

## ORIGINAL ARTICLES

# A phase II trial of neoadjuvant doxorubicin plus cyclophosphamide followed by lapatinib plus docetaxel sequential with adjuvant trastuzumab for treatment of early HER2 positive breast cancers

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## ABSTRACT

**Background:** The use of HER2 targeting therapy has revolutionized the treatment of HER2 positive breast cancers. Here, we investigate whether a sequential approach to dual HER2 blockade of lapatinib followed by trastuzumab will result in improved clinical outcomes.

**Methods:** This was a single institution, open label, single arm, phase II trial in women with HER2 positive breast cancer. Volunteers were treated with sequential neoadjuvant doxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) (AC) for 4 cycles followed by docetaxel (100 mg/m<sup>2</sup>) concurrent with lapatinib (1,250 mg) (TL) daily for 21 days for four cycles before definitive surgery. The primary end point was pathologic complete response (pCR).

**Results:** The study accrued only 21 of the 71 planned patients from 2/28/2007 to 5/25/2010. All patients (100%) experienced down staging. The pCR rate was 41% (7/18). 11 patients had tumor size of T3 or greater, 3 of which experienced pCR and only 1 underwent breast conservation (lumpectomy). The most common hematologic AE (all grades) was anemia 17/21 (81%). There were no incidences of grade 3 or 4 anemia. 10 of 21 (48%) patients experience a non-hematologic grade 3 AE. The most common non-hematologic AEs (all grades) were irregular menses 20/21 (95%) and hand-foot-skin reactions 20/21 (95%). No increase cardiac abnormalities were noted. The DFS at data cut off was 87.5%.

**Conclusion:** The provocative pCR and DFS results in this high risk locally advanced patient population should be viewed with caution given results of the Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation study (ALTTO) clinical trial.

**Key Words:** Lapatinib, Taxotere, HER2 positive, Breast cancer, Neo-adjuvant

## 1. INTRODUCTION

Approximately 20% of breast cancers overexpress epidermal growth factor (EGFR) molecule ERBB2 (HER2). The overexpression of HER2 protein concurrent with gene ampli-

fication was associated with decreased survival rate. The discovery of HER2 directed monoclonal therapy—trastuzumab, pertuzumab, and ado-trastuzumab (trastuzumab conjugated to emtansine chemotherapy)—has resulted in increased pro-

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gression free and overall survival in both the metastatic and curative settings.<sup>[1-4]</sup> Trastuzumab and ado-trastuzumab inhibit ligand dependent activation of the HER2 dependent pathway, while pertuzumab inhibits receptor dimerization. In addition, all three molecules facilitate antibody dependent cell-mediated cytotoxicity (ADCC).<sup>[5-7]</sup> By contrast the tyrosine kinase inhibitor Lapatinib shuts down the intracellular tyrosine kinase domain. Given that dual targeting of HER2 with trastuzumab and lapatinib results in prolongation of progression free survival in the metastatic setting,<sup>[8]</sup> the investigation of this agent in the curative setting makes sense. Neo-adjuvant chemotherapy as a strategy in breast cancer has equivalent outcomes as adjuvant chemotherapy.<sup>[9]</sup> Moreover, pCR following a neo-adjuvant approach may result in better outcomes.<sup>[10,11]</sup> The FDA has therefore considered pCR as an acceptable endpoint for consideration of drug approval.<sup>[11]</sup> The combination of lapatinib and trastuzumab sequential with chemotherapy has resulted in statistically significant pCR rates.<sup>[12,13]</sup> In addition, secondary endpoints of event free survival and 3 years overall survival for patient experiencing pCR were superior to the outcomes of patients who did not.<sup>[14]</sup> The promise of this treatment strategy has faded with the presentation of the ALTTO, which failed to show any survival benefit for the combination in the adjuvant setting. The discrepancy of these results will continue to be argued by the experts. Our study, which began prior to the presentation of the ALTTO and NeoALTTO results, afforded patients a complete neoadjuvant cytotoxic regimen as well as adjuvant trastuzumab. The goal was to determine whether lapatinib combined with chemotherapy was safe and resulted in increased pathologic complete response rates.

## 2. PATIENTS AND METHOD

### 2.1 Study design and treatments

A phase II trial study conducted at a single institution under investigational new drug application (IND) at Stanford University Cancer Center (IND 74200). The Stanford's institutional review board approved this open-label phase II study. All participants provided written informed consent. All patients were expected to receive doxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) every 2 weeks for 4 cycles followed by oral lapatinib (1,250 mg) daily in combination with docetaxel (100 mg/m<sup>2</sup>) every 3 weeks for 4 cycles in the neo-adjuvant setting. Patients proceeded to surgery +/- radiation and then to adjuvant trastuzumab. The first 3 patients were treated with docetaxel 100 mg/m<sup>2</sup> plus lapatinib 1,250 mg PO. If there were no unexpected dose limiting toxicities (DLT) or if expected DLT recovered to grade 1 or less (according to CTC criteria V3.0) within 3 weeks of stopping drug, then 6 more patients would be treated with

the combination at the full dose of docetaxel plus lapatinib. If there were no unexpected DLT at this level or if expected DLT recovered to grade 1 or less within 3 weeks of stopping the drug, then the protocol would be opened up to full enrollment. If there was an unexpected DLT or the patient did not recover from a DLT within 3 weeks of drug hold, then an additional 3 patients would be enrolled. If no additional unexpected DLT or unrecovered expected DLT was seen in the additional 3 patients, then the protocol would be opened up to full enrollment. If in the additional 3 patients an unexpected DLT or an unrecovered expected DLT occurred, the trial enrollment would be held and safety and treatment tolerability would be assessed

### 2.2 Patients

Eligible women age  $\geq 18$  years with newly diagnosed stage II/III HER2 positive breast cancer (IHC 3+ or FISH ratio  $\geq 2.2$ ) were recruited for study. These patients had tumor  $\geq 2$  cm, tumors of any size associated with skin or chest wall involvement, axillary node involvement, and/or ipsilateral infraclavicular or supraclavicular lymph nodes. We also required ECOG  $\leq 2$  or Karnofsky  $\geq 60\%$  and normal cardiac ejection fraction within institutional range and measured by MUGA or ECHO. Adequate hematologic, hepatic, and renal function were required, including absolute neutrophil count  $\geq 1,500/\text{mm}^3$  and platelet count of  $\geq 100,000/\text{mm}^3$ . Key exclusions were prior chemotherapy, immunotherapy, or hormonal therapy for breast cancer; disease outside the ipsilateral breast or chest wall except for ipsilateral supraclavicular or infraclavicular lymph nodes; and more than 3 months between histologic diagnosis and registration on study.

### 2.3 AEs of special interest

Adverse events were documented throughout the study and graded according to Common Toxicity Criteria (CTCAE) appendix III. If patients developed stomatitis on day 1 of any cycle, treatment was held until stomatitis had resolved. If Grade 3/4 stomatitis occurred at any time, the dose of docetaxel was reduced for subsequent cycles. If grade 2 peripheral neuropathy developed, docetaxel was reduced without treatment delays, and for grade 3 or 4 peripheral neuropathy treatment was discontinued. No dose reduction was undertaken for fluid retention. Oral diuretic was allowed per physician's preference. If cutaneous toxicity was observed, no change in therapy was indicated for grade 0-1. For grade 2, topical or oral antibiotics as well as topical steroids were permitted per physician's preference. For grade 3 and 4 skin toxicity, docetaxel was held for a maximum of 2 weeks until symptoms reduced to grade 1 or lower at which point treatment would resume at 75% of the original dose. Docetaxel

was discontinued if inappropriate recovery after 2 weeks, and the patient was removed from study. If mucositis, dysphagia, or diarrhea was believed to be the result of docetaxel or doxorubicin and was present on day 1 of a cycle, the therapy was held for no more than 2 weeks until recovery. If diarrhea was attributed to lapatinib, no treatment alteration was performed for grade 1. If grade 2 or 3 diarrhea was noted, loperamide was initiated. If grade 3 or worse diarrhea was present despite optimal therapy with loperamide, then lapatinib was held for a maximum of 21 days until recovery to < grade 1. An assessment of cardiac function was performed every 3 months. If clinically significant or grade 3/4 CHF was noted, lapatinib was held and then restarted once recovered ≤ grade 1. Cardiac protective medication was allowed as indicated by treating physicians.

**2.4 Study endpoints**

The primary endpoint was pathologic complete response evaluated after neoadjuvant therapy. Secondary endpoints were radiologic complete response, rate of breast conserving surgery, side effect and toxicity profile of docetaxel and lapatinib, and disease free survival (DFS). Pathologic complete response was defined as no invasive disease in the breast or axilla. In situ disease was not accounted for in defining pathologic complete response.

**2.5 Statistical analysis**

This was based on the Simon’s stage II design controlled ClinicalTrials with the “optimal” criterion. Of a total of 71 subjects, 20 were to be accrued during stage 1, and 51 during stage 2. If 5 or fewer pathologic complete responses were observed during the first stage, then the trial was stopped early (for futility). If 6 or more responses were observed, the study would accrue the remaining 51, for a total of 71 patients. If there were 23 or fewer responses by the end of the trial, then no further investigation of the treatment would be warranted. If 24 or more responses were observed out of 71 patients, the treatment would be deemed worthy of further investigation.

**3. RESULTS**

**3.1 Patients’ characteristics**

Between February 28, 2007 and May 25, 2010, 21 of the planned 71 patients enrolled in this trial. Patient characteristics are summarized in Table 1. At data cut off, the average DFS follow up period was approximately 3.5 years (1.9 to 6.0 years). Median age was 48 years old, and all patients had an EGOG performance status of 0. 57% of enrollers were described as White and 38% Asian. All patients had nodal involvement, and 60% were ER negative HER2 positive. All patients received surgery, radiation when clinically indicated,

and adjuvant HER2 directed therapy with trastuzumab. Of the patients who received TL, 45% had dose reduction or discontinuation of docetaxel. Four patients withdrew from study, but all completed 4 cycles of AC. The first patient was never treated with TL and instead was switched to weekly paclitaxel and trastuzumab. The second tolerated one full cycle of TL and was taken directly to surgery. She did not receive any further neoadjuvant or adjuvant chemotherapy. The third patient tolerated only 1 cycle of docetaxel and 7 days of lapatinib. She was switched to weekly paclitaxel and trastuzumab off study. The final patient received full dose docetaxel in cycle 1 of TL but only tolerated 5 days of lapatinib. She was rechallenged at reduced dose (75 mg/m<sup>2</sup>) of docetaxel in cycle 2 but did not start lapatinib. She completed her treatment off study with 2 cycles of dose dense paclitaxel and weekly trastuzumab. Dose modification of lapatinib was not allowed but treatment delays were permitted. No other delays in lapatinib were experienced.

**Table 1.** Baseline Patients’ characteristics

Characteristics		Patients (N=21) No (%)
Age (range)		48(37-67)
Race	Black	0
	White	12(57)
	Asian	8(38)*
	Hispanic	1(5)
Menopausal state	Pre-	4(19)
	Post-	17(81)
Histology	Ductal	21(100)
	Lobular	0
TMN stage	I	0
	II	10(45)*
	III	12(55)*
Nodal involvement	N1	3(14)
	N2	13(62)
	N3	5(24)
Tumor size	T1	0
	T2	10(45)*
	T3	9(41)*
	T4	3(14)
Grade	1	1(4)*
	2	13(59)*
	3	8(36)
ER or PR	Positive	9(41)
	Negative	13(59)
HER2	Positive	22(100)*

**3.2 Clinical outcome**

All patients were confirmed to be radiologically free of distant disease on enrollment. Most had locally advance disease (95% with T3 and/or N1 disease). One patient presented with bilateral HER2 positive disease, with T4 disease in the right

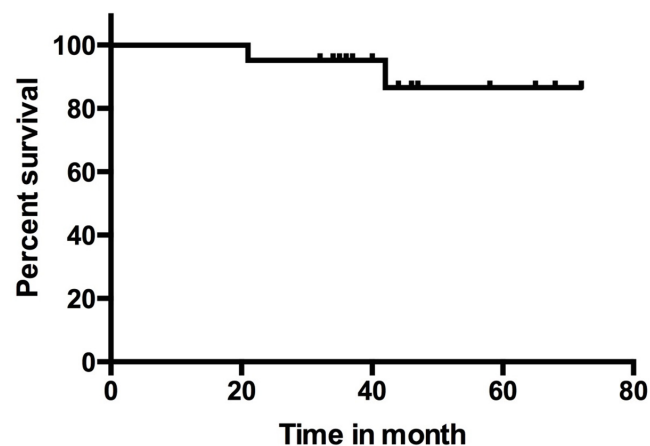
breast and T3 disease in the left. Neither axilla was involved. The pCR rate was 41% (9/21) (see Table 2) and included the patient with bilateral breast cancer. Hormone negative patients accounted for 56% of pCR group, and the remaining 44% expressed estrogen and/or progesterone receptors. All but 1 of the patients who achieved pCR had an in situ component present as surgery. All patients experienced down staging. The breast conservation therapy (BCT) rate was

27%, but only 1/3 (33%) of the patients experiencing pCR underwent BCT surgery. A minority of the women (33%) undertaking BCT had stage IIIa or greater disease. At data cut off, after 7 years of follow-up, only 2 women had disease recurrence. The DFS at data cut off was 87.5%. The median DFS was not reached (see Figure 1). Median follow up time was 42 months.

**Table 2.** Response (%) table (N = 22)

DFS at 5 years (%)	pCR rate (%)	Rate of down staging (%)	Breast conservative therapy rate (%)	Rate of metastatic disease (%)
18/21 (85)	*9/22 (41)	*22/22 (100)	*6/22 (27)	2/21 (9)

Note. \*1 patient with bilateral breast.



**Figure 1.** DFS curve

**3.3 Safety**

The most common hematologic AEs (all grades) were anemia 17/21 (81%). None were grade 3 or 4, and only two patients developed anemia following the start of TL. The most common non-hematologic AEs (all grades) were irregular menses 20/21 (95%), hand foot syndrome 20/21 (95%), nausea 14/21 (67%), nail bed changes 14/21 (67%), and rash 14/21 (67%). 10 different AEs had an incidence of >50%. Among the AEs attributed only to TL (initiated after completion of AC), 4 had an incidence of > 50%. They were hand foot syndrome 13/20 (65%), peripheral neuropathy 11/20 (55%), nail bed changes (55%), and diarrhea 10/20 (50%). 10/21 (47%) patients experience at least 1 non-hematologic grade 3 AEs. The grade 3 toxicities attributed to TL are listed in Table 3. With the exception of alopecia, all grade 3 AE's were noted following the start of TL. No grade 4 non-hematologic AEs were noted. No increase cardiac abnormalities were noted. Dose modification and/or stopping were frequent—15/21 (71%) patients. Of those 15, 13 had

alterations in lapatinib and 8 in docetaxel. Two patients tolerated only 1 week of lapatinib, and one patient never got lapatinib or docetaxel. The latter withdrew from study after completion of AC.

**Table 3.** Grade 3 and 4 adverse event table attributed to Lapatinib (N = 21)

Adverse event	Toxicity by grade	
	All events (%)	
	3	4
Adrenal insufficiency	1 (5)	-
Arthralgia	1 (5)	-
Dysphagia	1 (5)	-
Fatigue	2 (10)	-
Hand foot syndrome	5 (23)	-
Mucositis	2 (10)	-
Pain	2 (10)	-

**4. DISCUSSION**

Our study was small and highly underpowered due to lack of pre-specified enrollment numbers. Importantly, this was not due to specific toxicity or futility signals, but because of factor related to study staff, independent of the study itself.

The excitement surrounding the benefit of lapatinib in the curative setting quickly subsided after the data from ALTTO clinical trial was presented.<sup>[15]</sup> In this adjuvant trial the combination of lapatinib and trastuzumab (sequentially or concurrently) failed to show significant DFS benefit. Importantly, the lapatinib only arm was stopped due to futility after being unable to demonstrate non-inferiority to trastuzumab. The addition of lapatinib also added significant toxicity. Some experts have postulated that there may still be a role for lapatinib in the treatment of early breast cancer, given the significant increase in pathologic complete response seen in the companion neoadjuvant clinical trial (NeoALTTO).<sup>[12]</sup>

That trial randomized HER2 overexpressing curable patients to trastuzumab, lapatinib, or the combination for six weeks followed by 12 weeks of treatment concurrent with paclitaxel. The addition of lapatinib proved to almost double the pCR rate. Similar benefit was noted in NSABP-41 (B-41) trial. The latter compared the pCR rate for the combination of lapatinib and trastuzumab in the neoadjuvant setting. B-41 patients received neoadjuvant anthracycline based chemotherapy whereas patients on the NeoALTTO study received this adjuvantly. These results were expected to translate to a survival benefit as pCR had been suggested as an acceptable surrogate for survival.<sup>[11,16,17]</sup> In an update to NeoALTTO, the event-free survival and 3 years overall survival was not statistically significant between the three treatment groups, though it was certainly greater for patients who achieved a pCR.<sup>[14]</sup> Despite its small size and lack of statistical power, the pCR rate for the lapatinib only arm in our study was comparable to the studies mentioned above. The results of NeoALTTO and ALTTO were intended to answer a specific question, but they appear to have created more questions of their own. Is there an explanation for the discrepancies noted? Is there a group of patients for whom lapatinib and trastuzumab combination maybe beneficial? Do these studies simply demonstrate the effectiveness of anthracycline containing regimen in the treatment of breast cancer, or is it that pCR may identify a patient population in whom addition of anthracycline offer no further benefit? The latter is supported by late breaking abstract from The European Breast Cancer Conference 2016 (EBCC), showing an 27% pCR and minimal residual disease (MRD) rate following 11 days of preoperative treatment with the combination of lapatinib and trastuzumab.<sup>[18]</sup> Appropriately designed studies will be needed to conclusively answer these questions.

The phase III APHINITY study (Adjuvant chemotherapy

plus Trastuzumab and Pertuzumab) will certainly enlighten on dependability of pCR as a surrogate for survival. This is the highly anticipated confirmatory companion study to the NeoSphere trial.<sup>[2]</sup> In this trial patients with early HER2 positive breast cancer were randomized to docetaxel and trastuzumab (TH) or docetaxel and trastuzumab and pertuzumab (THP) or trastuzumab and pertuzumab (TP) only. Neosphere demonstrated a 58% increase in pCR rate for THP when compared to standard of care (TH) and resulted in accelerated approval from the FDA based on pCR as a surrogate for survival. In this study adjuvant anthracycline based chemotherapy was mandated. In contrast to APHINITY, NeoSphere was not powered for survival.

Compared to our study, NeoALTTO, B-41 and ALTTO, the NeoSphere regimen appeared much better tolerated. That toxicity was directly related to the addition of lapatinib. In our study nearly half of the patients experienced a non-hematologic serious adverse event. Dose reductions were common. The adverse events were similar across lapatinib containing regimens. These included but were not limited to diarrhea, hand foot syndrome, and fatigue. There were 19% and 23% grade 3 GI toxicity with lapatinib in our study and NeoALTTO respectively.<sup>[12]</sup> By contrast, only 10% of patients in NeoSphere experienced a grade 3 toxicity which was reduced to 4% in the non-chemotherapy arm. Given comparable responses in the neoadjuvant setting, the risk to benefit ratio favors pertuzumab. Lapatinib is therefore too toxic and does not show enough clinical benefit to affect a change in standard of care at this time. Though provocative, this study is underpowered to make any DFS comparison to similar studies.

## CONFLICTS OF INTEREST DISCLOSURE

The authors declare that there is no conflict of interest statement.

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