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Efficacy of Neoadjuvant Therapy with Trastuzumab Concurrent with Anthracycline- and Non-anthracycline-based Regimens for HER2-Positive Breast Cancer

Soley Bayraktar, MD¹, Ana M. Gonzalez-Angulo, MD^{2,3}, Xiudong Lei, PhD⁴, Aman U. Buzdar, MD², Vicente Valero, MD², Amal Melhem-Bertrandt, MD², Henry M. Kuerer, MD⁵, Gabriel N. Hortobagyi, MD², Aysegul A. Sahin, MD⁶, and Funda Meric-Bernstam, MD⁵

¹Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

²Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

³Department of Systems Biology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

⁴Department of Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

⁵Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

⁶Department of Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Abstract

Background—To evaluate the pathologic complete response (pCR) rates and relapse-free survival (RFS) and overall survival (OS) of patients receiving neoadjuvant systemic therapy (NST) with trastuzumab in combination with an anthracycline- or a non-anthracycline-based regimen.

Methods—In this retrospective non-randomized study, we reviewed records of 300 patients with HER2-positive breast cancer treated with either sequential paclitaxel and trastuzumab and FEC75 in combination with trastuzumab (PH-FECH) or docetaxel, carboplatin and trastuzumab (TCH). The Kaplan-Meier product-limit method was used to estimate RFS and OS rates. Logistic regression models and Cox proportional hazards models were fit to determine the associations between NST, pCR and survival.

Results—There was no significant difference in the decline in cardiac ejection fraction, however, patients who received PH-FECH had less cardiac comorbidities at baseline ($P = 0.002$). pCR rates were 60.6% and 43.3% for patients who received PH-FECH ($n=235$) and TCH ($n=65$), respectively ($P=0.016$). Patients who received PH-FECH were 1.45 times more likely to have a pCR (Odds ratio [OR]:1.45; 95% confidence interval (CI):1.06-1.98; $P=0.02$). Three-year RFS rates were 93% and 71% ($P<0.001$), and 3-year OS rates were 96% and 86% ($P=0.008$) for patients who received

Corresponding Author: Funda Meric-Bernstam, MD, Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 444, Houston, TX, 77030-4009, fmeric@mdanderson.org, Tel: (713) 745-4453, Fax: (713) 745-4926.

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PH-FECH and TCH, respectively. Patients who received PH-FECH had a lower risk of recurrence (Hazard ratio [HR]:0.27; 95% CI:0.12-0.60; P=0.001) and death (HR:0.37; 95% CI:0.12-1.13; P=0.08) than those treated with TCH.

Conclusion—The type of NST in HER2-positive breast cancer is predictive of pCR rate independent of disease and patient characteristics. While TCH is active, PH-FECH shows a higher pCR rate and RFS advantage.

Keywords

HER2-positive breast cancer; neoadjuvant therapy; trastuzumab; anthracyclines; pCR; survival

Introduction

Neoadjuvant systemic therapy (NST) has been the standard of care for patients with inflammatory and locally advanced breast cancer, and is increasingly being used for early-stage disease. NST allows us to measure treatment response in addition to survival. Several studies have indicated that, pathologic complete response (pCR) to NST is predictive of improved recurrence-free survival (RFS) and overall survival (OS)¹⁻³.

With the introduction of anthracycline-based regimens, 5-year survival rates have significantly improved in patients with early-stage breast cancer⁴. With the addition of trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor-2 (HER2), improvements in OS have been observed among patients with advanced HER2-positive disease^{5, 6}. However, in a pivotal phase III trial in metastatic breast cancer, the concurrent administration of anthracyclines and trastuzumab resulted in an unacceptably high rate (27%) of cardiotoxicity⁷. Findings from the N9831 adjuvant trial suggested the superiority of concomitant chemotherapy and trastuzumab (doxorubicin plus cyclophosphamide followed by paclitaxel with trastuzumab) over sequential use of the same therapies (doxorubicin plus cyclophosphamide followed by paclitaxel, followed by trastuzumab)⁷⁻⁹. Although cardiotoxicity was more frequent with sequential doxorubicin/cyclophosphamide and taxane-trastuzumab than non-anthracycline-based trastuzumab regimens, the majority of patients who received therapy displayed neither acute nor delayed cardiac dysfunction (CD). Afterwards, several studies¹⁰⁻¹² have evaluated concurrent administration of anthracycline-based chemotherapy and trastuzumab in the neoadjuvant setting. In contrast to previous reports, trastuzumab plus anthracycline-based NST was both effective and well tolerated.

Therefore, we conducted this retrospective analysis to determine the efficacy of concurrent trastuzumab in combination with anthracycline-based or non-anthracycline-based NST. Our primary objective was to compare the pCR rates between the two treatment groups. Secondary endpoints included clinical and radiologic response rates, RFS, and OS.

Material and Methods

Patient Population

The Breast Cancer Management System database of The University of Texas M.D. Anderson Cancer Center (MDACC) identified 300 women who were diagnosed with HER2-positive invasive breast cancer and treated with NST using either sequential paclitaxel and trastuzumab and FEC-75 in combination with trastuzumab (PH-FECH) or docetaxel, carboplatin and trastuzumab (TCH), between 2001 and 2009. We excluded patients who were male, who had metastatic disease, bilateral breast cancer or more than one primary tumor, whose pathologic response could not be assessed, or who were enrolled in the American College of Surgeons Oncology Group (ACOSOG) Z1041 trial. Initial clinical and

final pathologic stage were based on the seventh edition of the American Joint Committee on Cancer (AJCC) staging criteria¹³.

The study was approved by the MDACC Institutional Review Board. Accuracy of clinical variables recorded within the database was verified by retrospective review of patient records.

Pathologic Evaluation

Pathologic specimens were reviewed by dedicated breast pathologists at MDACC. Histologic type and grade were defined according to the WHO classification system¹⁴ and modified Black's nuclear grading system¹⁵, respectively. Nuclear staining 10% of estrogen-receptor (ER) or progesterone-receptor (PR) was considered strongly positive. HER2 positivity was defined as 3+ receptor overexpression on IHC staining and/or gene amplification on fluorescence in situ hybridization (FISH).

Treatment

The type of NST was at the discretion of the patient and treating oncologist; 235 patients received PH-FECH, and 65 received TCH chemotherapy. PH-FECH included paclitaxel 80 mg/m² intravenously (IV) weekly for 12 weeks or paclitaxel 225 mg/m² IV over 24 hours every 3 weeks, followed by 4 cycles of FEC-75 (fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m²) IV on Day 1, every 3 weeks. A loading dose of 4 mg/kg IV trastuzumab was given on Day 1 followed by 2 mg/kg weekly, during the 24 weeks of NST. The non-anthracycline-based NST (TCH) included docetaxel 75 mg/m² IV on Day 1, carboplatin at an area-under-the-concentration curve (AUC) of 6 IV on Day 1, and trastuzumab 8 mg/kg IV on Day 1 followed by 6 mg/kg maintenance dose, administered at 3-week intervals for six cycles. PH-FECH and TCH NST were given as planned in 231 (98%) and 61 patients (94%), respectively. However, seven patients that received PH-FECH (2%) and nine that received TCH (14%) did not complete a year of trastuzumab.

Surgical intervention was BCS for 29% of patients (n=87) and mastectomy for 68% (n=204); 3% (n=9) did not have surgery as a result of the development of progressive disease or patient refusal. Radiation therapy was given for patients who had BCS, locally advanced disease, or IBC. Women with hormone receptor-positive disease were offered 5 years of adjuvant endocrine therapy.

Response and Toxicity Assessments

A clinical complete response (cCR) was defined as no detectable disease in breast and axilla on physical examination. Radiological response was evaluated at baseline and before surgery based on Response Evaluation Criteria in Solid Tumors [RECIST]¹⁶. pCR was defined as the absence of invasive disease in the breast, and the absence of micro- or macrometastases in the ipsilateral axillary lymph nodes. Left ventricular ejection fraction (LVEF) was evaluated by an echocardiogram (ECHO) or multigated cardiac blood pool scan (MUGA) at baseline, 3, 6, 12, and 18 months after initiation of NST. Adverse events (AEs) for non-laboratory toxicities were summarized according to CTCAE version 4.0¹⁷.

Statistical Analysis and Outcome Measures

Patient demographics, clinical characteristics, pCR rate, comorbidities, and AEs were compared between the two groups with chi-square test. Multivariate logistic regression models were fitted to examine the relationship between NST groups and pCR. RFS was defined as the time from the first dose of NST until the first date of documented local or distant recurrence or the date of last follow-up. Patients who died from unrelated causes were censored. OS was measured from the first dose of NST until the date of death from any

cause or last follow-up. Survival outcomes were estimated with the Kaplan-Meier product-limit method. Cox proportional hazards models were fitted to determine the association of NST with survival outcomes after adjustment for significant patient and clinical characteristics identified in univariate analyses. Statistical analyses were carried out using SAS 9.1 (SAS Institute Inc., Cary, NC) and S-Plus 7.0 (Insightful Corporation, Seattle, WA).

Results

Three hundred patients were included in the study; 235 (78%) were treated with PH-FECH, and 65 (22%) with TCH. Patient demographics and clinical characteristics are summarized in Table 1. Patients treated with PH-FECH were younger ($P = 0.005$), had lower tumor stage ($P = 0.001$), and were less likely to have IBC ($P < 0.001$), compared with patients treated with TCH. Patients who received PH-FECH at baseline had less cardiac comorbidities ($P = 0.002$) and cardiac risk factors ($P = 0.12$) when compared to patients who received TCH (Table 1).

Efficacy

Of 300 patients, 80.8% had cCR in the PH-FECH group vs. 58.9% in the TCH group ($P = 0.006$; Table 2). The radiological overall response rates (ORR) were 97.0% in the PH-FECH group vs. 98.1% in the TCH group ($P = 0.67$). Excluding IBC patients, cCR rates were 79.9% and 51.3% ($P = 0.002$); and radiological ORR were 97.2% and 97.3% ($P = 0.98$) in the PH-FECH and TCH groups, respectively.

The pCR rate was significantly higher in patients treated with PH-FECH compared to patients treated with TCH (60.6% vs. 43.3%; $P = 0.016$) (Table 2). In the PH-FECH group, pCR was achieved in 57% (105/183) of patients treated with weekly paclitaxel and 61% (32/52) of patients treated with every 3-week paclitaxel.

pCR rate was higher for ER- compared with ER+ tumors in both the PH-FECH (70.3% vs. 47.6%) and the TCH group (57.1% vs. 25.7%). The pCR rate with PH-FECH vs. TCH respectively was 64.1% (93/145) vs. 39.4% (13/33) for T1/2 tumors, 52.3% (22/42) vs. 50% (3/6) for T3 tumors, 35.7% (10/28) vs. 50% (2/4) for T4b tumors, and 55.5% (10/18) vs. 38.1% (8/21) for IBC. Excluding the IBC patients, pCR rate was 60.5% for patients who received PH-FECH compared to 42.9% for those who received TCH ($P = 0.035$).

On multivariate analysis, PH-FECH was associated with a higher pCR rate (Odds Ratios [OR]: 1.45; 95% confidence interval [CI]: 1.06 to 1.98; $P = 0.02$). In addition, patients with ER-negative/weak tumors ($P < 0.001$), higher nuclear grade ($P = 0.05$) and pretreatment T1-3 status ($P = 0.043$) were more likely to achieve a pCR (Table 3). After excluding the IBC patients, PH-FECH remained an independent significant predictor for pCR (OR: 1.46; 95% CI: 1.02 to 2.08; $P = 0.039$).

Survival estimates

Median follow-up of survivors was 26.8 months (range 5–99 months); the follow-up was 29 months and 18 months for PH-FECH group and the TCH group respectively. The estimated 3-year RFS was 93% in the PH-FECH vs. 71% in the TCH group; $P < 0.001$ (Table 4). Excluding IBC patients, the 3-year RFS estimates were again better for the patients that received PH-FECH compared to the patients that received TCH (94% vs. 80%; $P = 0.01$) (Figure 1C).

Patients who achieved pCR had better RFS than patients who did not (95% vs. 83%; $P = 0.003$). Among patients with pCR, patients who received PH-FECH had better 3-year

RFS compared to TCH (97% vs. 82%; $P=0.008$). In the multivariate model, PH-FECH was associated with a lower risk of recurrence (Hazard ratio [HR] = 0.27; 95% CI: 0.12 to 0.60; $P=0.001$). This association remained when excluding IBC patients (HR = 0.28; 95% CI: 0.10 to 0.82; $P=0.02$).

The 3-year OS estimates were 96% in the PH-FECH group compared to 86% in the TCH group ($P=0.008$). Patients who achieved pCR had better 3-year OS than patients who did not (98% vs. 93%; $P=0.008$). Among patients with pCR, patients who received PH-FECH had better 3-year OS compared to patients that received TCH (100% vs. 76%; $P<0.001$). In the 261 patients without IBC, there were no differences in the 3-year OS estimates for the patients who received PH-FECH compared to the patients who received TCH (96% vs. 100%; $P=0.98$). The multivariate Cox proportional hazards model showed that PH-FECH tended to be associated with a lower risk of death (HR=0.37, 95% CI: 0.12-1.13; $P=0.08$). When excluding patients with IBC, there was no association (HR = 1.06; 95% CI: 0.13 to 8.61; $P=0.96$).

Toxicity

No significant differences were noted in non-laboratory AEs and cardiotoxicity with respect to NST regimen received (Table 5). The mean LVEF at baseline was 64.3% in the PH-FECH group and 64.7% in the TCH group. The mean calculated percent decline in LVEF from baseline to the lowest detected during follow-up was 8% in both treatment groups ($P=0.52$). However, one patient on PH-FECH developed CHF and died from sudden cardiac death.

Discussion

Several trials have examined the potential benefits of concurrent trastuzumab in combination with anthracycline-based^{11, 12, 18-21} or non-anthracycline-based neoadjuvant therapy²²⁻²⁹ in HER2-positive breast cancer, with reported pCR rates of up to 76%³⁰. In this retrospective non-randomized study, we showed that while TCH is active, trastuzumab combined with a taxane and then with an anthracycline (PH-FECH) shows higher pCR rate.

The high pCR rates in our study are consistent with previous trials which assessed the use of trastuzumab as part of an anthracycline-based NST regimen in operable and locally advanced breast cancer. In the MDACC¹⁰ trial, patients with HER2-positive breast cancer received paclitaxel followed by FEC75, with or without concurrent trastuzumab. The pCR rate increased from 26% to 65% ($P=0.02$) with trastuzumab. An expansion cohort in the experimental arm ($n=22$) continued to show high rates of pCR (54.5%) without significant cardiac toxicity¹⁹. The combined pCR rate for all patients that received trastuzumab was 60%, and at a median follow-up of 36.1 months, there had been no recurrences. The Neoadjuvant Herceptin (NOAH) trial evaluated the sequential administration of three cycles of doxorubicin and paclitaxel followed by four cycles of paclitaxel alone, then three cycles of cyclophosphamide, methotrexate, and 5-fluorouracil with or without concomitant trastuzumab¹¹. Patients with HER2-positive disease who received concurrent trastuzumab had a significantly higher pCR rate (43% vs. 23%; $P=0.002$), ORR (89% vs. 77%; $P=0.02$), and 3-year disease-free survival (DFS) (70.1% vs. 53.3%; $P=0.007$) compared to those who received chemotherapy alone. A pCR benefit with the addition of trastuzumab was also observed among IBC patients (39% vs. 20%; $P=0.002$). In the phase III German Breast Group/Gynecologic Oncology Study Group trial (the GeparQuattro trial)¹², patients with HER2-positive locally advanced breast cancer were treated with epirubicin/cyclophosphamide followed by docetaxel with or without capecitabine, and trastuzumab every 3 weeks. Neoadjuvant trastuzumab plus chemotherapy demonstrated a significant increase in pCR rates (15.7% vs. 31.7%; $P<0.001$). pCR rates with neoadjuvant

trastuzumab and anthracycline-free regimens in other studies range from 11% to 76%^{22, 24, 25, 30-35}.

Due to concerns about cardiotoxicity, there has been interest in developing non-anthracycline-containing regimens. BCIRG 006³⁶ evaluated AC followed by docetaxel (AC/T) vs. AC followed by docetaxel plus trastuzumab (AC/TH) vs. TCH for the adjuvant treatment of HER2-positive breast cancer. In a recent updated analysis with 656 DFS events, DFS was improved by 36% with AC/TH ($P = 0.001$) and by 25% with TCH ($P = 0.04$) relative to the AC/T arm. The risk of death was reduced by 37% with AC/TH ($P < 0.001$) and 23% with TCH ($P = 0.038$) relative to the AC/T arm³⁷. There was no statistically significant difference in 5-year DFS ($P=0.21$) and OS ($P=0.14$) between the trastuzumab-containing regimens. The results of this trial not only confirmed the importance of trastuzumab for HER2-positive breast cancer, but it also greatly increased interest in the use of non-anthracycline-trastuzumab-base regimen, TCH, for adjuvant therapy.

In our study, PH-FECH and TCH NST yielded different pCR rates (60.6% vs. 43.3%; $P=0.016$). However, pCR rates relate inversely to larger tumor size, lower nuclear grade and ER-positivity^{22, 38}. In addition to the significant differences in age and T stage between our study groups, the patients in the TCH group were more overweight and had more frequent unfavorable disease characteristics (non-ductal histologies, stage IIIB, and N1/2 disease) that may have led to lower pCR rates and worse survival outcomes. In our multivariate analysis, PH-FECH demonstrated superiority in clinical outcome even when other variables were considered. While the multivariable analysis compensates for much of the covariate imbalances, it probably does not account for all. It remains to be determined whether the differences in outcomes between the groups were the result of the antitumor effect of anthracyclines, synergy from the combination of anthracyclines with trastuzumab, or the additional duration of therapy. Future randomized studies with larger prospective cohorts and longer-term follow-up are needed to validate these findings.

Although trastuzumab-based therapies have been associated with an increased incidence of CD, especially when combined with anthracyclines, three large clinical trials¹⁰⁻¹² demonstrated that the combination was both effective and well tolerated. Overall, the CD incidence in the neoadjuvant and adjuvant settings ranged from none-observed^{10, 27} to 10.5%³⁹; and 2.0%³⁶ to 3.3%^{40, 41}, respectively. Caution should be exercised in women with risk factors for cardiac toxicity, since data from B-31 indicate that women who develop severe cardiac toxicity from anthracycline-based regimens do not always fully recover⁴². Additionally, B-31⁴² and N9831⁴³ demonstrated that 5.0%–6.6% of women who received anthracyclines were unable to receive trastuzumab. Nonetheless, in the GeparQuattro trial¹² concurrent administration of trastuzumab with epirubicin yielded persistent decrease in LVEF to less than 50% in only one patient. In this study, although the patients who received TCH had more baseline cardiac comorbidities and cardiac risk factors, there were no differences in the baseline LVEF or magnitude of decrease in the LVEF after NST.

The treatment benefits need to be weighed against the risk of cardiotoxicity. The cardiac death in a patient who received PH-FECH further highlights the importance of careful patient selection and close cardiac monitoring. One potential approach to minimize cardiotoxicity would be to administer trastuzumab after completion of anthracyclines. However, the comparative anti-tumor efficacy of this approach is not known. This specific question is currently being tested in the ongoing ACOSOG Z1041 trial.

Our study is limited by its retrospective nature and small sample size in the TCH cohort. Patient selection for individual treatment regimens may have impacted the differences in oncologic outcome. Fewer patients with cardiac co-morbidities received PH-FECH, which

may have minimized CD observed in the anthracycline cohort. On the other hand, we showed that the incidence of CD is comparable with previous trials in which more selective eligibility criteria and better cardiac monitoring are applied.

In conclusion, the results of our retrospective analysis suggest that the type of NST in HER2-positive breast cancer is predictive of pCR rate independent of disease characteristics. While TCH is active, trastuzumab combined with an anthracycline-based NST showed higher pCR rate and a RFS advantage.

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References

1. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol.* 1999; 17(2):460–469. [PubMed: 10080586]
2. Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber CP, Baloch Z. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg.* 1995; 180(3):297–306. [PubMed: 7874340]
3. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998; 16(8):2672–2685. [PubMed: 9704717]
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005; 365(9472):1687–1717. [PubMed: 15894097]
5. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005; 353(16):1659–1672. [PubMed: 16236737]
6. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005; 353(16):1673–1684. [PubMed: 16236738]
7. Slamon DJ, Leyland-Jones B, Shak SI. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001; 344:783–792. [PubMed: 11248153]
8. Pegram MD, Konecny GE, O'Callaghan C, Beryt M, Pietras R, Slamon DJ. Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. *J Natl Cancer Inst.* 2004; 96(10):739–749. [PubMed: 15150302]
9. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol.* 2005; 23(19):4265–4274. [PubMed: 15911866]
10. Buzdar AU, Ibrahim N, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol.* 2005; 23:3676–3685. [PubMed: 15738535]
11. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet.* 375(9712):377–384. [PubMed: 20113825]
12. Untch M, Rezaei M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol.* 28(12):2024–2031. [PubMed: 20308670]
13. Seventh Edition of the AJCC Cancer Staging Manual and Handbook. 2010.

14. The world Health Organization Histological Typing of Breast Tumors--Second Edition. The World Organization. Am J Clin Pathol. 1982; 78(6):806–816. [PubMed: 7148748]
15. Black MM, Speer FD. Nuclear structure in cancer tissues. Surg Gynecol Obstet. 1957; 105(1):97–102. [PubMed: 13442910]
16. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. Eur J Cancer. 2006; 42(8):1031–1039. [PubMed: 16616487]
17. Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC) version 4.0
18. Chia, S.; Bryce, C.; Pansegrau, G., et al. Phase II trial of neoadjuvant chemotherapy of sequential FEC100 followed by docetaxel, carboplatin and trastuzumab (TCH) for HER-2 over-expressing locally advanced breast cancer (LABC): a multi-centre study from British Columbia. Breast Cancer Res Treat; San Antonio Breast Cancer Symposium; 2008. Poster session V (abstr 5118)
19. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res. 2007; 13(1):228–233. [PubMed: 17200359]
20. Livasy C, Carey L, DeMichele A, et al. Influence of anthracycline- and taxane-based neoadjuvant chemotherapy on tumor HER2 protein expression in locally advanced breast cancers: results from the I-SPY trial (CALGB 150007/150012 & ACRIN 6657). Cancer Res. 2009; 69((2 suppl)(97s))
21. Masuda N, Nakayama T, Matsunami N, et al. Phase II trial of neoadjuvant 5-fluorouracil, epirubicin and cyclophosphamide (FEC100) followed by weekly paclitaxel and trastuzumab (PH) for HER2 positive breast cancer (Kinki Multidisciplinary Breast Oncology Group; KMBOG-0402). Cancer Res. 2009; 69((2 suppl)(256s))
22. Burstein HJ, Harris LN, Gelman R, et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. J Clin Oncol. 2003; 21(1):46–53. [PubMed: 12506169]
23. Chang HR, Prati R, Gornbein JA, Chung D, Glaspy JA. Survival in patients with locally advanced breast cancer after neoadjuvant docetaxel (T), carboplatin (C), and trastuzumab. J Clin Oncol. 2009; 27(suppl) abstr e11573.
24. Harris LN, You F, Schnitt SJ, et al. Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. Clin Cancer Res. 2007; 13(4):1198–1207. [PubMed: 17317830]
25. Hurley J, Doliny P, Silva O, et al. Neoadjuvant Herceptin/ taxotere/cisplatin in the treatment of locally advanced and inflammatory breast cancer. Proc Am Soc Clin Oncol. 2002; 21(50a)
26. Jahanzeb M, Brufsky A, Erban J, Lewis D, Limentani S. Dose-dense neoadjuvant treatment of women with breast cancer utilizing docetaxel, vinorelbine and trastuzumab with growth factor support. J Clin Oncol. 2005; 23((16S)(26S))
27. Paz IB, Lau S, Garberoglio C, et al. NAB-paclitaxel and carboplatin with or without trastuzumab (trast) as part of neoadjuvant chemotherapy (NCT) in patients (pts) with stage II-III breast cancer (BC). J Clin Oncol. 2008; 26((15S)(22s))
28. Raefsky E, Castillo R, Lahiry A, et al. Phase II study of neoadjuvant bevacizumab and trastuzumab administered with albumin-bound paclitaxel (NAB paclitaxel) and carboplatin in HER2+ locally advanced breast cancer. J Clin Oncol. 2008; 26((15 S)(37s))
29. Wildiers H, Neven P, Christiaens MR, et al. Multicenter phase II study of neoadjuvant capecitabine (X), docetaxel (T), trastuzumab (H) for patients (pts) with locally advanced breast cancer (LABC): final analysis. Cancer Res. 2009; 69(2 suppl):343.
30. Sikov WM, Dizon DS, Strenger R, et al. Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. J Clin Oncol. 2009; 27(28):4693–4700. [PubMed: 19720916]
31. Bines J, Murad A, Lago S, Ferrari B, Andrade J, Abdo E. Multicenter Brazilian study of weekly docetaxel and trastuzumab as primary therapy in stage III, HER-2 overexpressing breast cancer. Proc Am Soc Clin Oncol. 2003; 22:67. abstr 268.

32. Chang HR, Slamon D, Prati R, et al. A phase II study of neoadjuvant docetaxel/carboplatin with or without trastuzumab in locally advanced breast cancer: response and cardiotoxicity. *J Clin Oncol.* 2006; 18S:569s.
33. Coudert BP, Arnould L, Moreau L, et al. Pre-operative systemic (neo-adjuvant) therapy with trastuzumab and docetaxel for HER2-overexpressing stage II or III breast cancer: results of a multicenter phase II trial. *Ann Oncol.* 2006; 17(3):409–414. [PubMed: 16332965]
34. Coudert BP, Largillier R, Arnould L, et al. Multicenter phase II trial of neoadjuvant therapy with trastuzumab, docetaxel, and carboplatin for human epidermal growth factor receptor-2-overexpressing stage II or III breast cancer: results of the GETN(A)-1 trial. *J Clin Oncol.* 2007; 25(19):2678–2684. [PubMed: 17515572]
35. Limentani SA, Brufsky AM, Erban JK, Jahanzeb M, Lewis D. Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer. *J Clin Oncol.* 2007; 25(10):1232–1238. [PubMed: 17296975]
36. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC/T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC/TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER-2 positive early breast cancer patients: BCIRG 006 study. *San Antonio Breast Cancer Symposium 2005. Vol 94 (Suppl 1): Breast Cancer Res Treat.* 2005; 94:S5. abstr 1.
37. Slamon, D.; Eiermann, W.; Robert, N., et al. *San Antonio Breast Cancer Symposium. 2009. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC/T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC/TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients: BCIRG 006 study.*
38. Hurley J, Doliny P, Reis I, et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *J Clin Oncol.* 2006; 24(12):1831–1838. [PubMed: 16549824]
39. Chumsri S, Jeter S, Jacobs LK, et al. Pathologic complete response to preoperative sequential doxorubicin/cyclophosphamide and single-agent taxane with or without trastuzumab in stage II/III HER2-positive breast cancer. *Clin Breast Cancer.* 10(1):40–45. [PubMed: 20133257]
40. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol.* 2008; 26(8):1231–1238. [PubMed: 18250349]
41. Perez, EA.; S, V.; Davidson, NE., et al. *San Antonio Breast Cancer Symposium. 2009. Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial.*
42. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol.* 2005; 23(31):7811–7819. [PubMed: 16258083]
43. Rastogi, P.; Jeong, J.; Geyer, CE., et al. Five year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)/paclitaxel (T) versus AC/T with trastuzumab (H).

Figure 1. Kaplan-Meier estimates of recurrence-free survival (RFS) and overall survival (OS) by neoadjuvant systemic therapy type for all 300 patients (1A); for 261 patients excluding inflammatory breast cancer (1B); and for 39 patients with inflammatory breast cancer (1C).

Table 1
Patient demographics and baseline clinical characteristics by neoadjuvant systemic chemotherapy type

	PH-TECH (N=235)		TCH (N=65)		P
	N	Percent	N	Percent	
Age					
Median (Range)		49 (21-81)		53 (29-80)	0.005
Race					
White	133	56.6	38	58.5	0.88
Black	34	14.5	10	15.4	
Hispanic	46	19.6	13	20.0	
Other	22	9.4	4	6.2	
BMI					
Normal/underwt	84	35.9	14	23.0	0.06
Overweight/obese	150	64.1	47	77.0	
ER Status					
Negative/weak	108	46.2	28	44.4	0.81
Positive	126	53.8	35	55.6	
HER2 IHC Status					
IHC 3+	128	54.5	36	55.4	0.90
Other	107	45.5	29	44.6	
Histology					
Ductal	215	91.5	55	84.6	0.10
Other	20	8.5	10	15.4	
Nuclear Grade					
II	58	25.1	13	21.0	0.50
III	173	74.9	49	79.0	
Clinical Stage					
I	7	3.0	2	3.1	0.17
IIA	63	26.8	14	21.5	

	PH-FECH (N=235)		TCH (N=65)		P
	N	Percent	N	Percent	
IIB	48	20.4	11	16.9	
IIIA	34	14.5	8	12.3	
IIIB	17	7.2	12	18.5	
IIIC	66	28.1	18	27.7	
Clinical Tumor Stage					
T1	30	12.9	6	9.4	<0.001
T2	115	49.4	27	42.2	
T3	42	18.0	6	9.4	
T4b	28	12.0	4	6.3	
T4d	18	7.7	21	32.8	
Clinical Nodal Stage					
N0	67	28.5	13	20.0	0.51
N1	91	38.7	30	46.2	
N2	11	4.7	4	6.2	
N3	66	28.1	18	27.7	
Cardiac comorbidity					
No	232	98.7	58	89.2	
CAD/CHF	3	1.3	7	10.8	0.002
HTN					
No	154	65.5	34	52.3	
Yes	81	34.5	31	47.7	0.051
Dyslipidemia					
No	206	87.7	51	78.5	
Yes	29	12.3	14	21.5	0.061
DM					
No	215	91.9	51	86.4	
Yes	19	8.1	8	13.6	0.20
Cardiac risk factors					

	PH-FECH (N=235)		TCH (N=65)		P
	N	Percent	N	Percent	
None	141	60.0	32	49.2	
HTN/Dyslipidemia/DM	94	40.0	33	50.8	0.12
Surgery					
BCS	69	30.0	18	29.5	0.94
Mastectomy	161	70.0	43	70.5	

ER= estrogen receptor; BMI= body mass index; HER2 = human epidermal growth factor receptor-2; IHC= immunohistochemistry; BCS=breast conserving surgery; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; DM = diabetes mellitus; PH-FECH = Taxol / 5-FU / Epirubicin / Cyclophosphamide / Herceptin; TCH = Taxotere / Carboplatin / Herceptin.

Table 2
Pathologic complete response and clinical response rates by neoadjuvant systemic chemotherapy type

	PH-FECH (N=235)		TCH (N=65)		P
	N	Percent	N	Percent	
Pathologic Response					
No pCR	89	39.4	34	56.7	0.016
pCR	137	60.6	26	43.3	
Clinical Response					
CR	172	80.8	33	58.9	0.006 [‡]
PR	15	7.0	11	19.6	
SD	16	7.5	11	19.6	
PD	10	4.7	1	1.8	
Radiological Response					
CR	96	41.2	15	28.8	0.21 [‡]
PR	130	55.8	36	69.2	
SD	7	3.0	1	1.9	

pCR = pathologic complete response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; PH-FECH = Taxol / 5-FU / Epirubicin / Cyclophosphamide / Herceptin; TCH = Taxotere / Carboplatin / Herceptin; CI = confidence interval;

[‡]Test for the association of “CR” versus not “CR” with treatment.

Table 3
Multivariate logistic regression model for pathologic complete response

	pCR		
	OR	95% CI	P
PH-FECH vs. TCH	1.45	1.06 - 1.98	0.02
Age: >50 vs. ≤50	1.14	0.68 - 1.91	0.61
Race: Black vs. Non-Black	0.69	0.34 - 1.4	0.30
BMI: Overweight/obese vs. Normal/underweight	1.22	0.69 - 2.14	0.49
ER Status: positive vs. Negative/weak	0.32	0.19 - 0.55	<0.001
Grade: III vs. II	1.81	1.00 - 3.27	0.05
Clinical T: T4 vs. T1-3	0.52	0.27 - 0.98	0.043
Clinical N: N1-3 vs. N0	1.11	0.62 - 1.99	0.73

pCR = pathologic complete response; OR = Odds ratio; CI = confidence interval; PH-FECH = Taxol / 5-FU / Epirubicin / Cytosol / Herceptin; TCH = Taxotere / Carboplatin / Herceptin; BMI= body mass index; ER = estrogen receptor.

Table 4
Three-year recurrence-free and overall survival estimates in patient subgroups

	N Patients	Recurrence-Free Survival			Overall Survival		
		N Events	3-Year Estimates (95% CI)	P	N Events	3-Year Estimates (95% CI)	P
Treatment							
TCH	65	13	0.71(0.52- 0.83)		6	0.86(0.64- 0.95)	
PH-FECH	235	15	0.93(0.88- 0.96)	<0.001	9	0.96(0.91- 0.98)	0.008
Pathologic response							
No pCR	123	17	0.83(0.73- 0.89)		9	0.93(0.85- 0.97)	
pCR	163	7	0.95(0.89- 0.98)	0.003	2	0.98(0.91- 0.99)	0.008
Treatment among pCR *							
TCH	26	3	0.82(0.54- 0.94)		2	0.76(0.34- 0.94)	
PH-FECH	137	4	0.97(0.91- 0.99)	0.008	0	1.00(1.00- 1.00)	<0.001
Age							
50	159	16	0.87(0.79- 0.92)		7	0.95(0.89- 0.98)	
> 50	141	12	0.9(0.83- 0.94)	0.69	8	0.93(0.86- 0.97)	0.55
Race							
Non-Black	256	21	0.91(0.86- 0.94)		10	0.96(0.92- 0.98)	
Black	44	7	0.75(0.54- 0.88)	0.04	5	0.84(0.65- 0.93)	0.009
BMI							
Normal/underwt.	98	7	0.94(0.86- 0.97)		5	0.96(0.89- 0.99)	
Overwt/obese	197	20	0.86(0.79- 0.91)	0.22	10	0.93(0.87- 0.96)	0.80
ER Status							
Negative/weak	136	11	0.91(0.83- 0.95)		7	0.93(0.85- 0.97)	
Positive	161	16	0.87(0.79- 0.92)	0.46	8	0.96(0.9- 0.98)	0.92
Nuclear Grade							
II	71	5	0.94(0.83- 0.98)		3	0.98(0.87- 1.00)	
III	222	22	0.87(0.81- 0.91)	0.36	12	0.93(0.87- 0.96)	0.54
Clinical T Stage							
T1-3	226	13	0.94(0.88- 0.97)		7	0.97(0.93- 0.99)	
T4	71	14	0.73(0.58- 0.84)	<0.001	8	0.84(0.68- 0.92)	0.001

	N Patients	Recurrence-Free Survival			Overall Survival		
		N Events	3-Year Estimates (95% CI)	P	N Events	3-Year Estimates (95% CI)	P
Clinical N Stage							
N0	80	7	0.92(0.82-0.97)		3	0.97(0.88-0.99)	
N1-3	220	21	0.87(0.81-0.92)	0.55	12	0.93(0.88-0.96)	0.37

pCR = pathologic complete response; CI = confidence interval; PH-FECH = Taxol / 5-FU / Epirubicin / Cytosan/ Herceptin; TCH = Taxotere / Carboplatin / Herceptin; BMI= body mass index; ER = estrogen receptor;

* Outcomes of patients who achieved pCR presented by treatment received

Table 5

Adverse events by neoadjuvant systemic chemotherapy type

	PH-FECH (N=235)		TCH (N=65)	
	N	Percent	N	Percent
Cardiac Toxicity				
Grade 1	131	61.5	27	71.1
Grade 2	59	27.7	8	21.1
Grade 3	22	10.3	3	7.9
Grade 4	1	0.5	0	0.0
Cardiac Toxicity				
Grade 1	131	61.5	27	71.1
Grade 2-4	82	38.5	11	28.9
Ejection Fraction, Mean (SD)				
EF at baseline	217	64.3(6.4)	46	64.7(7.0)
EF at 3 months	209	63.1 (5.6)	32	64.0 (6.2)
EF at 6 months	203	61.7 (7.2)	39	62.4 (5.6)
EF at 12 months	152	61.3 (7.7)	34	64.2 (6.1)
EF at 18 months	103	60.8 (7.7)	22	62.0 (7.3)
% EF decrease [‡]	213	8(11)	38	8(8)
Nausea and Vomiting				
None	222	94.5	61	93.8
Grade 3	13	5.5	4	6.2
Diarrhea				
None	228	97.0	62	95.4
Grade 3	7	3.0	3	4.6
Mucositis				
None	231	98.3	65	100.0
Grade 3	4	1.7	0	0.0
Fatigue				
				0.29

	PH-FEC (N=235)		TCH (N=65)		P
	N	Percent	N	Percent	
None	212	90.2	57	87.7	
Grade 3	23	9.8	8	12.3	0.55
Neuropathy					
None	223	94.9	62	95.4	
Grade 3	12	5.1	3	4.6	0.87
Neutropenic Fever					
None	205	87.2	62	95.4	
Grade 3	30	12.8	3	4.6	0.06

T+FEC+H = Taxol / Cytosan / 5-FU / Epirubicin / Herceptin; TCH = Taxotere / Carboplatin / Herceptin.

[†]Two sample t-test.

[‡]Calculated as percent EF drop from baseline to the lowest EF among 3, 6, 12, and 18 months.