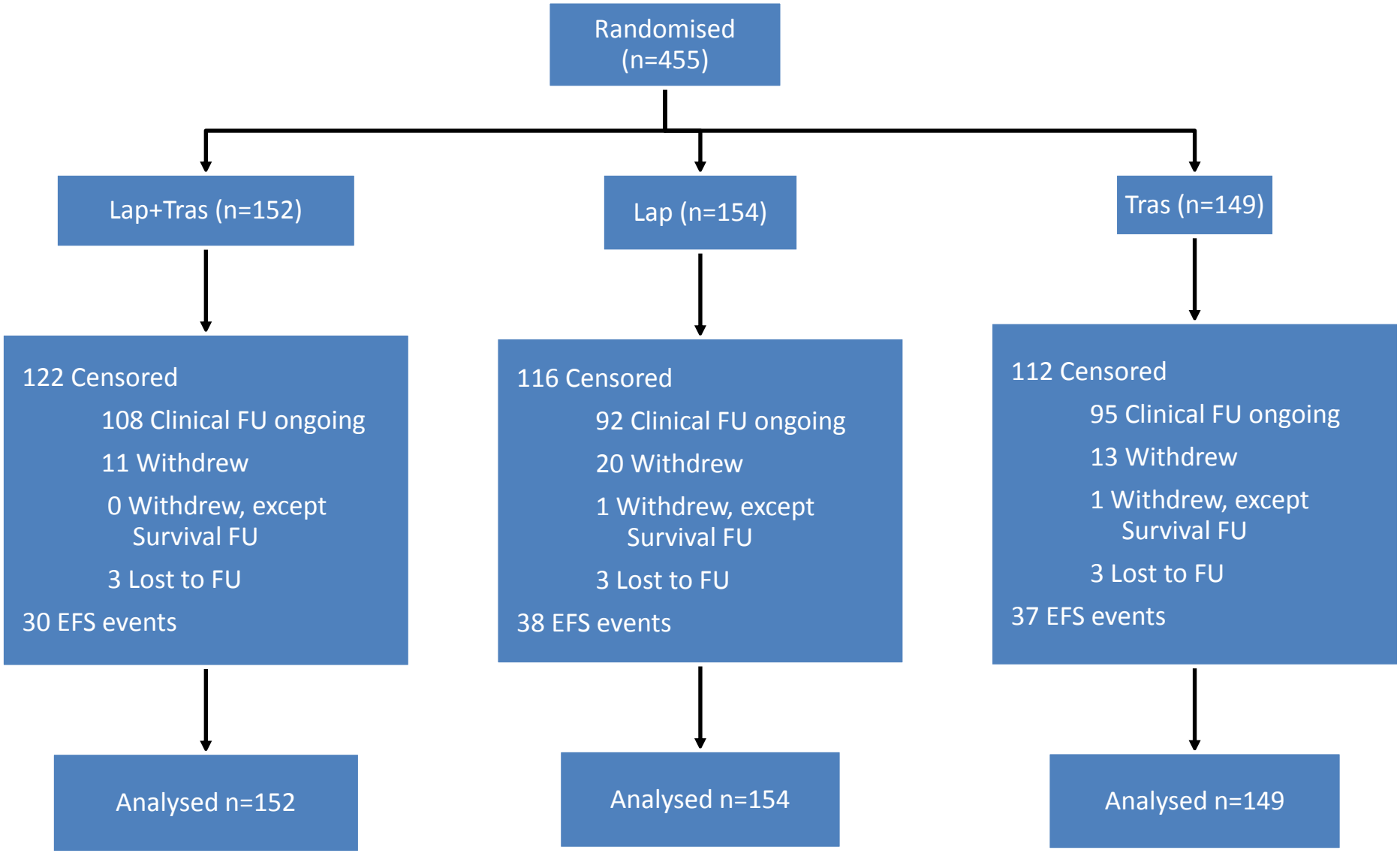


Figure 1A. Trial profile: event-free survival (EFS) for the ITT population

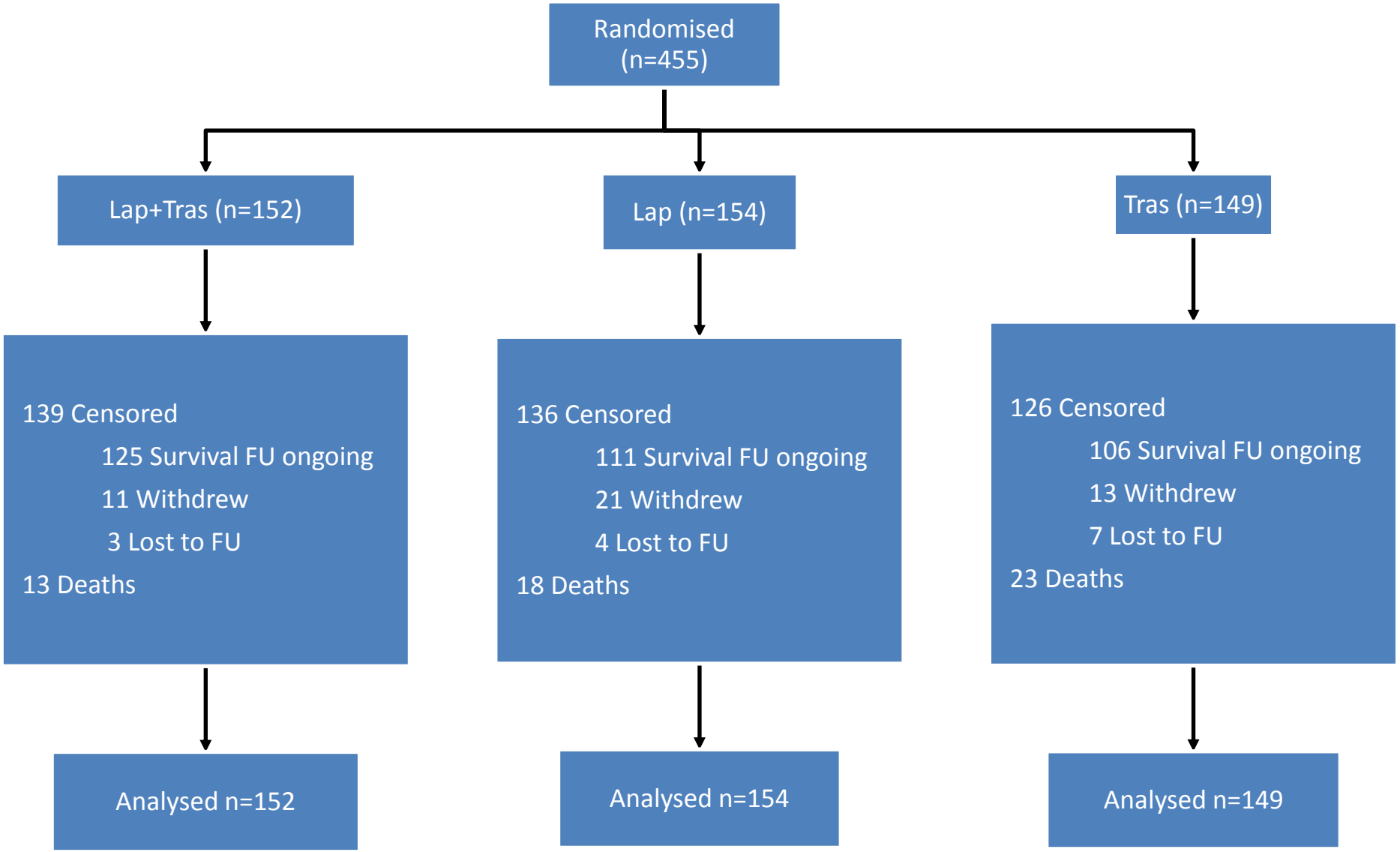


Figure 1B. Trial profile: overall survival (OS) for the ITT population

the lapatinib plus trastuzumab group. The demographic characteristics, sex, geographical location and medical history were described elsewhere (7). This report presents a pre-specified analysis at 3 years after the last woman had breast cancer surgery. The median clinical follow-up is 3·77 years (95% CI 3·72-3·98) and the median survival follow-up is 3·84 years (95% CI 3·77-3·98) from randomisation. For these analyses, stratification factors (hormone receptor status, clinical tumour size, clinical status of lymph nodes and planned breast conserving surgery) were well balanced across the three treatment groups in the intention-to-treat (ITT) population (Web appendix 2).

Adverse events were assessed in 448 women who received at least one study drug dose. Generally, more adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0) occurred in both groups receiving lapatinib compared to the trastuzumab alone group (Table 2). Of note, the protocol applied strict definitions for hepatic adverse events, which were only applicable to the lapatinib-containing arms, leading to permanent lapatinib discontinuation and reporting of serious adverse events. There was a higher incidence of neutropenia adverse event in the lapatinib-containing groups without increase in febrile neutropenia (excluding FEC administration period). The incidence of primary cardiac events remained very low in all three treatment groups (0·67% overall). The incidence of any cardiac events was higher in the lapatinib plus trastuzumab group compared to either lapatinib or trastuzumab groups (4·70% vs. 1·32% vs. 1·35%, respectively) (Table 2). No fatal adverse event related to the study drugs was observed in this study.

Table 2. Frequency of adverse events per patient by treatment group (N=448)

	Lapatinib (N= 151)	**Trastuzumab (N= 148)**	**Lapatinib plus Trastuzumab (N= 149)**
Grade 1-2			
Diarrhoea	87 (58%)	48 (32%)	92 (62%)
Rash or Erythema	98 (65%)	52 (35%)	95 (64%)
Hepatic*	42 (28%)	31 (21%)	54 (36%)
Neutropenia[£]	14 (9%)	9 (6%)	14 (9%)
Grade 3			
Diarrhoea	38 (25%)	4 (3%)	38 (26%)
Rash or Erythema	8 (5%)	1 (<1%)	7 (5%)
Hepatic	32 (21%)	11 (7%)	16 (11%)
Neutropenia[£]	23 (15%)	3 (2%)	11 (7%)
Grade 4			
Diarrhoea	0 (0%)	0 (0%)	0 (0%)

Rash or Erythema	0 (0%)	0 (0%)	0 (0%)
Hepatic	2 (1%)	0 (0%)	1 (<1%)
Neutropenia[£]	3 (2%)	2 (1%)	2 (1%)
Cardiac Events			
Primary cardiac event	1 (0·68%)	0 (0·0%)	2 (1·34%)
Any cardiac event	2 (1·32%)	2 (1·35%)	7 (4·70%)

Note: No grade 5 toxicities occurred in this trial.

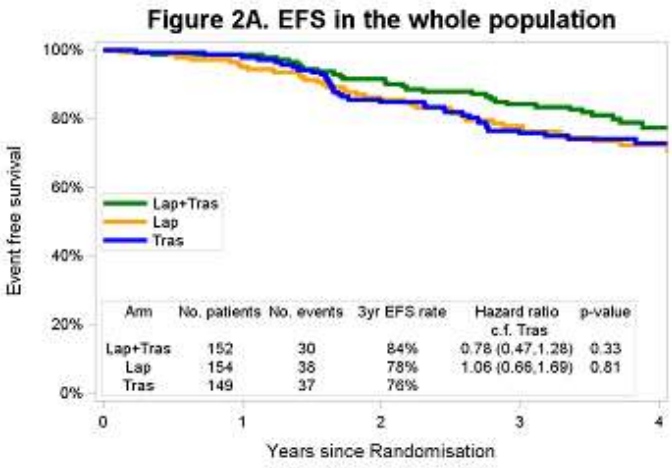
* Includes 4 women (2 on the trastuzumab group and 2 on the lapatinib group) with possible Hy's law criteria (drug-related concomitant elevation of alanine transaminase or aspartate transaminase greater than three times upper limit of normal and total bilirubin greater than two times the upper limit of normal).

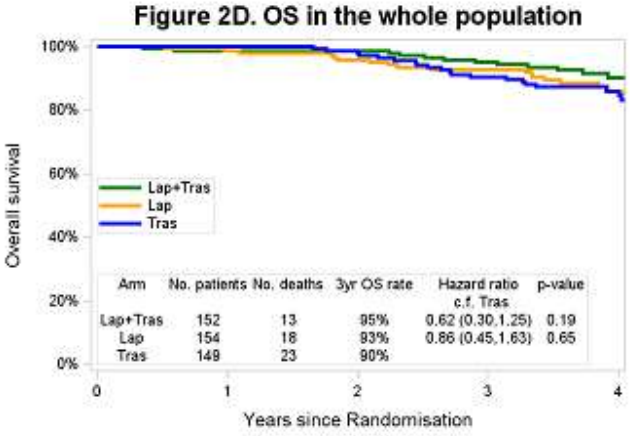
[£] Neutropenia adverse events not occurring during FEC administration

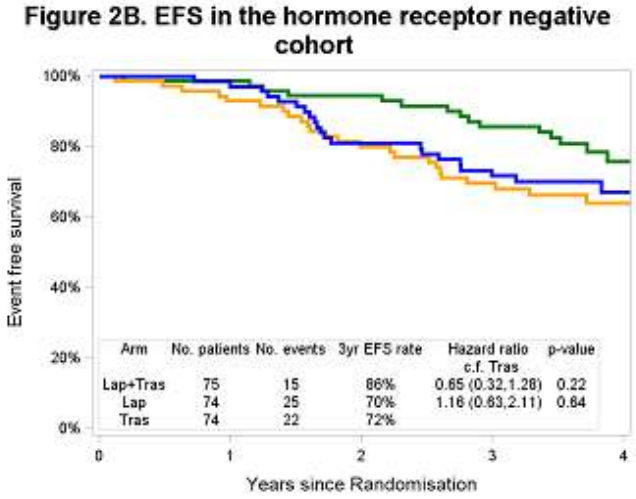
Women completed trastuzumab more frequently than lapatinib in the trastuzumab alone and in the lapatinib plus trastuzumab groups in both phases of the trial (neoadjuvant and adjuvant) (Table 3). In the lapatinib and in the lapatinib plus trastuzumab groups, approximately 3/4 of the women started their assigned treatment in the adjuvant phase. FEC chemotherapy was completed in 84%, 92% and 93% of women in the lapatinib, trastuzumab and lapatinib plus trastuzumab groups.

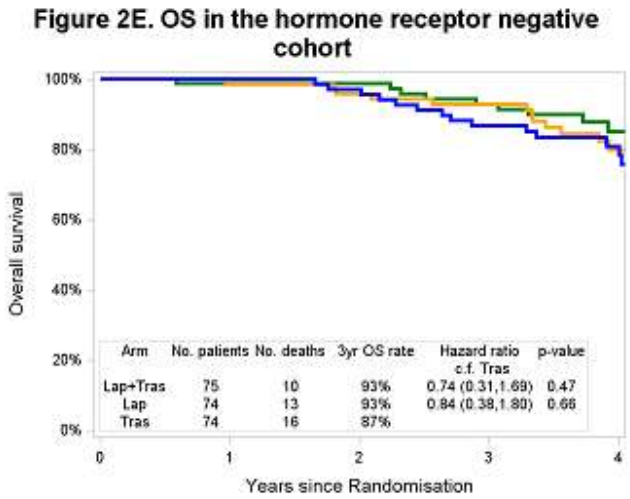
With 105 EFS events, the 3-year EFS was numerically higher in women treated with lapatinib plus trastuzumab compared to either lapatinib or trastuzumab alone in the whole population [84% (95% CI 77%-89%) vs. 78% (95% CI 70%-84%) vs. 76% (95% CI 68%-82%), respectively] (Figure 2A; Web appendix 3). Hazard ratios for EFS were 0·78 (95% CI 0·47-1·28; p=0·33) for the lapatinib plus trastuzumab group and 1·06 (95% CI 0·66-1·69; p=0·81) for the lapatinib group compared to trastuzumab group. Tests of proportionality of the hazards assumption showed no evidence of non-proportionality for the analysis of EFS in the lapatinib plus trastuzumab group (p=0.70) and the lapatinib group (p=0.62) comparisons.The higher 3-year EFS percent for the combination group compared with trastuzumab alone was particularly prominent in the hormone receptor negative cohort and less so in the hormone receptor positive cohort at this point in follow up (Figures 2B and 2C). Central nervous system as first site of relapse occurred in 21 (5%) women and was equally distributed across the groups (Web appendix 3).

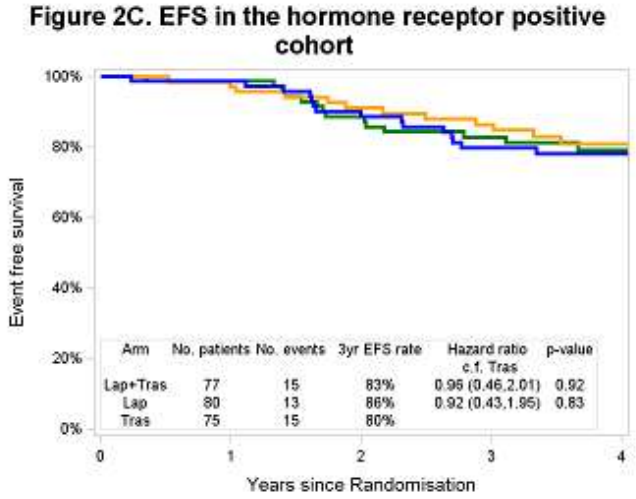
With 54 OS events, the 3-year OS was better in the lapatinib plus trastuzumab group compared to either lapatinib or trastuzumab alone for the whole











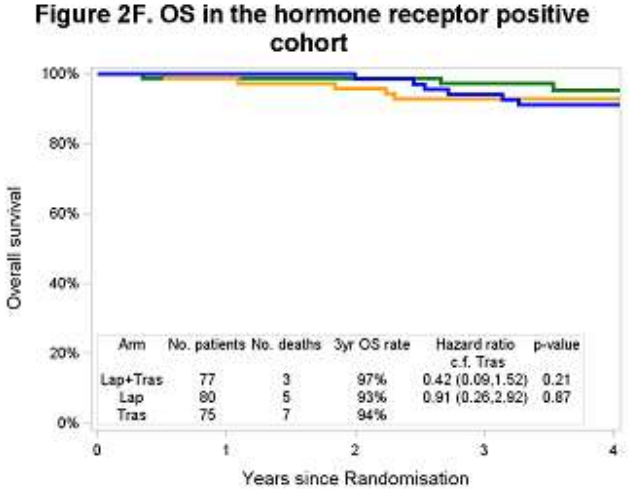


Figure 2. Kaplan-Meier Plots for event-free survival (EFS) and overall survival (OS) in the ITT population; A) EFS for all patients; B) EFS for hormone receptor negative disease; C) EFS for hormone receptor positive disease; D) OS for all patients; E) OS for hormone receptor negative disease; F) OS for hormone receptor positive disease

EFS: event-free survival; OS: overall survival;

Table 3. Study drugs administration and reasons for discontinuation (N=455)

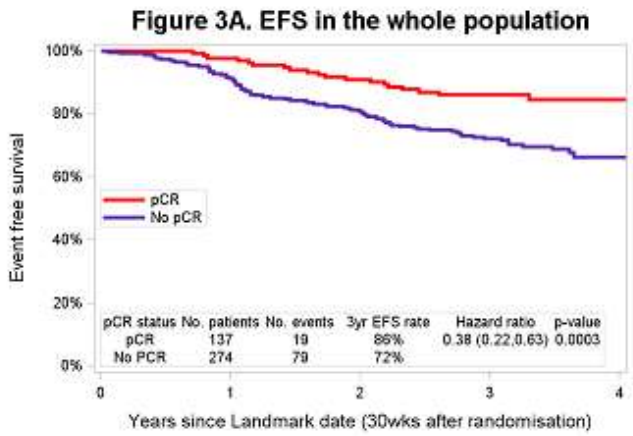
	Lapatinib (N= 154)	Trastuzumab (N= 149)	Lapatinib in the combination group (N= 152)	Trastuzumab in the combination group (N= 152)
Neoadjuvant phase				
Started neoadjuvant phase	151 (98%)	148 (99%)	149 (98%)	149 (98%)
Completed as planned	102 (66%)	138 (93%)	92 (61%)	137 (90%)
Not completed as planned	49 (32%)	10 (7%)	57 (38%)	12 (8%)
Adverse event	32 (21%)	2 (1%)	34 (22%)	7 (5%)
Progression of disease	3 (2%)	4 (3%)	1 (<1%)	1 (<1%)
Other cause	14 (9%) [a]	4 (3%)	22 (14%) [b]	4 (3%) [c]
Adjuvant phase				
Started adjuvant phase	115 (75%)	137 (92%)	116 (76%)	141 (93%)
Completed as planned	99 (64%)	121 (81%)	99 (65%)	120 (79%)
Not completed as planned	16 (10%)	16 (11%)	17 (11%)	21 (14%)
Adverse event	5 (3%)	6 (4%)	11 (7%)	9 (6%)
Disease recurrence	4 (3%)	5 (3%)	1 (<1%)	2 (1%)
Other cause	7 (5%) [d]	5 (3%)	5 (3%) [e]	10 (7%) [e]

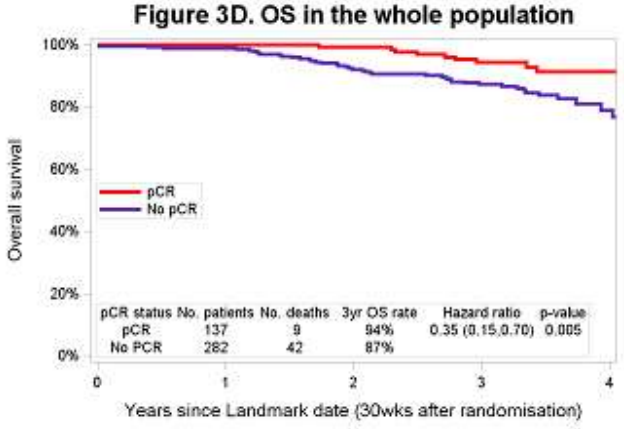
[a] Includes 3 women who withdrew from study; [b] Includes 3 women who withdrew from investigational product; [c] Includes 2 women who withdrew from investigational product; [d] Includes 3 women who withdrew from investigational product and 1 patient who withdrew from study; [e] Includes 3 women who withdrew from investigational product and 2 women who withdrew from study.

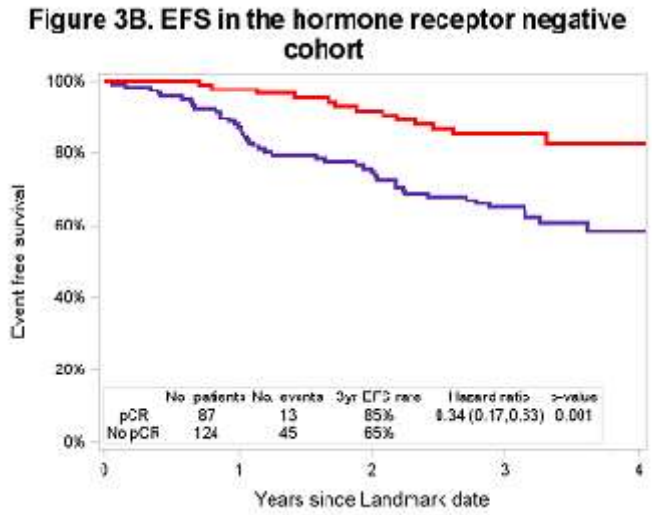
population [95% (95% CI 90%-98%) vs. 93% (95% CI 87%-96%) vs. 90% (95% CI 84%-94%), respectively], independently of the hormone receptor status, although the number of OS events was very low (Figures 2D, 2E and 2F; Web appendix 3). Hazard ratios for OS were 0·62 (95% CI 0·30-1·25; p=0·19) for the lapatinib plus trastuzumab group and 0·86 (95% CI 0·45-1·63; p=0·65) for the lapatinib group compared to the trastuzumab group. Tests of proportionality of the hazards assumption showed no evidence of non-proportionality for the analysis of OS in the lapatinib plus trastuzumab group (p=0.39) and the lapatinib group (p=0.12) comparisons. These results should be interpreted with caution as the trial was not powered to detect significant differences in survival outcomes.

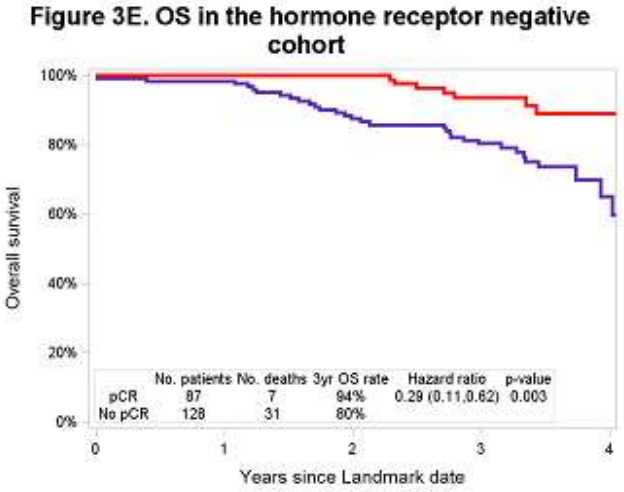
We considered the pCR status at the 30-week landmark for the 411 patients (out of 455 enrolled) in the 30-week landmark population. 427 (94%) of patients had surgery, 423 of these occurred before the landmark date. The 14 patients with missing pCR status did have surgery. The missing status occurs when pathological N status is not known. Patients whose breast ypT status is unknown (because they did not have primary breast cancer surgery) are regarded as not having achieved pCR.

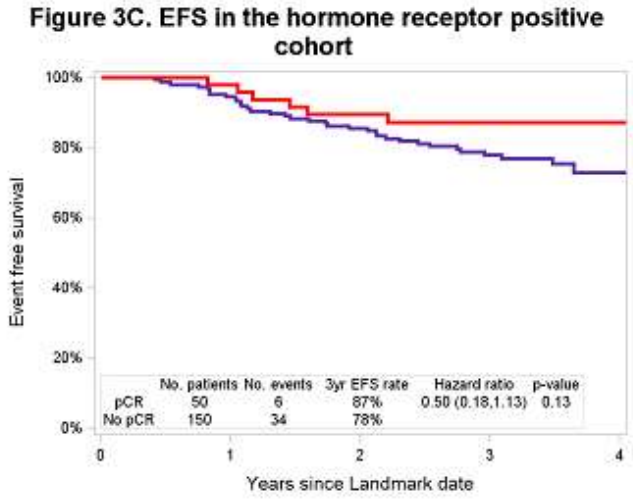
The landmark analysis of EFS included 137 women with pCR versus 274 women without pCR. Forty-four women were excluded from the landmark analysis: 6 with events prior to landmark, 24 with clinical follow-up ended prior to the landmark and 14 with missing pCR status. The 3-year EFS was significantly better for women with pCR compared to those without pCR (HR 0·38, 95% CI 0·22-0·63; p=0·0003) (Figure 3A). In pre-planned analyses, the hazard ratios for the hormone receptor negative cohort (HR 0·34, 95% CI 0·17-0·63; p=0·001;











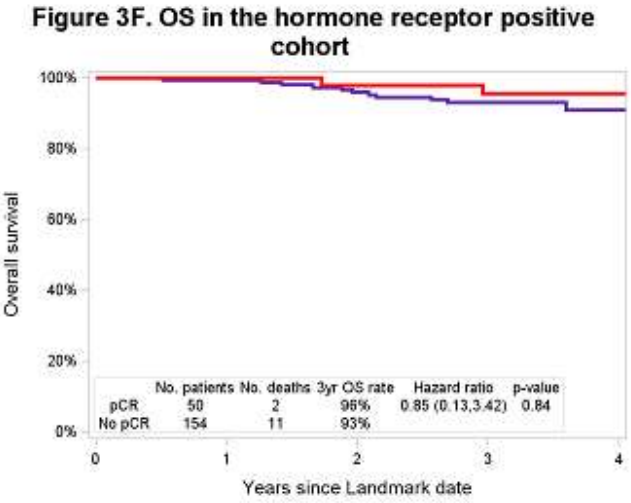


Figure 3. Kaplan-Meier Plots for event-free survival (EFS) and overall survival (OS) in landmark analyses; A) EFS for all patients; B) EFS for hormone receptor negative disease; C) EFS for hormone receptor positive disease; D) OS for all patients; E) OS for hormone receptor negative disease; F) OS for hormone receptor positive disease

EFS: event-free survival; OS: overall survival; pCR: pathologic complete response

Figure 3B) and for the hormone receptor positive cohort (HR 0·50, 95% CI 0·18-1·13; p=0·13; Figure 3C) were not significantly different (interaction p=0·34). Compared with the hormone receptor positive cohort, patients with hormone receptor negative disease were more likely to be included in the landmark analysis [211/223 (95%) versus 200/232 (86%); p=0.0025], more likely to have a pCR in the landmark analysis [87/211 (41%) versus 50/200 (25%); p=0.00055], and more likely to have an EFS event during this relatively short follow up [58/211 (27%) versus 40/200 (20%); p=0.083]. Also, women treated with lapatinib plus trastuzumab had a better EFS with pCR than without pCR (HR 0·32; 95% CI 0·12-0·74; p=0·012).

The landmark analysis of OS included 137 women with pCR versus 282 women without pCR. Thirty-six women were excluded from the landmark analysis: 2 with deaths prior to landmark, 20 with survival follow-ups that ended prior to the landmark and 14 with missing pCR status. The 3-year OS was significantly better for women with pCR compared to those without pCR (HR 0·35, 95% CI 0·15-0·70; p=0·005) (Figure 3D). In pre-planned analyses, the hazard ratios for the hormone receptor negative cohort (HR 0·29, 95% CI 0·11-0·62; p=0·003; Figure 3E) and the hormone receptor positive cohort (HR 0·85, 95% CI 0·13-3·42; p=0·84; Figure 3F) were not significantly different (interaction p=0.36).

The time-dependent Cox proportional models for EFS and OS showed similar results to those observed in the landmark analyses. The hazard ratios for the time-dependent covariate were 0·37 for EFS (95% CI 0·22-0·63; p=0·0002) and 0·34 for OS (95% CI 0·16-0·72; p=0·0046). This indicated that patients who

achieved a pCR after neoadjuvant therapy had a reduced risk of subsequent EFS events and death compared with those who had not achieved pCR.

Discussion:

Although the NeoALTTO trial was not powered to detect significant differences in survival outcomes, the study results suggest that the combination of lapatinib plus trastuzumab prolongs EFS and OS [hazard ratio 0·78 (95% CI 0·47-1·28) for EFS and 0·62 (95% CI 0·30-1·25) for OS]. It also confirms that women achieving pCR after neoadjuvant anti-HER2 therapies experience a significantly better EFS and OS [HR 0·38 (95% CI 0·22-0·63) and 0·35 (95% CI 0·15-0·70), respectively]. We also demonstrated that women treated with lapatinib plus trastuzumab who reached pCR had a better 3-year EFS and a significant reduction in the risk of an EFS event (hazard ratio 0·32; 95% CI 0·12-0·74) compared to no pCR. Importantly, our trial is unique since all women received anti-HER2 therapy in the adjuvant phase that was the same as the anti-HER2 therapy randomly assigned for the neoadjuvant phase. Also, to our knowledge, this is the first trial to correlate pCR with survival outcomes in women treated with dual anti-HER2 drugs (lapatinib plus trastuzumab).

Our findings are supported by a recent FDA meta-analysis involving 1·989 HER2-positive EBC patients showing that patients achieving pCR after neoadjuvant therapy experience a significantly better EFS and OS irrespective of the hormone receptor status. In this group of patients, those with HER2-positive hormone receptor negative tumours treated with trastuzumab had the greatest benefit of adding trastuzumab [EFS hazard ratio 0·15 (95% CI 0·09-0·27)] (8). Based on this, the FDA is able to expedite approval of new treatments

in this subset of patients. In our study, women with HER2-positive hormone receptor negative tumours treated with lapatinib plus trastuzumab had the best outcome [3-year EFS rate 86% (95% CI 75%-92%)].

Other trials have also shown that patients treated with neoadjuvant chemotherapy and trastuzumab and experiencing pCR have better survival outcomes compared to no pCR (16-18). The NOAH trial showed that patients treated with neoadjuvant trastuzumab and experiencing pCR had a better EFS compared to those without pCR after a median follow-up of 5·4 years (hazard ratio 0·17; 95%CI 0·08-0·38; p<0·0001) (19). In our trial, we demonstrated that pCR is correlated with better EFS and OS and that patients treated with the combination of lapatinib plus trastuzumab have the largest benefit of it, particularly in the hormone receptor negative cohort.

Importantly, our findings support the notion that HER2-positive hormone receptor positive and hormone receptor negative are two distinct diseases. In the landmark analysis, there was a significant difference in the hormone receptor negative cohort [EFS hazard ratio 0·34 (95% CI 0·17-0·63) and OS hazard ratio 0·29 (95% CI 0·11-0·63)] which was not present in the hormone receptor positive cohort. Our trial previously showed that patients with hormone receptor negative tumours experience more pCR than the hormone receptor positive cohort (7). This was also demonstrated in other neoadjuvant trials testing the combination of lapatinib plus trastuzumab (20,21). Therefore, the authors do believe that new neoadjuvant trials should address these two patient populations separately. In the metastatic setting, the combination of both anti-HER2 drugs (without chemotherapy) showed a significantly better progression-

free survival (PFS) and OS compared to lapatinib alone [hazard ratio, 0·74 (95% CI 0·58-0·94) for PFS and 0·74 (95% CI 0·57-0·97) for OS] (22). Therefore, the dual anti-HER2 blockade has emerged as a superior strategy both in the metastatic and in the neoadjuvant settings. Recently, the results of the large phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO – ClinicalTrials.gov, NCT00490139) trial, which enrolled 8·381 patients with HER2-positive EBC in four arms (trastuzumab, lapatinib, their sequence or their combination), were presented (23). At a median follow-up of 4.5 years and with less DFS events than planned (555 instead of 850), the dual blockade with lapatinib plus trastuzumab did not significantly improve DFS compared to trastuzumab alone (HR 0·84; 97.5% CI 0·70-1·02; p=0·048 [p≤0.025 required for statistical significance to adjust for multiple testing]). Of note, the patient population included in ALTTO had a low risk of recurrence (small and node negative tumours) as documented by the lower than anticipated DFS event rate.

Toxicity rates were higher in both lapatinib-containing groups although they were as expected (diarrhoea, rash or erythema, and hepatic toxicity). Also, more patients had to stop neoadjuvant treatment (21-22%) due to side effects in the lapatinib-containing groups (Table 3). Importantly, no major cardiac concerns were raised particularly with the combination of both anti-HER2 drugs (any cardiac event, 4·7%). In case of adjuvant trastuzumab, there are some data showing the reversibility of trastuzumab-related cardiotoxicity at 8 years of median follow-up (24). Nevertheless, longer follow-up data on the combination of lapatinib plus trastuzumab is still lacking.

In an exploratory analysis in our trial, early rash (i.e., before starting paclitaxel) was independently associated with a higher chance of pCR, mainly in patients older than 50 years (odds ratio [OR] = 3·76; 95% CI, 1·69-8·34), but not in those ≤ 50 years (OR = 0·92; 95% CI, 0·45-1·88; P for interaction = 0·01). No significant association was observed between pCR and diarrhoea or hepatic AEs (25). At this time, there are no tools available to identify the patients who will benefit the most from the combination of lapatinib plus trastuzumab in the neoadjuvant setting. The authors are also not able to identify a subgroup of patient that could discriminate those likely to experience adverse events at this moment.

A limitation of our study is that the sample size was powered to detect differences in pCR but not in EFS or OS; therefore all survival analyses are meant to be descriptive as mentioned. On the other hand, our trial has a unique feature which is using in the adjuvant setting the same assigned neoadjuvant anti-HER2 therapy. This was not that case for other neoadjuvant trials which have completed 1 year of adjuvant therapy with trastuzumab (standard of care).

In terms of pCR rates, one neoadjuvant trial testing dual HER2 blockade (pertuzumab plus trastuzumab) reported similar pCR rates compared to our trial while other trial reported a higher pCR rate (26, 27); However it is difficult to compare pCR rates across studies since the definitions used may be different and the type and duration of chemotherapy also varies. For example, in one of them, patients received all chemotherapy prior to surgery (27). In one study, Tryphaena, definition of pCR included breast only (ypT0/is) and did not take into account axillary lymph nodes (27). The NSABP B-41 trial also tested lapatinib

plus trastuzumab in the neoadjuvant setting and found a non-significant increase in pCR rates with this combination compared to single HER2 agent (21).

In summary, our results show that patients experiencing pCR after neoadjuvant anti-HER2 therapies have a better survival outcome compared to those without pCR. These findings support the neoadjuvant approach to test new drugs in EBC allowing rapid assessment of drug efficacy since pCR is a short-term outcome and the number of patients included in neodjuvant trials is not large. If this approach is proven to be optimal, this could expedite development and approval of new treatments in patients with HER2-positive EBC. However, more proof of this concept is desirable at this moment. A pre-planned protocol efficacy analysis will be performed in 2.5 years.

Panel: research in the context:

Systematic review:

We searched Pubmed from Jan 1, 2001 to April 30, 2014, for full reports of randomised clinical trials in patients with HER2-positive early breast cancer and treated with neoadjuvant therapy. Term used was “lapatinib plus trastuzumab”. We identified full text of two randomized study of patients treated with neoadjuvant lapatinib plus trastuzumab combined with chemotherapy and one combined with endocrine therapy (18, 19, 28). The combination of lapatinib plus trastuzumab was also tested in an adjuvant trial recently presented (23).

Interpretation:

Dual blockade with lapatinib plus trastuzumab combined with weekly paclitaxel increases pCR compared to either agent alone plus chemotherapy. Patients

achieving pCR following neoadjuvant therapy have longer EFS and OS. Women treated with the combination of lapatinib plus trastuzumab and with pCR have a better 3-year EFS compared to those without pCR.

Contributors:

EA contributed to study design, trial conduct, data interpretation, literature search, manuscript write and review.

APH contributed to literature research, study design and data analysis

MP-G contributed to trial design and conduct, data collection, data interpretation and manuscript writing

EH contributed to statistical analysis and data interpretation

SdiC contributed to trial design, data collection, data analysis and data interpretation RFS contributed to study conduct, data interpretation, manuscript draft and review

MU contributed to trial concept and design, patient accrual, data collection and interpretation, manuscript writing

CJ contributed to trial design and conduct, manuscript writing, literature review, data analysis and interpretation

IL contributed to patient enrolment, trial conduct, data collection and manuscript review

IS contributed to study design, data interpretation and editing original draft

FB contributed to the study design, management of the trial, interpretation of the data and manuscript review

BX contributed to study design, data collection, data analysis and interpretation

CHB contributed to trial conduct, data interpretation and manuscript review

EAP contributed to the conception and design, data analysis and interpretation, manuscript writing and final approval of the manuscript

HA jr contributed to medical monitoring of the study, data interpretation, manuscript review and approval

S-BK contributed to patient enrolment, data collection and manuscript review

SK contributed to patient enrolment, data interpretation

C-SH contributed to patient enrolment, data collection and manuscript review

PV contributed to patient recruitment and manuscript review

R-KH contributed to concept of the study, data acquisition, manuscript review

VG contributed to acquisition of data, data collection and interpretation

AE contributed to patient enrolment, data collection and manuscript reviewLD contributed to patient recruitment and data submission

NT contributed to patient recruitment, data collection and manuscript review

RDG contributed to study design, data analysis and interpretation, manuscript writing

HE contributed to study design, study administration, data interpretation, manuscript discussion and correction

JB contributed to study design, enrolment of patients, data analysis and interpretation

All authors were involved in writing/reviewing the report and approved the final version.

Conflict of interest:

EA reports grant from GSK during the conduct of the study; grant from GSK and Roche and personal fees from Roche outside this work

MP-G reports personal fees from Roche

RFS is an employee from GSK, the study sponsor

IS reports occasional honoraria from Roche (5000 pounds more than 18 months ago)

CHB reports grants from GSK during the conduct fo the study; personal fees from GSK outside the submitted work

HA Jr reports grant from GSK during the conduct of the study; personal fees from GSK and Novartis outside the submitted work

S-BK reports research funds from Novartis

PV reports travel grants from Roche and GSK

AE reports grants and personal fees from GSK during the conduct of the study; grants and personal fees from Roche, AstraZeneca; grants from Novartis, grants and personal fees form Amgen

LD reports honoraria, congress sponsorship and research grant from Roche

RDG reports funds from GSK to support a portion of his academic salary

JB reports personal fees from Roche

APH, EH, SdiC, MU, CJ, IL, FB, BX, EAP, C-SH, SK, R-KH, VG, NT and HE indicated no conflict of interest

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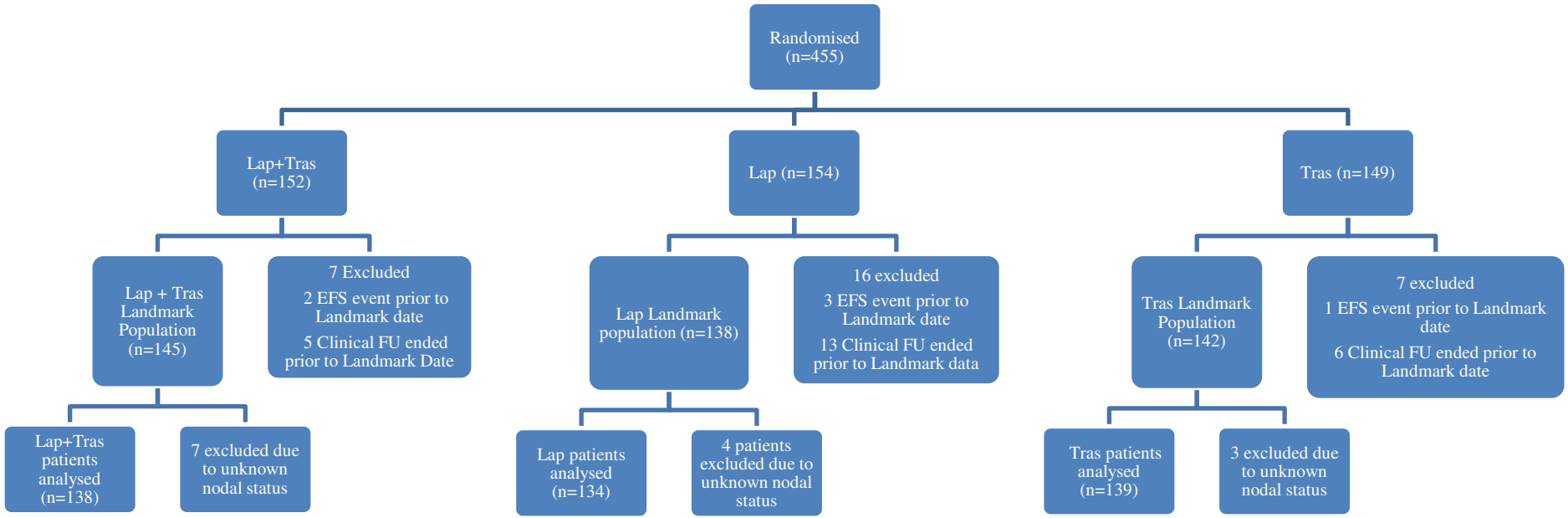
Supplementary appendix

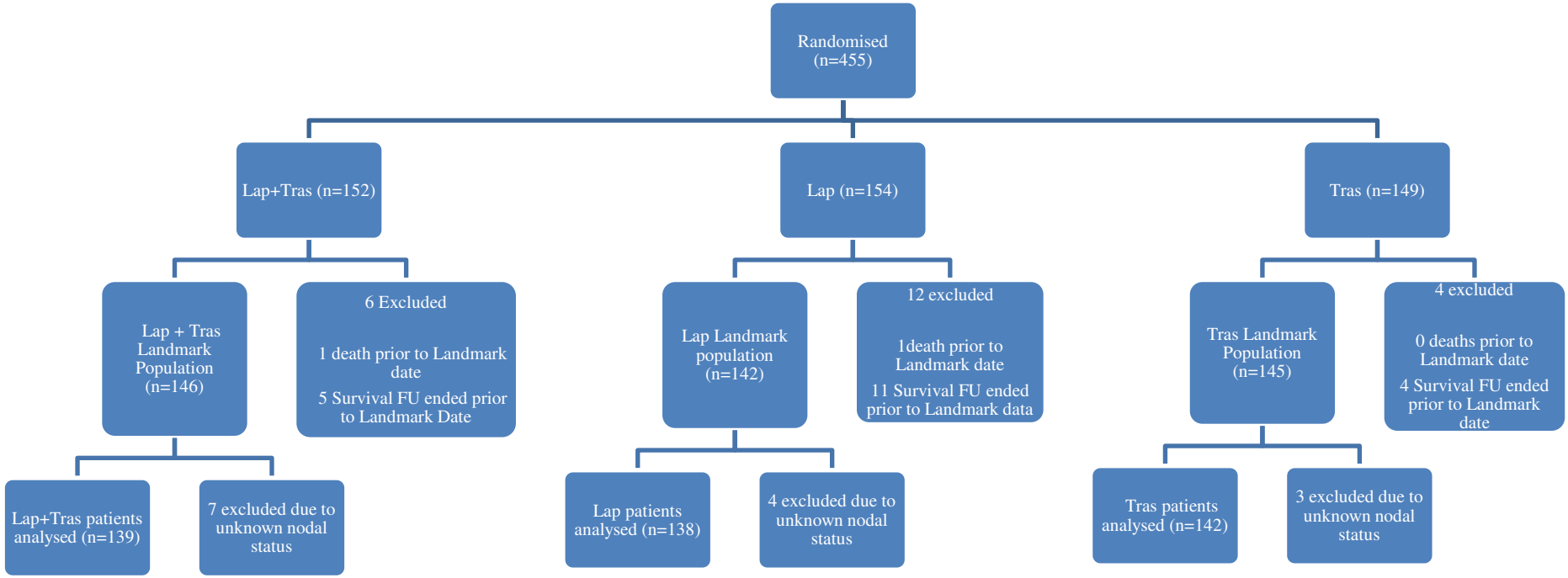
Web appendix page 1. Distribution of stratification factors by treatment arm in the ITT population

	Lapatinib (N= 154)	Trastuzumab (N= 149)	Lapatinib plus trastuzumab (N=152)	Total (N=455)
Age (years)	50 (42-56)	46 (44-57)	50 (43-59)	50 (43-57)
Local receptor status				
Positive	80 (51·9%)	75 (50·3%)	77 (50·7%)	232 (51·0%)
Negative	74 (48·1%)	74 (49·7%)	75 (49·3%)	223 (49·0%)
Tumour size (cm)				
≤5 cm	92 (59·7%)	93 (62·4%)	89 (58·6%)	274 (60·2%)
>5 cm	62 (40·3%)	56 (37·6%)	63 (41·4%)	181 (39·8%)
Clinical lymph node status				
N0/1	129 (83·8%)	126 (84·6%)	128 (84·2%)	383 (84·2%)
N2+, Nx or missing	25 (16·2%)	23 (15·4%)	24 (15·8%)	72 (15·8%)
Intention of breast conservation				
Not candidate for BCS	107 (69·5%)	112 (75·2%)	106 (69·7%)	325 (71·4%)
Candidate for BCS	47 (30·5%)	37 (24·8%)	46 (30·3%)	130 (28·6%)

Abbreviations: BCS: breast conserving surgery
Note: tumour size from the randomisation system was used for this analysis.



Webappendix 1A. Trial profile: event-free survival (EFS) for the landmark analysis



Webappendix 1B. Trial profile: overall survival (OS) for the landmark analysis