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Epirubicin With Cyclophosphamide Followed by Docetaxel With Trastuzumab and Bevacizumab as Neoadjuvant Therapy for HER2-Positive Locally Advanced Breast Cancer or as Adjuvant Therapy for HER2-Positive Pathologic Stage III Breast Cancer: A Phase II Trial of the NSABP Foundation Research Group, FB-5

John W. Smith
National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, Columbia River Oncology Program

Marc E. Buyse
International Drug Development Institute

Priya Rastogi
National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, University of Pittsburgh Cancer Institute

See next page for additional authors

Authors
John W. Smith, Marc E. Buyse, Priya Rastogi, Charles E. Geyer Jr., Samuel A. Jacobs, Erica J. Patocskai, André Robidoux, Alison K. Conlin, Bilal Ansari, George P. Keogh, Philip J. Stella, Howard M. Gross, Raymond S. Lord, Jonathan A. Polikoff, Celine Mauquoi, Eleftherios P. Mamounas, Sandra M. Swain, and Norman Wolmark

Original Study

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John W. Smith, II,[1,2] Marc E. Buyse,[3] Priya Rastogi,[1,4] Charles E. Geyer, Jr,[1,5] Samuel A. Jacobs,[1,4] Erica J. Patocskai,[1,6] André Robidoux,[1,6] Alison K. Conlin,[1,7] Bilal Ansari,[1,8] George P. Keogh,[1,9] Philip J. Stella,[1,10] Howard M. Gross,[1,11] Raymond S. Lord,[1,12] Jonathan A. Polikoff,[1,13] Celine Mauquoi,[3] Eleftherios P. Mamounas,[1,14] Sandra M. Swain,[1,15,16] Norman Wolmark[1,17]

Abstract

We conducted a phase II study in patients with HER2-positive locally advanced breast cancer or pathologic stage 3 breast cancer. Patients received epirubicin with cyclophosphamide followed by docetaxel. Targeted therapy with trastuzumab and bevacizumab were administered for 1 year. The pathologic complete response was comparable with other chemotherapy regimens and the high recurrence-free survival and overall survival are of interest in these high-risk populations.

Background: The purpose of this study was to determine the cardiac safety and clinical activity of trastuzumab and bevacizumab with docetaxel after epirubicin with cyclophosphamide (EC) in patients with HER2-positive locally advanced breast cancer (LABC) or pathologic stage 3 breast cancer (PS3BC). **Patients and Methods:** Patients received every 3 week treatment with 4 cycles of EC (90/600 mg/m^2) followed by 4 cycles of docetaxel (100 mg/m^2). Targeted therapy with standard-dose trastuzumab with bevacizumab 15 mg/kg was given for a total of 1 year. Coprimary end points were (1) rate of cardiac events (CEs) in all patients defined as clinical congestive heart failure with a significant decrease in left ventricular ejection fraction or cardiac deaths; and (2) pathologic complete response (pCR) in breast and nodes in the neoadjuvant cohort. An independent cardiac review panel determined whether criteria

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[1]National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, Pittsburgh, PA
[2]Columbia River Oncology Program, Portland, OR
[3]International Drug Development Institute, Louvain-la-Neuve, Belgium
[4]Department of Medicine, Oncology, University of Pittsburgh Cancer Institute, and Magee-Womens Hospital Womens Cancer Clinic, Pittsburgh, PA
[5]Virginia Commonwealth University Massey Cancer Center, Richmond, VA
[6]Centre hospitalier de l'Université de Montreal (CHUM), Montréal, Québec, Canada
[7]Western Oncology Research Consortium, Portland, OR
[8]Community Clinical Oncology Program (CCOP) Northern Indiana Cancer Research Consortium, Mishawaka, IN
[9]Southeast Clinical Oncology Research Consortium, Roper St Francis Cancer Care, Charleston, SC
[10]Community Clinical Oncology Program (CCOP) Michigan Cancer Research Consortium Community, Ann Arbor, MI
[11]Community Clinical Oncology Program (CCOP) Dayton, Dayton, OH
[12]Community Clinical Oncology Program (CCOP) Kalamazoo, and the West Michigan Cancer Center, Kalamazoo, MI
[13]Kaiser Permanente, San Diego, CA
[14]Department of Oncology, UF Cancer Center at Orlando Health, Orlando, FL
[15]Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC
[16]Georgetown University Medical Center, Washington, DC
[17]Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA

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Address for correspondence: Priya Rastogi, MD, NSABP Foundation, Inc, Nova Tower Two/Two Allegheny Center – 12th Fl, Ste 1249, Pittsburgh, PA 15212
Fax: 412-697-6623; e-mail contact: rastogip@upmc.edu

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for a CE were met. **Results:** A total of 105 patients were accrued, 76 with LABC treated with neoadjuvant therapy and 29 with PS3BC treated with adjuvant therapy. Median follow-up was 59.2 months. Among 99 evaluable patients for cardiac safety, 4 (4%; 95% confidence interval [CI], 1.1%-10.0%) met CE criteria. The pCR percentage in LABC patients was 46% (95% CI, 34%-59%). Five-year recurrence-free survival (RFS) and overall survival (OS) for all patients was 79.9% and 90.8%, respectively. **Conclusion:** The regimen met predefined criteria for activity of interest with an acceptable rate of CEs. Although the pCR percentage was comparable with chemotherapy regimens with trastuzumab alone the high RFS and OS are of interest in these high-risk populations.

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Introduction

Results from 4 large adjuvant trials showed that incorporating trastuzumab into standard adjuvant chemotherapy regimens provided substantial improvements in outcomes for women with HER2-positive breast cancer.[1-5] Despite these impressive results, some patients will develop recurrences after trastuzumab-based adjuvant therapy, so efforts to identify more effective regimens are appropriate.

Preclinical data show that increased expression of vascular endothelial growth factor (VEGF) is associated with HER2 overexpression and occurs downstream of the activated HER2 signaling pathway.[6,7]

In HER2-overexpressing xenografts treatment with bevacizumab, a humanized monoclonal antibody directed at VEGF, and trastuzumab results in a significantly greater reduction in tumor volume than with either treatment alone.[8] A correlative study that evaluated specimens from an adjuvant trial of chemotherapy regimens showed that women with HER2-positive breast cancers were more likely to express high levels of VEGF than their HER2-negative counterparts. Women whose tumors contained high levels of HER2 and VEGF had the worst clinical outcome of any subgroup.[9]

The combination of trastuzumab and bevacizumab was shown to be feasible in a phase I study.[10] A phase II study of the combination as first-line treatment in women with HER2-positive advanced breast cancer showed an objective clinical response of 48%, median time to progression of 7.1 months, and median overall survival (OS) of 43.8 months.[11]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation FB-5 was a phase II study that evaluated the safety of incorporating bevacizumab into a standard neoadjuvant/adjuvant regimen of sequential anthracycline with cyclophosphamide treatment followed by docetaxel with trastuzumab. The primary safety aim was to determine the cardiac safety of dual antibodies administered with chemotherapy. The primary efficacy aim was to evaluate the activity of the regimen as neoadjuvant therapy for locally advanced breast cancer (LABC) by assessing pathologic complete response (pCR) in the breast and nodes. The secondary end points were to evaluate 5-year recurrence-free survival (RFS) and OS, noncardiac toxicities for all patients, and pCR for breast cancer patients, clinical complete response (cCR), and surgical complications in patients who received neoadjuvant therapy.

All authors had full access to the data in the study; Dr Buyse and Celine Mauquoi take responsibility for the data analyses.

Patients and Methods

Patient Eligibility and Entry Procedures

Women who presented with clinical stage IIIA, IIIB, or IIIC invasive primary HER2-positive breast cancer diagnosed using core or limited incisional biopsy were eligible to receive neoadjuvant therapy in cohort A.

The primary breast tumor had to measure $\geq$2.0 cm in clinical examination unless inflammatory breast cancer was present. Women with resected pN2 (4-9 nodes) or pN3 ($\geq$10 nodes) breast cancer comprised cohort B. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate bone marrow, renal, and hepatic functions. The left ventricular ejection fraction (LVEF) assessed using echocardiogram (multigated acquisition (MUGA) scan could be substituted on the basis of institutional preference) before study entry had to be $\geq$55%, regardless of the institution's lower limit of normal. Patients with active cardiac disease, Grade $\geq$2 peripheral neuropathy, or metastatic disease, were ineligible. The study was approved by local institutional review boards in accordance with assurances filed with and approved by the Department of Health and Human Services. Patients were required to give written consent to enter the study.

Treatment

Chemotherapy in both cohorts consisted of epirubicin 90 mg/m^2 intravenously (I.V.) and cyclophosphamide 600 mg/m^2 I.V. (EC) on day 1 every 21 days for 4 cycles followed by docetaxel 100 mg/m^2 I.V. on day 1 every 21 days for 4 cycles supported by pegfilgrastim 6 mg subcutaneous on day 2 or 3 after docetaxel treatment. Patients received weekly trastuzumab (first dose, 4 mg/kg I.V. and subsequent doses 2 mg/kg I.V.) concurrently with docetaxel. After completion of docetaxel treatment, patients received trastuzumab 6 mg/kg every 21 days to complete a year of trastuzumab treatment.

In cohort A, bevacizumab 15 mg/kg was initiated with the last cycle of EC and administered every 3 weeks with the first 3 cycles of docetaxel, held for surgery, then resumed postoperatively and administered with trastuzumab for a year. In cohort B, bevacizumab was initiated with the first cycle of docetaxel at 15 mg/kg every 3 weeks and administered with trastuzumab for a year.

Patients who received neoadjuvant therapy underwent lumpectomy or mastectomy after recovery from chemotherapy. Patients who received adjuvant therapy were eligible after mastectomy or lumpectomy. Breast reconstruction with implants and use of tissue expanders was prohibited with bevacizumab treatment and for at least 3 months after the last dose. It was recommended that breast

reconstruction be delayed for at least 6 months after completion of bevacizumab treatment.

Patients with hormone receptor-positive tumors were to receive endocrine therapy for a minimum of 5 years. Radiotherapy to the chest wall was required when postmastectomy microscopic margins were positive and otherwise was at investigator discretion along with regional node radiotherapy. Whole-breast radiotherapy and regional nodal radiotherapy were recommended for patients who had undergone a lumpectomy. Partial breast radiotherapy was prohibited. Evaluation of LVEF using echocardiogram (assessment using MUGA scan was permitted) was performed at baseline, after EC (before docetaxel), approximately 6 months from study entry, and at 9, 12, 15, and 18 months after study entry. All symptoms suggestive of possible congestive heart failure (CHF) were reported within 14 days. Source documents were reviewed by an independent cardiac review panel consisting of 2 cardiologists who independently determined whether criteria for a cardiac event (CE) were met. If one cardiologist considered the case to be a CE, the case was considered an event. During 5 years of follow-up, at each visit, specific data were collected for Grades 2 to 5 left ventricular systolic dysfunction and Grades 2 to 5 cardiac ischemia/infarction.

The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used to grade the severity of adverse events.

Tumor Assessment and Evaluation of Response (Cohort A)

Pathologic complete response in the breast and lymph nodes was defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel lymph nodes identified after preoperative chemotherapy. Specimens in which only noninvasive cancer was found were also classified as pCR. Assessment of pCR was made by institutional pathologists without central review.

Clinical tumor measurement by physical examination was required before study entry to determine eligibility. Protocol-required tumor assessments by physical examination were performed between EC and docetaxel treatment and after the last cycle of docetaxel to determine the presence or absence of cCR, defined as the disappearance of all lesions with no evidence of progressive disease.

Recurrence-free survival was defined as the time from the first dose of EC therapy until the first date of recurrence (ipsilateral or regional invasive breast cancer recurrence or distant recurrence) or the date of death from any cause in evaluable patients who were rendered free of disease with surgery. Patients in whom disease had not recurred or had not died were censored at their last date of assessment. OS in evaluable patients was measured from the first dose of study therapy until the date of death from any cause. Patients who had not died were censored at their last contact date.

Statistical Methods

The primary cardiac safety end point was the rate of overall CEs in cohorts A and B. CEs were defined as New York Heart Association class III/IV CHF with either a decrease in LVEF to $<50\%$ or a decrease from baseline LVEF of >10 percentage points to 50% to 54%, and cardiac deaths (death due to CHF, myocardial infarction, documented primary arrhythmia, or sudden death without documented etiology). CEs were analyzed on the basis of review by a cardiac advisory panel.

The study was designed with a 2-stage optimum design.[12] The overall sample size of the trial was chosen to reject, with high probability (0.99), a regimen having a true CE rate $>11\%$ and to accept, with high probability (0.99), a regimen having a true CE rate $\leq 1\%$. A sample size of a total of 100 evaluable patients in cohorts A and B was needed to define the primary safety end point in the trial. All patients who received any treatment with trastuzumab and bevacizumab were considered evaluable. Assuming for 5% nonevaluable patients, a total of 105 patients were entered in the trial.

The efficacy primary end point was the pCR rate in the breast and axillary lymph nodes in the evaluable patients in cohort A. The decision rule stated that the regimen would be considered worthy of further investigation if this rate reached 25%.

After study therapy was completed, patients had follow-up visits every 6 months through year 5 from study entry. The following secondary end points were analyzed with a descriptive intent only: toxicities, RFS and OS for evaluable patients in cohorts A and B, and pCR in breast, cCR, and surgical complications for evaluable patients in cohort A.

The proportions were estimated with their 2-sided exact 95% confidence interval (CI). The 5-year RFS and OS were estimated using the Kaplan–Meier method.

Adverse events were analyzed according to treatment regimen.

Results

Patient Population and Tumor Characteristics

From April 2007 to May 2009, 105 women were accrued, 76 in cohort A and 29 in cohort B. The evaluable population for the cardiac safety analysis consisted of 99 patients, because 6 of the 76 patients in cohort A did not initiate docetaxel-based therapy (THB). Seventy patients were evaluable for the primary efficacy end point of pCR in breast and nodes. These 70 patients and all of the 29 patients in cohort B were evaluable for the secondary end points of RFS and OS. Median follow-up was 59.2 months.

Patient characteristics are provided in Table 1.

Therapy, Compliance, and Adverse Events

Four cycles of EC were completed in 104 (99%) patients. One patient had progressive disease after 3 cycles of EC in cohort A (Figure 1) and was removed from the study. Five additional patients in cohort A did not start THB: 4 for side effects/complications and 1 for disease progression/treatment failure. Four cycles of THB were completed in 93 of the 99 patients who began THB. Five did not complete THB because of side effects/complications, and 1 for withdrawal/patient refusal. Two patients who did not complete THB resumed postchemotherapy bevacizumab and trastuzumab treatment. Two patients in cohort A, who completed THB, discontinued treatment after surgery because of side effects/complications.

After THB, 93 patients continued trastuzumab treatment. Of these 93 patients 14 received 1 to 6 doses, 6 received 7 to 9 doses, and 73 received ≥ 10 doses. Postchemotherapy bevacizumab treatment was continued in 79 patients: 24 patients received 1 to 6 doses, 9 patients received 7 to 9 doses, and 46 patients received ≥ 10 doses. Postchemotherapy bevacizumab was discontinued because of side effects/complications (26 patients), disease progression/

Table 1 Demographic and Tumor Characteristics of Patients in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5

Characteristic	n (%)
Race	
White	91 (87)
Black or African American	13 (12)
Asian	1 (1)
Age, Years	
<50	49 (47)
50-59	35 (33)
>59	21 (20)
Clinical Stage, Cohort A	
IIIA	38 (50)
IIIB	26 (34)
IIIC	12 (16)
Resected Stage III, Cohort B	
pN2	14 (48)
pN3	15 (52)
Clinical Evidence of IBC[a], Cohort A	
Yes	19 (25)
No	57 (75)
Hormone Receptor Status (ER, PR)	
Either positive	62 (59)
Both negative	43 (41)

The sixth edition of the American Joint Committee on Staging was used.
Abbreviations: ER = estrogen receptor; IBC = inflammatory breast cancer; PR = progesterone receptor.
[a]IBC (T4d) included in IIIB unless N3 nodes present.

treatment failure (4 patients), patient preference (1 patient), and other reasons (4 patients).

Of the 76 patients in cohort A, 74 were rendered disease-free with surgery. Two patients were unable to undergo surgery: 1 for disease progression/treatment failure and 1 for side effects/complications. Both occurred during EC treatment before initiation of docetaxel and targeted therapies and the patients were removed from the study per the investigator.

Whole-breast/chest wall and regional lymph node radiotherapy was administered to 89 (85%) of the 105 patients entered. Six additional patients had whole-breast/chest wall radiotherapy without regional lymph node radiotherapy.

Toxicity

Cardiac Toxicity. Among the 99 patients evaluable for cardiac safety, 4 (4%; 95% CI, 1.11-10.02) met criteria for a CE (4 CHFs and no cardiac deaths). On the most recent evaluations of LVEF measurements, 2 of the 4 patients had recovered LVEF to at least 50%. One patient's ejection fraction remained at 23% at the 18-month evaluation. The other patient's ejection fraction improved to >45%.

Grade 2 and 3 LVEF systolic dysfunction was reported in 14 (14%) and 4 (4%) patients, respectively. Mean LVEF values at baseline and during the treatment and early follow-up period are shown in Figure 2.

Overall Toxicity. Selected Grade 2 to 4 adverse events during EC therapy are provided in Supplemental Table 2. Additional important toxicities in <10% of patients were Grade 3 febrile neutropenia (3%) and Grade 2 left systolic ventricular dysfunction (2%).

Grade 2 to 4 adverse events during THB are listed in Supplemental Table 2. Grade 2 and 3 fatigue occurred in 37% and 13%, respectively. Mucositis (functional/symptomatic) was also common with Grade 2 in 30% and Grade 3 in 4% of patients. Other important toxicities were Grade 2 and 3 hypertension (8% and 7%, respectively), Grade 2 and 3 left systolic ventricular dysfunction (5% and 1%, respectively), and Grade 3 febrile neutropenia (3%).

Grade 2 to 4 adverse events during targeted therapy alone are provided in Supplemental Table 2. Important Grade 2 and 3 toxicities were, respectively, fatigue (26% and 5%), hypertension (22% and 12%), and joint pain (15% and 1%). Grade 2 left ventricular systolic dysfunction was reported in 8 patients (9%).

Surgical complications for cohort A are provided in Supplemental Table 1 in the online version.

Clinical and Pathologic Responses to Preoperative Therapy (Cohort A)

A pCR in the breast and nodes was documented in 32 of the 69 patients (46%; 95% CI, 34.3-58.8) who initiated bevacizumab and trastuzumab treatment and for whom axillary nodal status was reported. No lymph nodes were identified in an axillary dissection of 1 patient, so pCR rate in the breast could be assessed in 70 patients and was 51% (36 of 70; 95% CI, 39.2-63.6). Among patients with hormone receptor-negative breast cancer the pCR rate in breast and nodes was 59% (19 of 31 patients) and was 34% (13 of 38) in patients with receptor-positive disease. The pCR for breast and nodes for patients with inflammatory breast cancer was 50% (9 of 18).

The cCR on the basis of investigator assessment (using physical examination) after EC therapy was 17% (12 of 70; 95% CI, 9.2-28) and 61% (43 of 70 patients; 95% CI, 49-72.8) after THB.

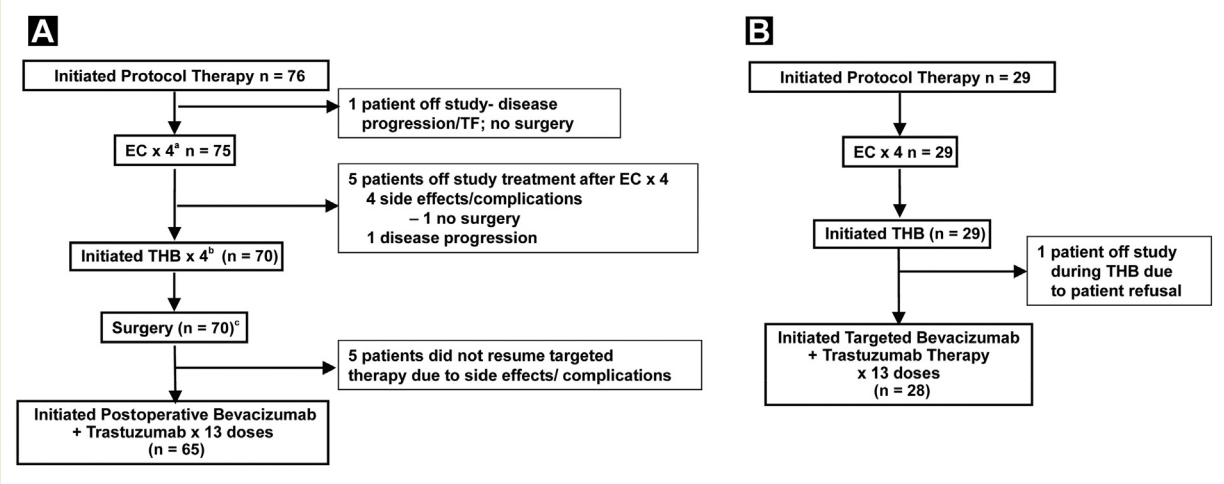
Recurrence-Free Survival and OS

Among the 99 evaluable patients in both cohorts the 5-year RFS was 79.9% (95% CI, 70.0-86.8; Figure 3) and 5-year OS was 90.8% (95% CI, 83.0-95.1; Figure 3). The 5-year RFS for the evaluable patients in cohort A, all of whom were rendered free of disease at surgery, was 76% (95% CI, 63.5-84.7) and was 89.7% (95% CI, 71.2-96.5) for cohort B. The 5-year OS for cohort A and B was 86.9% (95% CI, 76.3-93.0) and 100%, respectively (Figure 3). Five-year RFS and OS for cohort A was 74.4% and 80.5% for the estrogen receptor (ER)- and progesterone receptor (PR)-negative subset and 77.3% and 92.1% for the ER- or PR-positive group, respectively, and for cohort B was 75% and 100% for ER- and PR-negative breast cancer and 95.2% and 100% for the ER- or PR-positive group, respectively (see Supplemental Figure 1 in the online version). The 5-year RFS and OS for patients with inflammatory breast cancer were 65.7% and 77.8%, respectively, as shown in Supplemental Figure 2 in the online version.

Discussion

In the NSABP FB-5 study, the combination of bevacizumab with a regimen of EC followed by docetaxel/trastuzumab did not increase the expected rate of cardiac toxicity, because the 4% incidence of severe CEs

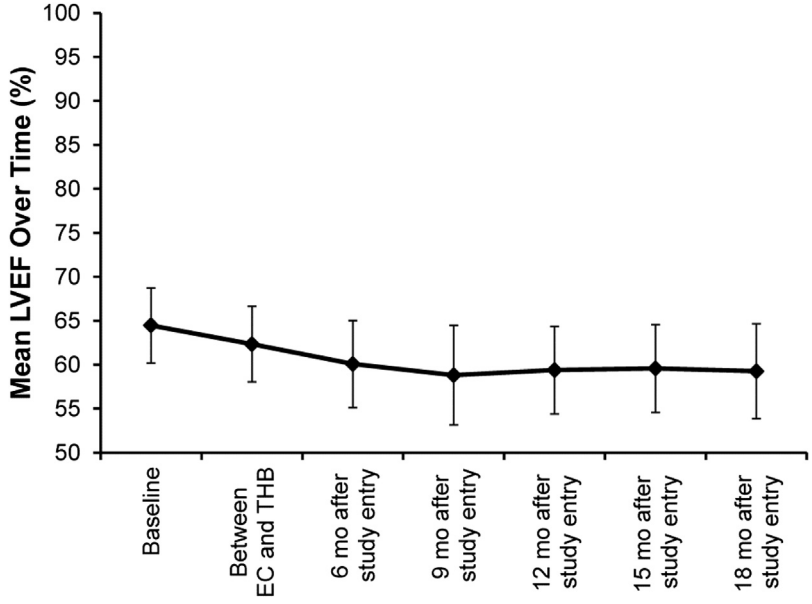
Figure 1 Consolidated Standards of Reporting Trials Diagram. (A) Cohort A: Neoadjuvant Therapy; (B) Cohort B: Adjuvant Therapy



Abbreviations: EC = epirubicin with cyclophosphamide therapy; TF = treatment failure; THB = docetaxel with trastuzumab with bevacizumab therapy.
[a]Bevacizumab given with ec cycle 4 only; [b]Bevacizumab given with initial 3 cycles of thb; [c]74 Patients had surgery including patients who discontinued therapy prior to surgery.

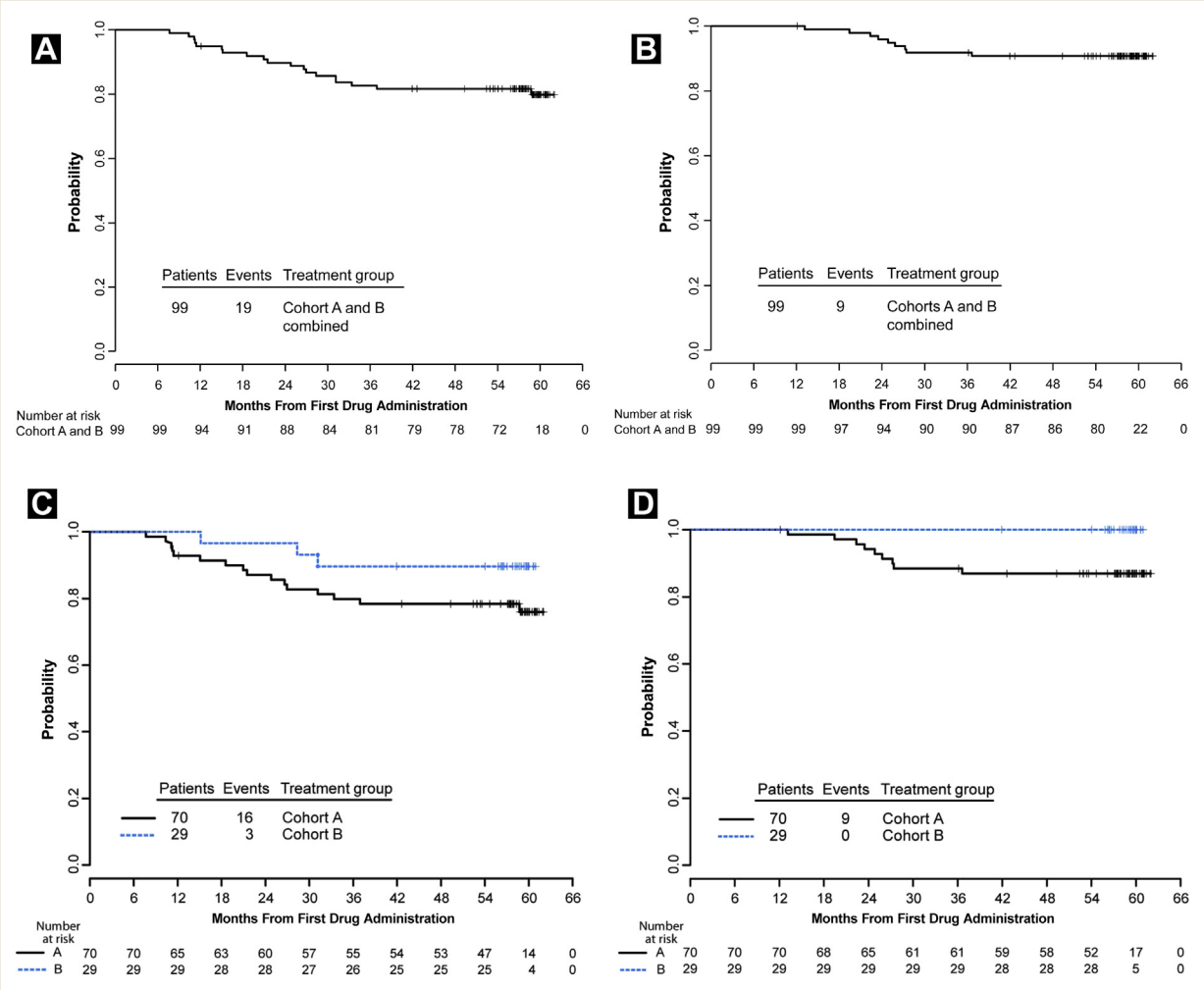
was similar to that reported in NSABP B-31.[13] Additionally, there were no late CEs with 5 years of follow-up on the basis of specific queries on the follow-up form. The safety profile of bevacizumab used in combination with the study regimen was also consistent with the known toxicities of the chemotherapy and targeted agents. In the neoadjuvant cohort, the regimen met prespecified criteria for activity of interest with a pCR rate in the breast and nodes of 46% in HER2-positive LABC. In triple-positive LABC, the pCR for breast and nodes was 34% and was 59% in those who were hormone receptor-negative. Secondary efficacy end points of RFS and OS were notable in this high-risk patient population. In the evaluable patients who received neoadjuvant treatment, the 5-year RFS and OS were 76% and 86.9%, respectively. In the hormone receptor-negative patients 5-year RFS and OS were 74.4% and 80.5%, respectively, and in the triple positive group were 77.3% and 92.1%,

Figure 2 Mean Left Ventricular Ejection Fraction (LVEF) Over Time in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5



Abbreviations: EC = epirubicin plus cyclophosphamide; THB = docetaxel with trastuzumab with bevacizumab therapy.
Six months after study entry includes for cohort a, after surgery, and for cohort b, after the last dose of docetaxel.

Figure 3 (A) Recurrence-Free Survival and (B) Overall Survival for Combined Cohorts A and B in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5. (C) Recurrence-Free Survival and (D) Overall Survival in Evaluable Patients in Cohorts A and B in NSABP FB-5



respectively. Five-year RFS and OS were even more striking in the 29 patients who received adjuvant therapy and presented with N2 or N3 disease (89.7% and 100%, respectively), compared with the 76% 5-year OS in similar patients in NSABP B-31 who were treated with adjuvant chemotherapy and trastuzumab.

The NeOAdjuvant Herceptin (NOAH) trial[14,15] evaluated the combination of trastuzumab with neoadjuvant chemotherapy in a similar population of women with HER2-positive locally advanced or inflammatory breast cancer, and also has reported pCR and long-term outcomes. Because NOAH reported pCR, event-free survival, and OS on the basis of all 117 patients randomly assigned to the trastuzumab and chemotherapy group, we also determined the pCR for breast and node rate and the 5-year OS for all 76 patients in cohort A (see Supplemental Figure 3 in the online version). The pCR rates in breast and node in the trials were similar: 38% for NOAH and 45% in all 76 patients who received neoadjuvant therapy in FB-5. The 5-year OS rate among all of the patients who received neoadjuvant treatment in FB-5 (84%) was somewhat higher than in NOAH (74%). Of interest, when the 5-year OS was compared according to hormone receptor status, although there was no difference among ER- and PR-negative patients between FB-5 and NOAH (76% vs. 78%), a striking difference was present in the triple-positive patients: 90% for FB-5 versus 65% for NOAH.

It is difficult to explain the favorable long-term outcomes in FB-5 in light of the negative results of the Bevacizumab with Trastuzumab Adjuvant Therapy in HER2+ Breast Cancer (BETH)[16] trial, which evaluated the combination of bevacizumab with standard adjuvant chemotherapy regimens in combination with trastuzumab. Most patients in BETH received TCH (taxotere carboplatin herceptin) with or without bevacizumab and only 21% had N2 or N3 disease. Patients who received chemotherapy and trastuzumab had a 3-year invasive disease-free survival of 90%, so improvements shown with the combination of bevacizumab in the relatively low-risk population entered into BETH might have precluded observation of some benefit in high-risk patients.

Conclusion

Because of the activity and safety of dual HER-targeted therapy with trastuzumab and pertuzumab combined with chemotherapy in the metastatic and neoadjuvant settings,[17-20] it is difficult to justify further evaluation of bevacizumab administered with trastuzumab in the treatment of HER2-positive LABC despite the encouraging findings in NSABP FB-5.

Clinical Practice Points

- Neoadjuvant studies that assess pCRs allow for rapid evaluation of the benefit of new treatments.
- The safety profile of bevacizumab combined with this regimen was consistent with the known toxicities of chemotherapy and targeted agents.
- In the neoadjuvant cohort, the regimen met prespecified criteria for activity of interest with a pCR rate in the breast and nodes of 46% in HER2-positive LABC.
- Favorable long-term outcomes were notable in this high-risk patient population.
- Because of the activity and safety of pertuzumab and trastuzumab combined with chemotherapy, it is difficult to justify further evaluation of bevacizumab administered with trastuzumab in this setting, despite the encouraging findings in this trial.

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Disclosure

Marc E. Buyse, ScD discloses employment and stock/ownership interests in the International Drug Development Institute (IDDI). Sandra M. Swain, MD, FACP discloses a research grant to institution from Genentech/Roche; honorarium from Roche; travel funds from Genentech; and has served, uncompensated, on steering committees for Genentech/Roche. Celine Mauquoi, MSc discloses employment at and travel expenses from IDDI. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures and tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2016.07.008.

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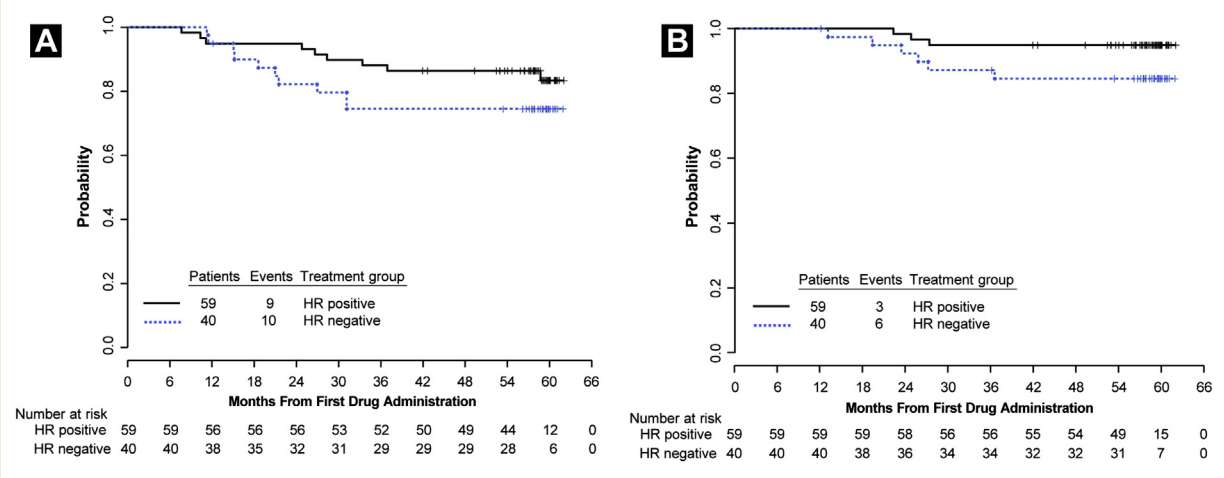
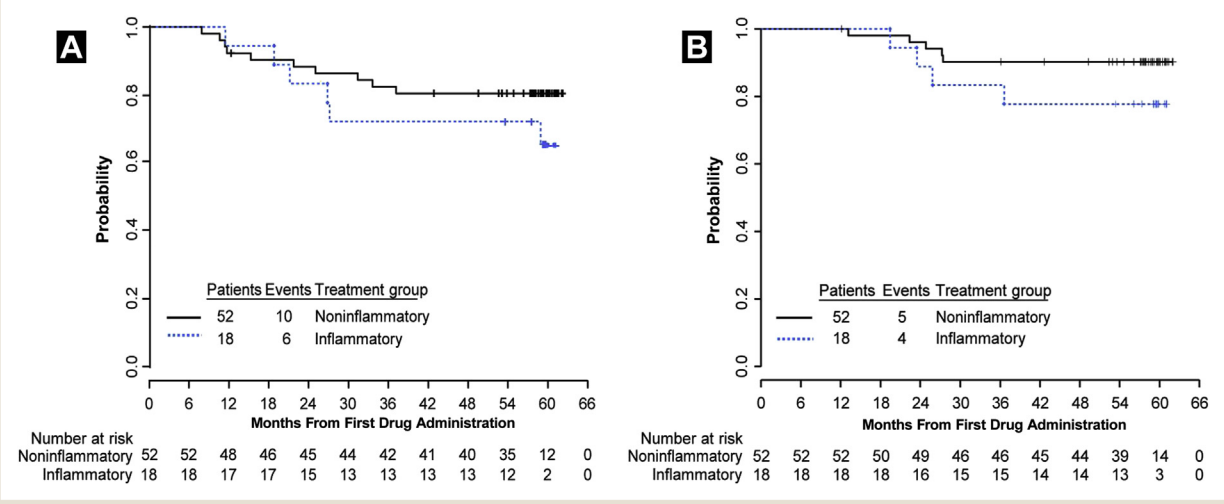
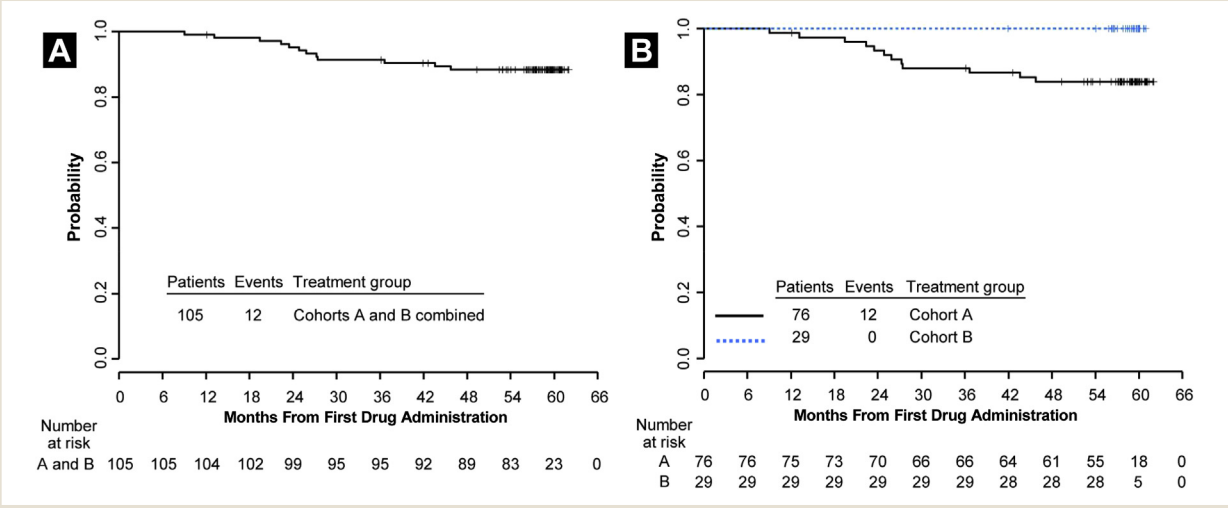
Supplemental Figure 1 (A) Recurrence-Free Survival and (B) Overall Survival According to Hormone Receptor (HR) Positive and Negative Breast Cancer in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5



Supplemental Figure 2 (A) Recurrence-Free Survival and (B) Overall Survival of Inflammatory and Noninflammatory Breast Cancer in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5



Supplemental Figure 3 All Patients Entered in Study for National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5. Overall Survival (A) for Combined Cohorts A and B; and (B) Cohorts A and B for NSABP FB-5



Supplemental Table 1 Surgical Complications of Patients in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5 for Cohort A (Total Patients With at Least 1 Complication)

Toxicity	CTCAE Version 3.0 Grade (n = 74), n (%)	
	Grade 2	Grade 3
One or More Complications	21 (28)[a]	11 (15)[a]
Seroma[b]	13 (18)	3 (4)
Wound Complications, Noninfectious[c]	4 (5)	3 (4)
Infection With Normal ANC or Grade 1 or 2 Neutrophils	5 (7)	8 (11)
Hematoma[d]	2 (3)	0

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.
[a]More than 1 complication could occur in 1 patient.
[b]Grade 2, simple aspiration; Grade 3, interventional radiology or surgical intervention.
[c]Grade 2, incisional separation >25%; Grade 3, fascial disruption or primary wound closure.
[d]Grade 2, simple aspiration; Grade 3, interventional radiology or surgical intervention.

Supplemental Table 2 Commonly Observed Grade 2-4 Adverse Events that Occurred in at Least 10% of Patients and Adverse Events of Special Interest According to CTCAE Version 3.0 in National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-5

Adverse Event	Grade 2	Grade 3	Grade 4
With EC Treatment (n = 105)			
Dehydration	11 (10)	1 (1)	0
Fatigue	34 (32)	3 (3)	0
Febrile neutropenia[a]	0	3 (3)	0
Headache	13 (12)	2 (2)	0
LVSD[a]	2 (2)	0	0
Nausea	25 (24)	2 (2)	0
Neutrophils	13 (12)	8 (8)	2 (2)
Thrombosis/embolism[a]	0	1 (1)	0
Vomiting	17 (16)	2 (2)	0
With THB Treatment (n = 99)			
Diarrhea	16 (16)	2 (2)	0
Fatigue	37 (37)	13 (13)	0
Febrile neutropenia[a]	0	3 (3)	0
Hand-foot	8 (8)	2 (2)	0
Hemorrhage			
GI	1 (1)	1 (1)	0
Nose	5 (5)	0	0
Hypertension	8 (8)	7 (7)	0
LVSD[a]	5 (5)[b]	1 (1)	0
Mucositis			
Functional/symptomatic	30 (30)	4 (4)	0
Clinical examination	11 (11)	2 (2)	0
Nail changes	12 (12)	0	0
Nausea	14 (14)	0	0
Rash	12 (12)	1 (1)	0
Sensory neuropathy	11 (11)	5 (5)	0
Taste alteration	14 (14)	0	0
Thrombosis/embolism[a]	0	1 (1)	0
Vomiting	10 (10)	1 (1)	0
Watery eye	9 (9)	2 (2)	0
Pain			
Bone	24 (24)	7 (7)	0
Muscle	23 (23)	7 (7)	0
Joint	17 (17)	3 (3)	1 (1)
Headache	8 (8)	1 (1)	1 (1)
During Targeted Therapy Alone (n = 93)			
Depression	8 (9)	1 (1)	1 (1)
Fatigue	24 (26)	5 (5)	0
Hemorrhage			
GI	1 (1)	0	0
Hot flashes	13 (14)	0	0
Hypertension	20 (22)	11 (12)	1 (1)
LVSD[a]	8 (9)[b]	0	0
Nail changes	13 (14)	1 (1)	0
Proteinuria	3 (3)	0	0
Rash	10 (11)	0	0
Sensory neuropathy	13 (14)	1 (1)	0
Pain			
Joint	14 (15)	1 (1)	0
Bone	12 (13)	0	0
Headache	8 (9)	2 (2)	0

Data are presented as n (%).
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; EC = epirubicin with cyclophosphamide; GI = gastrointestinal; LVSD = left ventricular systolic dysfunction; THB = docetaxel with trastuzumab and bevacizumab.
[a]Toxicity <10% (listed because of clinical significance).
[b]One patient with Grade 2 left ventricular ejection fraction (LVEF) had an asymptomatic decrease in LVEF during THB treatment. LVEF recovered and the patient resumed targeted therapy. She had a decrease in LVEF as a second event during targeted therapy.