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Updated results from the international phase III ALTTO trial (BIG 2–06/Alliance N063D)

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Abstract

Aim: To present the pre-specified analyses of >5-years follow-up of the Phase III ALTTO trial.

Patients and Methods: 8381 patients with stage I-III HER2 positive breast cancer randomized to chemotherapy plus 1-year of: trastuzumab (T), oral lapatinib (L; no longer evaluated), trastuzumab followed by lapatinib (T→L), and lapatinib + trastuzumab (L+T). Primary endpoint was disease-free survival (DFS). Secondary analysis examined DFS treatment effects by hormone receptor status, nodal status and chemotherapy timing; time to recurrence; overall survival (OS) and safety (overall and cardiac).

Results: At a median follow-up of 6.9 years, 705 DFS events for L+T vs. T were observed. Hazard Ratio (HR) for DFS was 0.86 (95% CI, 0.74–1.00) for L+T vs. T and 0.93 (95% CI, 0.81–1.08) for T→L vs. T. The 6-year DFS were 85%, 84%, and 82% for L+T, T→L, and T, respectively. HR for OS was 0.86 (95% CI, 0.70–1.06) for L+T vs. T and 0.88 (95% CI, 0.71–1.08) for T→L vs. T. The 6-year OS were 93%, 92%, and 91% for L+T, T→L, and T, respectively. Subset analyses showed a numerically better HR for DFS in favour of L+T vs. T for the hormone-receptor-negative [HR 0.80 (95% CI, 0.64–1.00; 6-yr DFS%=84% vs. 80%)] and the sequential chemotherapy [HR 0.83 (95% CI, 0.69–1.00; 6-yr DFS%=83% vs.79%)] subgroups.

Conclusion: T+L did not significantly improve DFS and OS over T alone, both with chemotherapy, and, therefore, cannot be recommended for adjuvant treatment of early stage HER2-positive breast cancer.

Trial Registration: clinicaltrials.gov Identifier NCT00490139

Keywords

Early breast cancer; HER2; lapatinib; trastuzumab; adjuvant chemotherapy

Introduction

Since 2005, adjuvant chemotherapy plus 1 year of the monoclonal antibody trastuzumab (T), has become standard of care therapy for patients with early stage HER2 positive breast cancer.[1–6] Lapatinib (L), an oral anti-HER1–2 tyrosine kinase inhibitor (TKI), demonstrated significant clinical activity against HER2 positive breast cancer in the metastatic setting[7–11] and the combination of lapatinib and trastuzumab significantly improved rates of pathological complete response (pCR) compared with either drug alone in the Neo-ALTTO trial.[12] The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial is the first large prospective randomized trial to report three anti-HER2 strategies that incorporated L and T and compared these with T alone as adjuvant therapy for patients with early stage HER2-positive breast cancer. The primary analysis of this trial was presented in 2014 and demonstrated that adjuvant treatment that includes L did not significantly improve DFS compared with T alone but added toxicity.[13,14] The current manuscript reports the pre-specified analyses foreseen when all patients had completed ≥5 years of follow-up.

Material and methods

Study Design and Settings

The ALTTO trial (NCT00490139) is a prospective randomized, phase 3, open-label, multicenter study conducted in 946 centers in 44 countries from 4 different continents. The patients were enrolled between June 2007 and July 2011. Participating medical centers' institutional review boards (or Ethics Committees) approved the study, and all patients provided written informed consent prior to study entry. The trial was coordinated by the Breast International Group (BIG) for Europe and rest of the world and by the North Central Cancer Treatment Group (NCCTG: now Alliance) for the United States of America (US) and Canada. Support was provided by the US National Cancer Institute (NCI), National Cancer Institute of Canada Clinical Trials Group (now Canadian Clinical Trials Group), Glaxo-Smith-Kline from its development until November 30, 2015 and by Novartis since then. Clinical database was located at the BrEAST Data Center (Institut Jules Bordet, Brussels) and statistical analyses were performed by Frontier Science Scotland (FSS, Scotland).

Participants

Eligible patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status 0–1, be at least 18 years of age, with clinical or pathologically confirmed stage I (pT=1–2 cm) to stage III, centrally confirmed HER2 positive (3+ by IHC and/or FISH positive) invasive breast cancer. The hematologic, renal and hepatic functions were to be adequate and a baseline left ventricular ejection fraction (LVEF) ≥50%, measured by echocardiography or MUGA scan, was required.

Procedures

Patients were randomly assigned centrally in a 1:1:1:1 ratio to receive the anti-HER2 targeted therapy in one of 4 arms: in Arm 1 patients received intravenous T (at a loading dose of 4 mg/kg once and then 2 mg/kg weekly during chemotherapy or at a loading dose of 8 mg/kg once and then 6 mg/kg every 3 weeks when given alone); in Arm 2 they received oral L (750 mg/day during chemotherapy and 1,500 mg/day when given alone); in Arm 3 a sequence of the two agents (T→L) that started with 12 weekly doses of T, followed after a 6-week washout, by 34 weeks of L at 1,500 mg/day; and in Arm 4 the combination of the two anti-HER2 agents (L+T) with T at the aforementioned dosages and L at 750 mg/day during chemotherapy (reduced from an initial dose of 1,000 mg/day based on safety data), with an escalation to 1,000 mg/day after the completion of chemotherapy.

The adjuvant chemotherapy regimens and timing of anti-HER2 were based on patients/physicians choice. The anti-HER 2 therapy was administered either sequentially at the completion of all chemotherapy (Design 1), concurrently with the taxane component of the chemotherapy (Design 2), or concurrently with a non-anthracycline regimen (Design 2B) (Figure 1). The chemotherapy regimens for Designs 1 and 2 consisted of at least 4 cycles of an anthracycline based regimen (several regimens available to choose from), followed by a taxane (weekly paclitaxel or 3-weekly docetaxel), and the regimen of Design 2B consisted of 6 cycles of every 3-week docetaxel and carboplatin.

Adjuvant endocrine therapy was given to patients with hormone receptor–positive disease. Radiotherapy was mandatory in cases of breast-conserving surgery and in accordance with institutional guidelines in cases of mastectomy. Both treatments were given after completion of all chemotherapy and concomitantly with anti-HER2 treatment.

Chemotherapy adverse effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[15]

Statistical Analyses

Randomization used permuted blocks stratified by timing of chemotherapy (Design 1 vs. Design 2/2B), central hormone receptor status (positive [≥ 1%] vs. negative), and lymph node status (not applicable [neoadjuvant chemotherapy], node negative, 1–3, ≥4 positive nodes). The primary endpoint was disease-free survival (DFS) defined as time from randomization to recurrence of invasive breast cancer at local, regional, or distant sites; contralateral invasive breast cancer; second non-breast malignancy; or death as a result of any cause, whichever occurred first. Secondary endpoints were overall survival (OS), safety in general and cardiac safety, time to recurrence, time to distant recurrence, and time to first brain metastasis.

Sample size calculations were based on the two-sided superiority comparison between the L+T arm and the T arm with 850 DFS events calculated to provide an 80% power to detect a hazard ratio (HR) of 0.80 at $\alpha = .0167$, using a log-rank test stratified by hormone receptor status (2 groups), nodal status (4 groups) and chemotherapy timing (2 groups). Estimation of hazard ratios and 95% confidence intervals were by Cox's proportional hazards model stratified by three stratification factors (16 strata)[16]; and estimation of survival functions

were by the Kaplan-Meier method with standard errors calculated using Greenwood's formula.[17,18] For efficacy analyses the intent to treat (ITT) population was utilized and for the safety analysis only those patients who received at least one dose of the anti-HER2 therapy were considered.

The L monotherapy arm is not evaluated in this manuscript because it was closed in 2011 due to statistical inferiority to T monotherapy at the first interim efficacy analysis, and patients free of disease were offered adjuvant T. For the 2014 Primary Analysis, the type I error of 5% was split evenly between the two comparisons of the remaining lapatinib combination arms versus T, and therefore all subsequent analyses are descriptive, not inferential.

Results

Participants

The trial accrued 8381 patients (Figure 2, CONSORT flow diagram); 2097 patients received T for 52 weeks, 2100 patients received L for 52 weeks, 2091 patients received T for 12 weeks followed by a wash out period of 6 weeks and then L for 34 weeks, and 2093 patients received L concurrently with T for 52 weeks. Design 1 recruited rapidly and closed enrollment in March 2009 to permit sufficient enrollment to Design 2, and Design 2B was only incorporated in 2009. Thus, the number of patients treated by a certain chemotherapy timing and the duration of follow-up differ among the different designs. Approximately 55% of patients (n = 4613) were treated under the sequential Design 1 and have a median follow-up of 7 years; 40% of patients (n = 3337) were treated under Design 2 and have a median follow-up of 6 years; and only 5% of patients were treated under Design 2B (n = 431) and the median follow-up of this group is 5 years. The median duration of follow-up for all patients is 6.9 years.

Detailed baseline characteristics of the intent-to-treat population (ITT), the tumors and the primary treatments were previously described[13] and pertinent baseline characteristics based on primary treatment by design and by treatment arm can be found in Supplement 1. Briefly, in the ITT population the median age was 51 years (range 18–82), 57% of patients were post-menopausal, 51% had node-positive disease, 50% had a tumor size >2 cm, and 57% had hormone receptor–positive (HR^+) disease. Approximately 8% of patients (12% on Design-1 and 6% on Design-2) received the chemotherapy in the neoadjuvant setting and were eligible as long as all chemotherapy was completed prior to randomization (Design-1) or the anthracycline-based chemotherapy was completed prior to receiving the targeted therapy concomitantly with the taxane (Design-2).

Safety

The incidence of adverse events (AEs) was higher in L-containing arms than in the T arm. AEs related to study treatment were 93% in the L+T arm vs. 64% in the T arm. There were also more discontinuations of study treatment (23% vs 8%), dose reductions (20% vs 4%) and dose interruptions/delays (46% vs. 20%) due to toxicity in the L+T arm vs. the T arm; and this was more pronounced when targeted therapy was provided concurrently with the

chemotherapy (design 2/2B). Generally, the most common AEs related to L and leading to dose changes were diarrhea, neutropenia, and rash. The incidence of primary or secondary cardiac endpoints was low in all treatment arms: 1% for L+T, 0.5% for T→L and 0.9% for T for primary endpoints. Additional safety results are available in Supplement 1.

Efficacy

The overall median follow-up of this study is 6.9 years (range, 1 day to 9.0 years). At this time there are still less than the anticipated number of events with only 705 total DFS events between the L+T and T arms (327 DFS events in the L+T arm vs. 378 events in the T arm). This is lower than the expected 850 events that were anticipated to occur. As one would expect with the passing of time, the number of events per 1000 patient-years has declined since the primary analysis (31.9 vs. 37.6 events per 1000 patient-years for L+T vs. T at the 2014 Primary analysis and 20.3 vs. 21.4 events per 1000 patient-years in L+T vs T since then). The 6-year DFS rates were 82% for T, 84% for T→L and 85% for L+T with HR of 0.93 (95% CI, 0.81–1.08) and 0.86 (95% CI, 0.74–1.00) for T→L vs. T and L+T vs. T, respectively (Figure 3A). The 6-year OS rates were 91% for T, 92% for T→L and 93% for L +T with HR of 0.88 (95% CI, 0.71–1.08) and 0.86 (95% CI, 0.70–1.06) for T→L vs. T and L+T vs. T, respectively (Figure 3B). There were no differences in sites of first DFS events according to treatment arm for central nervous system (2% for the 3 arms), loco-regional (≤2% for the 3 arms), or distant recurrences (≤5% for visceral recurrence and 2% for bone recurrence in the 3 arms). The rate of contralateral invasive breast cancer was 1% in each of the 3 arms and second (non-breast) primary malignancy occurred in ≤3% of patients in all arms. Time to recurrence (TTR) seemed to be shorter in the T vs. L+T arm (HR 0.86; 95% CI, 0.74–1.00).

Efficacy in Stratification Subgroups

Outcome analysis was stratified by timing of chemotherapy (design 1 vs. design 2/2B), central hormone receptor (ER/PgR) status (positive [≥ 1%] vs. negative), and lymph node (LN) status (not applicable [neoadjuvant chemotherapy], node negative, 1–3, ≥4 positive nodes) and results are outlined in Table 1. Subset analyses showed a better HR for DFS in favour of L+T vs. T for the hormone-receptor-negative [HR 0.80 (95% CI, 0.64–1.00; 6-yr DFS%=84% vs. 80%)] and the sequential chemotherapy [HR 0.83 (95% CI, 0.69–1.00; 6-yr DFS%=83% vs.79%)] subgroups

Discussion

A very meaningful improved clinical outcome (progression-free survival and OS) with dual HER2 blockade (T+ the monoclonal antibody pertuzumab [P]) was demonstrated in the metastatic setting in the phase III CLEOPATRA trial, which led to a new standard of care.[25,26] Additionally, a few phase II and phase III neoadjuvant clinical trials have demonstrated improved clinical outcome (pCR) with dual HER2 blockade (T plus either L or P), especially in the hormone receptor-negative population and when targeted therapy is given concurrently with chemotherapy.[12,19–24] The ALTTO trial was the first large phase III adjuvant trial to test the hypothesis that dual HER2 blockade could further improve survival outcomes of patients with early stage HER2-positive breast cancer compared with adjuvant

T. In this study, patients with hormone receptor-negative tumors, pN1disease and those receiving the targeted agents sequentially following the chemotherapy seemed to derive a non-statistically significant benefit from dual HER2 blockade. The overall conclusion of the trial is that ALTTO failed to demonstrate a statistically significant improvement in clinical outcomes (DFS/OS). However, in 2011 when the L monotherapy arm was discontinued, the Hochberg step-wise alpha-spending procedure was replaced by the Bonferroni procedure, which required a 2-sided p-value of ≤ 0.025 for statistical significance. Thus, the observed value of p = 0.048 was declared as not statistically significant. If, the original Hochberg procedure had been retained, both pairwise comparisons would have been declared statistically significant because both p-values were ≤ 0.05[27].

Other phase III trials tested the efficacy of dual HER2 blockade in the adjuvant setting. The APHINITY trial[28] tested T+ pertuzumab (P) vs. T + placebo (Pla) along with chemotherapy as adjuvant therapy for stage I-III HER2 positive breast cancer patients. The primary analysis results at a median follow-up of 45.4 months were published in 2017 and demonstrated a statistically significant p=0.045 result for the primary invasive-DFS (IDFS) analysis. Updated APHINITY results[29] at a median follow up of 74.1 months show 6-year IDFS of 90.6% in the T+P group and 87.8% in the T group (HR 0.76; 95% CI, 0.64–0.91). By contrast, the results of ALTTO reported here at a median follow-up of 83 months had 6-year IDFS of 85% in the T+L group and 82% in the T group (HR 0.86; 95% CI, 0.74–1.00). Thus, despite the differences with respect to statistical significance observed at the primary analysis (one p=048 [not significant] and the other p=0.045 [significant]), the efficacy results with respect to IDFS seen for T+L vs T in ALTTO and T+P vs T in APHINITY are remarkably similar.

Another phase III trial evaluating sequential T plus the oral irreversible pan-HER2 tyrosine kinase inhibitor neratinib (N) demonstrated improved outcome in the adjuvant setting. The ExteNET trial[30–31] compared N vs placebo (Pla), both given for 12 months after completion of 1 year of T. Neratinib led to a 2.5% absolute improvement in 5-year IDFS (90.2% for N vs 87.7% for Pla; HR 0·73, 95% CI 0·57–0·92, p=0·0083). Patients with HR^+ BC were allowed to take adjuvant endocrine therapy (ET) concurrently with N and they derived the largest benefit (an absolute 5.1% benefit in 5-year IDFS for patients with HR^+/HER2+ BC who started N within 1 year of completing adjuvant T; HR 0.58; 95% CI, 0.41–0.82). This was contrary of what was observed in ALTTO and also contrary of what was observed using N in the neoadjuvant I-SPY trial[32] and in the metastatic NALA[33] trial. Although in the I-SPY and NALA trials ET was not allowed while patients received N plus chemotherapy, 89% of HR^+ patients in the ALTTO trial received adjuvant ET.

Conclusion

T+L did not significantly improve DFS and OS over T alone and added significant non-cardiac toxicity. Therefore, it cannot be recommended for adjuvant treatment of early stage HER2-positive breast cancer. Over 90% of patients who participated in ALTTO are alive at this longer follow-up evaluation, a testimony of the continued improvement in the outcome of all patients with early stage HER2 positive breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest:

1. Dr. Moreno-Aspitia – Institutional research funding from GlaxoSmithKline, Genentech, Daiichi Sankyo, Novartis, Merck, Pfizer, AbbVie and Eli Lilly;

2. Dr. Holmes – none;

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9. Mr. Izquierdo – employment and stock/other ownership interests with Novartis;

10. Dr. McCullough – none;

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Highlights

- First phase III study of adjuvant dual HER2 blockade for HER2+ breast cancer
- 8381 patients with stage I-III HER2+ breast cancer, followed for at least 5 years
- Compared chemotherapy + trastuzumab vs chemotherapy + 3 lapatinib-containing arms
- Lapatinib associated with increased non-cardiac toxicity
- Chemotherapy + lapatinib/trastuzumab not superior to chemotherapy + trastuzumab

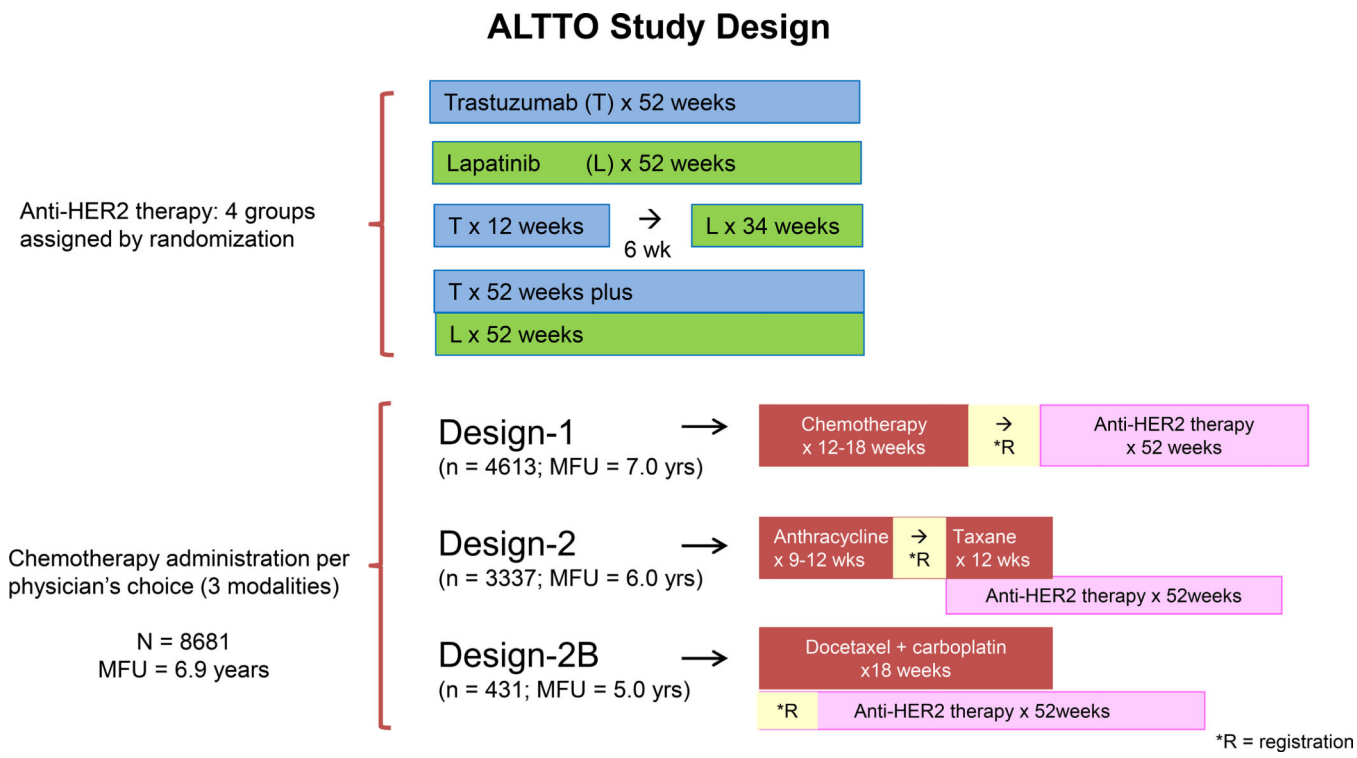

Figure 1.

ALTTO Study Design. ALTTO indicates Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization; MFU (median follow up); *R, registration.

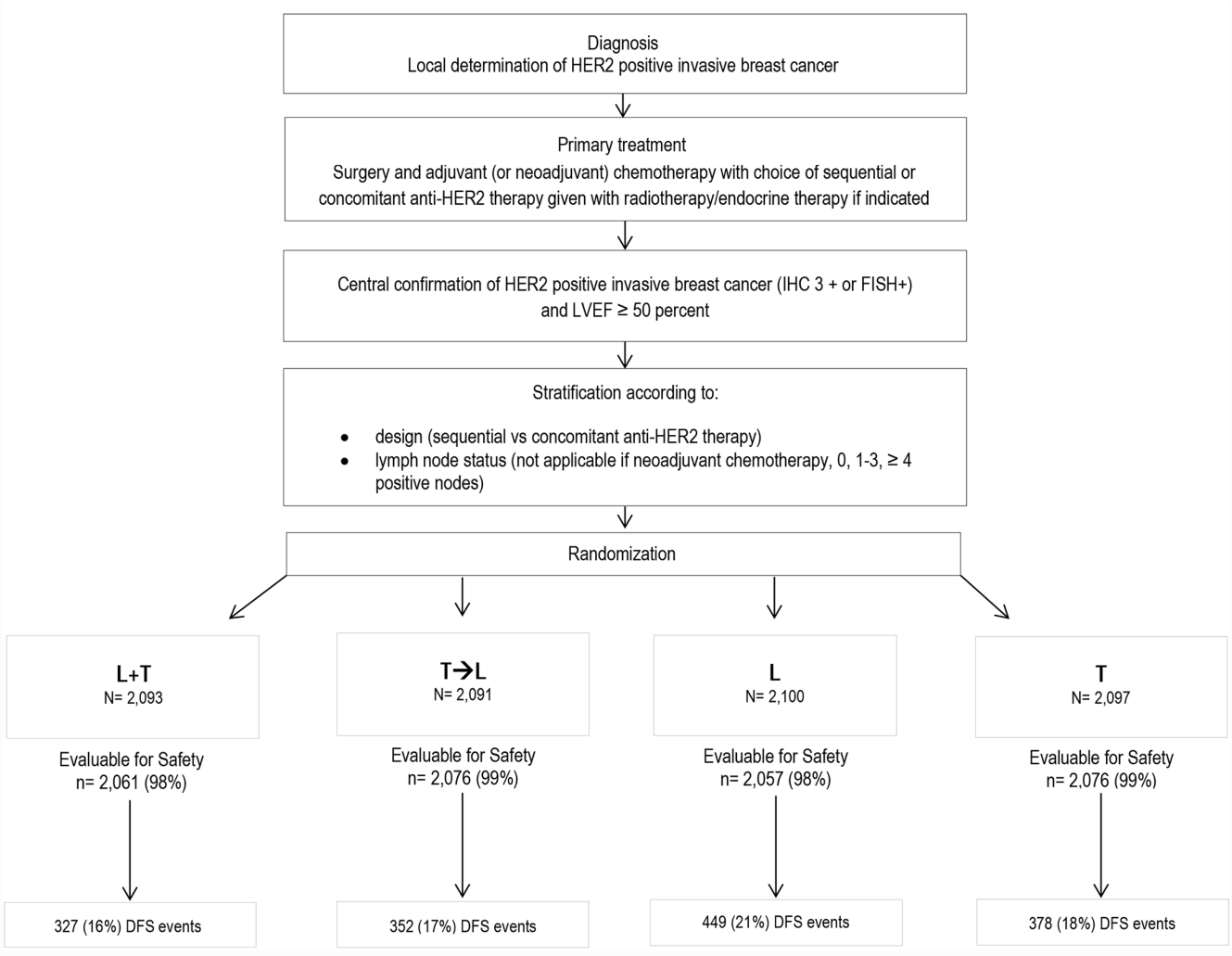

Figure 2.

CONSORT Chart. DFS indicates disease-free survival; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; L, lapatinib; LVEF, left ventricular ejection fraction; T, trastuzumab.

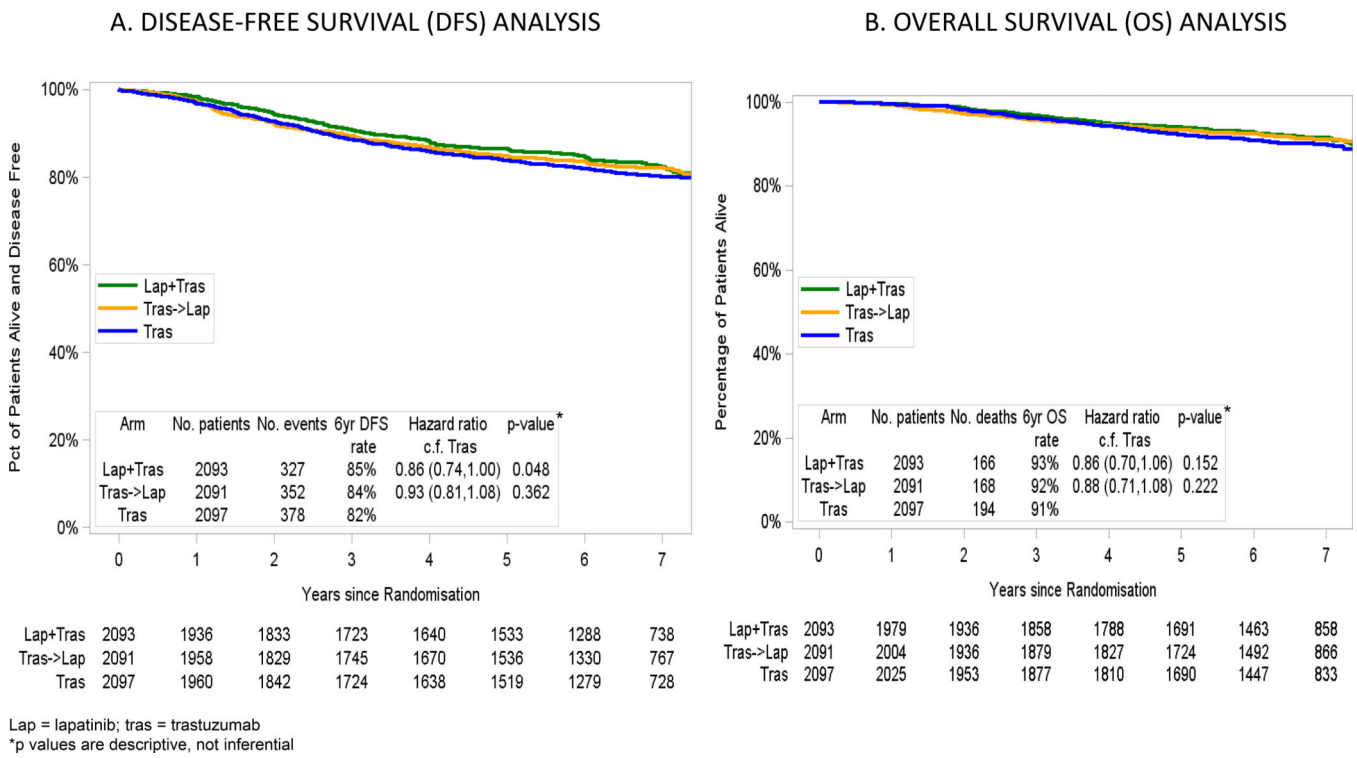

Figure 3.

3A. DISEASE-FREE SURVIVAL (DFS) ANALYSIS; 3B. OVERALL SURVIVAL (OS) ANALYSIS Kaplan-Meier curves. *p-values are descriptive, not inferential. DFS indicates disease-free survival; Lap, lapatinib; OS, overall survival; and Tras, trastuzumab.

Table 1.

DFS Overall and in Stratification Subgroups

		6-yr DFS	Hazard Ratio L+T vs T T→L vs T
Overall	L+T	85%	0.86 (95% CI, 0.74–1.00)
	T→L	84%	0.93 (95% CI, 0.81–1.08)
	T	82%	
Design-1	L+T	83%	0.83 (95% CI, 0.69–1.00)
	T→L	82%	0.87 (95% CI, 0.73–1.05)
	T	79%	
Design-2/2B	L+T	87%	0.92 (95% CI, 0.72–1.18)
	T→L	85%	1.05 (95% CI, 0.82–1.33)
	T	86%	
Hormone receptor positive	L+T	85%	0.91 (95% CI, 0.75–1.11)
	T→L	85%	0.90 (95% CI, 0.74–1.10)
	T	83%	
Hormone receptor negative	L+T	84%	0.80 (95% CI, 0.64–1.00)
	T→L	82%	0.97 (95% CI, 0.79–1.20)
	T	80%	
pN0	L+T	91%	0.91 (95% CI, 0.67–1.22)
	T→L	90%	1.02 (95% CI, 0.76–1.36)
	T	89%	
pN1	L+T	87%	0.78 (95% CI, 0.58–1.05)
	T→L	87%	0.76 (95% CI, 0.57–1.02)
	T	84%	
pN2–3	L+T	75%	0.92 (95% CI, 0.71–1.18)
	T→L	71%	1.09 (95% CI, 0.86–1.39)
	T	73%	

DFS: disease-free survival

L+T: trastuzumab concurrently with lapatinib

T→L: trastuzumab followed by lapatinib

T: trastuzumab alone