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Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomes of a phase 3, randomised controlled trial

Harry D Bear, **Gong Tang**, **Priya Rastogi**, **Charles E Geyer Jr**, **Qing Liu**, **André Robidoux**, **Luis Baez-Diaz**, **Adam M Brufsky**, **Rita S Mehta**, **Louis Fehrenbacher**, **James A Young**, **Francis M Senecal**, **Rakesh Gaur**, **Richard G Margolese**, **Paul T Adams**, **Howard M Gross**, **Joseph P Costantino**, **Soonmyung Paik**, **Sandra M Swain**, **Eleftherios P Mamounas**, and **Norman Wolmark**

National Surgical Adjuvant Breast and Bowel Project (NSABP/NRG Oncology), Pittsburgh, PA, USA (Prof H D Bear MD, P Rastogi MD, Prof C E Geyer Jr MD, Prof A Robidoux MD, L Baez-Diaz MD, Prof A M Brufsky MD, Prof R S Mehta MD, L Fehrenbacher MD, J A Young MD, F M Senecal MD, R Gaur MD, R G Margolese MD, P T Adams MD, H M Gross MD, Prof S Paik MD, Prof S M Swain MD, E P Mamounas MD, Prof N Wolmark MD);Virginia Commonwealth University School of Medicine and the Massey Cancer Center, Richmond, VA, USA (Prof H D Bear, Prof C E Geyer Jr); NRG Oncology and the University of Pittsburgh, Pittsburgh, PA, USA (G Tang PhD, Q Liu PhD, Prof J P Costantino DrPH); University of Pittsburgh Cancer Institute,

Correspondence to: Prof Harry D Bear, Box 980011, Division of Surgical Oncology, VCUHS, Richmond, VA 23298-0011, USA, hdbear@vcu.edu.

Contributors

HDB participated in the literature review, study design, data collection and validation, data interpretation, and writing and editing of the report. GT made contributions towards the study design, data collection, data analysis and interpretation, and writing of the report. PR provided oversight during accrual and follow-up, review and interpretation of the data, and drafting and editing of the report. CEG helped design and write the clinical trial protocol, provided oversight of the trial during accrual and follow-up, participated in review and interpretation of the data, and helped draft and edit the report.

QL provided data analysis. AR contributed to the study design, data collection, data analysis, and data interpretation, and writing of the report. LB-D approved the publication. AMB contributed to patient recruitment, data collection, report writing, and review of the report. RSM contributed to the literature search, writing, data interpretation, and data collection. LF was involved in group discussions regarding study design, patient accrual, data collection, data interpretation, and in report writing. JAY reviewed the data and provided review and feedback on the report. FMS primarily contributed to data collection. RG contributed to data collection and writing. RGM contributed to study design, writing, and data collection. PTA provided approval of the report and enrollment of study participants. HMG contributed patient accrual, data collection, data analysis, editing, and writing. JPC contributed to study design, data collection, data interpretation, and writing. SP contributed to design and writing of the clinical protocol and its translational research section, secured funding, and served as the central pathologist to coordinate biospecimen collection and banking. He also contributed to data analysis and interpretation as well as writing of the report and its final approval. SMS contributed to study design, data interpretation, and writing. EPM contributed to study design, data collection, data analysis, data interpretation, and writing. NW contributed to the study concept, provided administrative support, and manuscript approval.

Declarations of interests

HDB reports grants from the National Cancer Institute during the conduct of the study, and has received honorarium payments for continuing medical education activities from Genentech (Roche) outside of the submitted work. GT has served on a data monitoring committee at Incyte Corp. CEG Jr reports travel to serve on the steering committee for a clinical trial sponsored by Abbvie and a clinical trial sponsored by the NCI and Astra Zeneca, local principal investigator grants from Incyte, and travel to serve as an uncompensated member of a Genentech Advisory Board outside of the submitted work. AMB reports consultant fees from Roche/Genentech outside of the submitted work. JPC reports grants from the National Cancer Institute during the conduct of the study. SMS reports grants, personal fees, and travel fees from Genentech/Roche during the conduct of the study; and grants from Pfizer, grants from Puma, and personal fees from Clinigen outside of the submitted work. EPM reports holding a position on the speakers bureau from Genentech/Roche. NW discloses National Cancer Institute grants and support from Lilly and Roche Genentech, which provided funding for research sites to support costs not covered by a National Cancer Institute grant. Other authors declare no competing interests.

University of Pittsburgh, Pittsburgh, PA, USA (P Rastogi); Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada (Prof A Robidoux); Minority-Based CCOP, San Juan, Puerto Rico (L Baez-Diaz); University of Pittsburgh Cancer Institute, Magee Womens Hospital, Pittsburgh, PA, USA (Prof A M Brufsky); University of California at Irvine, Division of Hematology/Oncology, Chao Family Comprehensive Cancer Center, Orange, CA, USA (Prof R S Mehta); Kaiser Permanente Oncology Clinical Trials, Northern California, Vallejo, CA, USA (L Fehrenbacher); Colorado Cancer Research Program, Colorado Springs, CO, USA (J A Young); Northwest Medical Specialties, Tacoma, WA, USA (F M Senecal); CCOP, Kansas City, MO, USA (R Gaur); Jewish General Hospital, McGill University, Montréal, QC, Canada (R G Margolese); Genesys Regional Medical Center, Grand Blanc, MI, USA (P T Adams); CCOP, Dayton, Dayton, OH, USA (H M Gross); Severance Biomedical Science Institute and Department of Medical Oncology, Yonsei University College of Medicine, Seoul, Korea (Prof S Paik); Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC, USA (Prof S M Swain); UF Health Cancer Center at Orlando Health, Orlando, FL, USA (E P Mamounas); and Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA, USA (Prof N Wolmark)

Abstract

Background—NSABP B-40 was a 3 × 2 factorial trial testing whether adding capecitabine or gemcitabine to docetaxel followed by doxorubicin plus cyclophosphamide neoadjuvant chemotherapy would improve outcomes in women with operable, HER2-negative breast cancer and whether adding neoadjuvant plus adjuvant bevacizumab to neoadjuvant chemotherapy regimens would also improve outcomes. As reported previously, addition of neoadjuvant bevacizumab increased the proportion of patients achieving a pathological complete response, which was the primary endpoint. We present secondary patient outcomes, including disease-free survival, a specified endpoint by protocol, and data for distant recurrence-free interval, and overall survival, which were not prespecified endpoints but were collected prospectively.

Methods—In this randomised controlled trial (NSABP B-40), we enrolled women aged 18 years or older, with operable, HER2-non-amplified invasive adenocarcinoma of the breast, 2 cm or greater in diameter by palpation, clinical stage T1c–3, cN0, cN1, or cN2a, without metastatic disease and diagnosed by core needle biopsy. Patients received one of three docetaxel-based neoadjuvant regimens for four cycles: docetaxel alone (100 mg/m^2) with addition of capecitabine (825 mg/m^2 oral twice daily days 1–14, 75 mg/m^2 docetaxel) or with addition of gemcitabine (1000 mg/m^2 days 1 and 8 intravenously, 75 mg/m^2 docetaxel), all followed by neoadjuvant doxorubicin and cyclophosphamide (60 mg/m^2 and 600 mg/m^2 intravenously) every 3 weeks for four cycles. Those randomly assigned to bevacizumab groups were to receive bevacizumab (15 mg/kg, every 3 weeks for six cycles) with neoadjuvant chemotherapy and postoperatively for ten doses. Randomisation was done (1:1:1:1:1:1) via a biased-coin minimisation procedure to balance the characteristics with respect to clinical nodal status, clinical tumour size, hormone receptor status, and age. Intent-to-treat analyses were done for disease-free survival and overall survival. This study is registered with ClinicalTrials.gov, number NCT00408408.

Findings—Between Jan 5, 2007, and June 30, 2010, 1206 patients were enrolled in the study. Follow-up data were collected from Oct 31, 2007 to March 27, 2014, and were available for overall survival in 1186 patients, disease-free survival in 1184, and distant recurrence-free interval in 1181. Neither capecitabine nor gemcitabine increased disease-free survival or overall survival.

Median follow-up was 4.7 years (IQR 4.0–5.2). The addition of bevacizumab significantly increased overall survival (hazard ratio 0.65 [95% CI 0.49–0.88]; p=0.004) but did not significantly increase disease-free survival (0.80 [0.63–1.01]; p=0.06). Four deaths occurred on treatment due to vascular disorder (docetaxel plus capecitabine followed by doxorubicin plus cyclophosphamide group), sudden death (docetaxel plus capecitabine followed by doxorubicin plus cyclophosphamide group), infective endocarditis (docetaxel plus bevacizumab followed by doxorubicin plus cyclophosphamide and bevacizumab group), and visceral arterial ischaemia (docetaxel followed by doxorubicin plus cyclophosphamide group). The most common grade 3–4 adverse events in the bevacizumab group were neutropenia (grade 3, 99 [17%]; grade 4, 37 [6%]), hand-foot syndrome (grade 3, 63 [11%]), and hypertension (grade 3, 60 [10%]; grade 4, two [<1%]) and in the non-bevacizumab group were neutropenia (grade 3, 98 [16%]; grade 4, 36 [6%]), fatigue (grade 3, 53 [9%]), and hand-foot syndrome (grade 3, 43 [7%]).

Interpretation—The addition of gemcitabine or capecitabine to neoadjuvant docetaxel plus doxorubicin plus cyclophosphamide does not seem to provide any benefit to patients with operable breast cancer, and should not change clinical practice in the short term. The improved overall survival with bevacizumab contradicts the findings of other studies of bevacizumab in breast cancer and may indicate the need for additional investigation of this agent.

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Introduction

The National Surgical Adjuvant Breast and Bowel Project (NSABP; now part of NRG Oncology), undertook the B-40 trial with primary objectives of determining whether the addition of the gemcitabine or capecitabine, and the addition of bevacizumab to standard neoadjuvant chemotherapy would increase the proportion of women with operable breast cancer achieving a pathological complete response[1] (the trial's primary endpoint). We reported previously that addition of neoadjuvant bevacizumab increased the proportion of women achieving pathological complete responses, particularly for hormone-receptor-positive tumours.[1] Neoadjuvant chemotherapy is now used not only for locally advanced disease but also for earlier-stage cancers.[2–5] Increases in the proportion of women achieving pathological complete responses with new drugs in the neoadjuvant chemotherapy setting could be predictive of benefit in the adjuvant setting.[4,6–13] Indeed, the US Food and Drug Administration recently established a pathway of accelerated approval of drugs for breast cancer treatment in the neoadjuvant setting based on improvements in pathological complete responses.[14,15]

The requirement for neovascularisation for cancer micrometastases to become clinically detectable was described more than 40 years ago,[16] and is considered a hallmark of cancer.[17] Prognosis in early breast cancer is inversely related to angiogenesis in the primary tumour.[16,18] Paradoxically, primary tumours can also secrete anti-angiogenic factors,[19–24] which could account for the rapid growth of metastases after removal of primary tumours in animal models.[21–23,25]

In 1993, an anti-VEGF antibody was shown to reduce the density of blood vessels in tumours and to inhibit growth of tumours in mice.[26] Bevacizumab is a humanised monoclonal antibody that binds VEGF isoform A and inhibits angiogenesis.[27] Addition of bevacizumab to chemotherapy for breast cancer has resulted in increases in the proportion of women who achieve complete responses in the neoadjuvant setting and improved progression-free survival for women with metastatic breast cancer, but no trials have shown significant improvement in overall survival.[28–33] Unlike other studies in early breast cancer in which bevacizumab was used exclusively for either neoadjuvant or adjuvant treatment,[31–36] women in the B-40 trial randomly assigned to receive neoadjuvant bevacizumab were also to receive ten doses of adjuvant bevacizumab after surgery. Detailed rationale, methods, response rates, and toxicities have been reported previously.[1] Here, we present secondary patient outcomes, including disease-free survival, a specified endpoint by protocol, and data for distant recurrence-free interval, and overall survival, which were not prespecified endpoints, but for which data were collected prospectively.

Methods

Study design and participants

In this randomised controlled trial, we enrolled women aged 18 years and older, with operable, HER2-non-amplified invasive adenocarcinoma of the breast, 2 cm or greater in diameter by palpation, clinical stage T1c–3, cN0, cN1, or cN2a, without metastatic disease (M0), and diagnosed by core needle biopsy. ECOG performance status of 0 or 1 and adequate cardiac, hepatic, and renal function were required. In addition to adequate baseline left ventricular function assessment and electrocardiogram, potential patients were required to have an absolute neutrophil count of 1.2×10^9 cells per L or greater, platelet count 100×10^9 platelets per L or greater, haemoglobin 10 g/dL or greater, total bilirubin upper limit of normal (ULN) or less for the laboratory, serum creatinine ULN or less for the laboratory, creatinine clearance greater than 50 mL per min, and urine protein:urine creatinine ratio 1·0 or less. Patients with other malignancies, unless considered to be disease-free for 5 years or more, with cardiac disease, history of transient ischaemic attack or cerebrovascular accident, other arterial thrombotic event within 12 months, symptomatic peripheral vascular disease, non-traumatic bleeding within 6 months, non-healing wounds or fractures, gastroduodenal ulcers, recent invasive procedures, known bleeding diathesis or coagulopathy, neuropathy grade 2 or greater, any condition that would preclude treatment with the regimens in the protocol or corticosteroids, pregnancy or lactation, were not eligible. The protocol recommended that any patient with a life expectancy less than 10 years, excluding her diagnosis of breast cancer, should not be enrolled. Patients could not have received previous treatment for breast cancer, with the only exception being hormonal therapy, which could have been given for up to a total of 28 days any time after diagnosis and before study entry. In such a case, hormonal therapy must have been stopped at or before randomisation and was to be restarted, if indicated, after surgery.

The NSABP B-40 study protocol was approved by the National Cancer Institute's central international review board (IRB) and local human investigations committees or IRBs at each participating site with assurances approved by the US Department of Health and Human

Services. Written informed consent was obtained from all participants. Patients could stop study therapy or withdraw from the study at any time. The investigator could require a patient to discontinue study therapy if any of the following occurred: the patient developed a serious side-effect that she could not tolerate or that could not be controlled with other drugs; the patient's health got worse; the patient was unable to meet the study requirements; or, new information about the study drugs or other treatments for breast cancer became available.

Randomisation and masking

Patients were randomly assigned to treatment groups (1:1:1:1:1:1). A biased-coin minimisation procedure was implemented for the randomisation to balance the characteristics with respect to the following factors: clinical nodal status (negative *vs* positive), clinical tumour size (2.0–4.0 cm *vs* >4.0 cm), hormone receptor status (ER-positive or PgR-positive, or both *vs* ER-negative and PgR-negative), and age (<50 years *vs* ≥50 years).[37] Treatment assignment was done via an online program maintained by the NSABP Biostatistical Center and neither the patient nor the participating site could know the next assignment in the sequence. Neither patients nor treating physicians were masked as to treatment assignment. Histological tumour grade (low, intermediate, or high) was assessed from the diagnostic core needle biopsy sample.

Procedures

Women were randomly assigned to neoadjuvant chemotherapy with four cycles of docetaxel (100 mg/m^2 intravenously on day 1) every 3 weeks followed by four cycles of doxorubicin and cyclophosphamide (60 mg/m^2 and 600 mg/m^2 intravenously, respectively) every 3 weeks (T→AC); capecitabine (825 mg/m^2 oral twice daily on days 1–14) added to docetaxel (75 mg/m^2 intravenously, day 1), followed by doxorubicin and cyclophosphamide (60 and 600 mg/m^2 intravenously) every 3 weeks (TX→AC); or gemcitabine (1000 mg/m^2 intravenously, days 1 and 8) added to docetaxel (75 mg/m^2 intravenously, day 1) followed by doxorubicin and cyclophosphamide (60 and 600 mg/m^2 intravenously) every 3 weeks (TG→AC; figure 1). The taxane portions of the neoadjuvant chemotherapy regimen were given first to allow four cycles of the taxane with capecitabine or gemcitabine with or without bevacizumab to be completed without having to give bevacizumab closer than 6 weeks to surgery. The taxane first version of AC plus taxane has been used in other centres with results similar to giving the AC first.[11] Patients were also randomly assigned to receive either no bevacizumab or bevacizumab (15 mg/kg intravenously every 3 weeks) with each of the first six cycles of chemotherapy and for ten additional doses postoperatively. Left ventricular ejection fraction was required to be assessed by multigated acquisition scan or echocardiogram before study entry and before surgery in all patients; and at 18 months after study entry for all patients who received bevacizumab. Other details can be found in our previous publication of the response data,[1] and further details of protocol-specified dose reductions, laboratory monitoring, and radiographic assessments are provided in appendix pp 2–21. Information about post-operative hormonal therapy was collected from hormone receptor-positive patients after they received 5 years of hormonal therapy.

Outcomes

The primary protocol-specified endpoint was pathological complete response of the primary tumour in the breast, defined as no histological evidence of invasive tumour cells in the breast specimen removed at surgery. The primary endpoint (pathological complete response) was not centrally reviewed. Specified secondary endpoints included treatment effects on toxicity, cardiac function, surgical complications, and disease-free survival. Grades 2–5, but not grade 1, adverse events were collected prospectively. The main endpoints reported here are disease-free survival, defined as time from randomisation to disease recurrence or death, overall survival, defined as time from randomisation to death, and distant recurrence-free interval, defined as time from randomisation to distant recurrence, although the latter two were not prespecified in the protocol. However, data for survival were prospectively collected to allow for analysis of overall survival as well as disease-free survival; the follow-up forms prospectively collected information for cause of death. The decision to analyse distant recurrence-free interval was made after it was noted that distant metastases accounted for most of the difference in first events between the bevacizumab groups and the control groups, and is exploratory in nature. Events for disease-free survival include local recurrences in the chest wall or breast, regional recurrence, distant recurrence, contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), and death from any cause before recurrence. Events for overall survival include death from any cause. Events for distant recurrence-free interval include distant metastasis. Death without breast cancer is censored for distant recurrence-free interval. Secondary endpoints reported here were obtained from case report forms, supported by source documents. Disease-free survival and overall survival events were reviewed by NSABP physicians and research nurses. Follow-up data were to be collected every 6 months during years 1–5 and every 12 months in years 6–10 for all randomly assigned patients.

Statistical analysis

The sample size justification was based on the efficacy of additional capecitabine or gemcitabine to doxorubicin and cyclophosphamide plus taxane in improving pathological complete response. To have 80% power to detect an increment of pathological complete response from 26% to 36% with the addition of capecitabine or gemcitabine to doxorubicin and cyclophosphamide plus taxane, this study was designed to enrol 1200 patients in total. Although pathological complete response was the primary endpoint, which was used to determine the sample size for this study, we expected to have 80% power to detect a 30% reduction in disease-free survival hazard rate from adding bevacizumab to chemotherapy, with a two-sided type I error rate 0.05 when 252 disease-free survival events are observed. Three interim analyses were planned at 126, 166, and 209 events. Two-sided p-values of 0.0005, 0.0005, and 0.001 were used for the three interim analyses, respectively. After adjustment for these interim analyses, the two-sided significance level for the final analysis is 0.0499.[38]

The stratified log-rank test was used to compare treatment groups among three chemotherapy regimens and between the groups with bevacizumab and the groups without,

with two-sided α of 0.05.[39] Kaplan-Meier estimates at 5 years from entry were also compared.[40] Cox proportional hazards models were used to estimate the hazard ratios for treatment comparisons, to test interactions between treatment factors and clinical factors with two-sided α of 0.05 for statistical significance.[41] Standardised score process was used to check the validity of the proportional hazards assumption.[42] Tests of interaction between bevacizumab and patient characteristics, including the stratification factors, were prespecified in the protocol. All subset analyses were exploratory and not prespecified. The statistical analyses were done with SAS/STAT version 9.4 and R version 2.14.1.

This study is registered with ClinicalTrials.gov, number NCT00408408.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, or data interpretation, writing of the report, or decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The NSABP restricts sponsor access to outcomes data until submission of an abstract. Genentech, Roche Laboratories, and Lilly Research Laboratories, a division of Eli Lilly & Company, provided partial support and were given the opportunity to review this report before submission. There was no additional commercial support, and no person who is not an author contributed to the report.

Results

Between Jan 5, 2007, and June 30, 2010, 1206 patients were enrolled in the study. Follow-up data collected between Oct 31, 2007, and March 27, 2014, were available for overall survival in 1186, disease-free survival in 1184, and distant recurrence-free interval in 1181 (198 in T→AC group, 195 in T plus bevacizumab→AC plus bevacizumab group, 202 in TX→AC group, 195 in TX plus bevacizumab→AC plus bevacizumab group, 190 in TG→AC group, and 201 in TG plus bevacizumab→AC plus bevacizumab group; figure 1). Patient characteristics were balanced across treatment groups; tumour grade was missing from 15 patients (table 1). The cutoffdate for this report was March 31, 2014. Median follow-up was 4.7 years (IQR 4.0–5.2) and the follow-up was similar between patients who received bevacizumab and those who did not (log-rank p=0.65). In the analysis of overall survival, 20 patients who withdrew from the study without follow-up data were excluded. Two more without clinical follow-up were excluded in the disease-free survival analysis; one in the TX plus bevacizumab → AC plus bevacizumab group and one in the TG → AC group. Three early deaths without clinical assessment of cancer recurrence were excluded in the distant recurrence-free interval analysis (one in the T→AC group and two in the TX→AC group). There were 23 (2%) patients found to be ineligible were distributed similarly across treatment groups: six did not provide pre-entry urine protein:urine creatinine ratio, three had T4 tumours, and two had HER2-positive cancers. All analyses were on an intention-to-treat basis, excluding only those patients without follow-up data. Among 707 patients with hormone-receptor-positive cancers, data for postoperative hormonal therapy were received from 172 (24%).

The toxicities associated with the different neoadjuvant chemotherapy regimens and neoadjuvant bevacizumab were reported previously.[1] The comparison of overall toxicity between bevacizumab and non-bevacizumab patients, including the post-operative courses, was similar to what was reported previously (table 2).[1] More detailed enumeration of all adverse events, by chemotherapy group and by bevacizumab versus no bevacizumab treatment, is provided in the appendix (pp 22–43). The most common grade 3–4 adverse events were febrile neutropenia (five [3%] in the T→AC group, 17 [9%] in the T plus bevacizumab→AC plus bevacizumab group, 14 [7%] in the TX→AC group, 23 [12%] in the TX plus bevacizumab→AC plus bevacizumab group, 16 [8%] in the TG→AC group, and 18 [9%] in the TG plus bevacizumab→AC plus bevacizumab group), diarrhoea (seven [4%] in the T→AC group, seven [4%] in the T plus bevacizumab→AC plus bevacizumab group, 21 [10%] in the TX→AC group, 12 [6%] in the TX plus bevacizumab→AC plus bevacizumab group, 15 [8%] in the TG→AC group, and 12 [6%] in the TG plus bevacizumab→AC plus bevacizumab group), and leucopenia (28 [14%] in the T→AC group, 29 [15%] in the T plus bevacizumab→AC plus bevacizumab group, 42 [21%] in the TX→AC group, 37 [19%] in the TX plus bevacizumab→AC plus bevacizumab group, 64 [33%] in the TG→AC group, and 70 [35%] in the TG plus bevacizumab→AC plus bevacizumab group) with chemotherapy. Most frequent toxicities associated with bevacizumab compared with the control group were hypertension, hand–foot syndrome, and symptomatic mucositis. Surgical complications were higher in the bevacizumab groups than in the groups without bevacizumab: grade 2: 114 (20%) of 577 versus 81 (14%) of 577; grade 3: 51 (9%) versus 29 (5%); and grade 4: three (1%) versus one (<1%). Four deaths occurred during treatment due to: vascular disorder (on TX→AC, unrelated to protocol therapy), sudden death (on TX→AC, unrelated to protocol therapy), infective endocarditis (on T plus bevacizumab→AC plus bevacizumab, possibly related to docetaxel or bevacizumab), and visceral arterial ischaemia (on T→AC, possibly related to docetaxel). Of 587 patients treated with bevacizumab with postoperative bevacizumab treatment data, 121 (21%) did not start or discontinued post-operative bevacizumab due to side-effects or toxicities. There were 700 (59%) patients who had dose reductions (40 patients in the T→AC group, 54 in the T plus bevacizumab→AC plus bevacizumab group, 122 in the TX→AC group, 148 in the TX plus bevacizumab→AC plus bevacizumab group, 158 in the TG→AC group, and 178 in the TG plus bevacizumab→AC plus bevacizumab group).

Breast pathological complete response and pathological complete response for breast plus nodes correlated with improved disease-free survival and overall survival. When considering breast pathological complete response, the 5-year disease-free survival was 84.8% (95% CI 80.2–88.5) for patients with pathological complete response versus 68.0% (64.2–71.4) for those without (hazard ratio [HR] 0.42, 95% CI 0.31–0.57; p<0.0001; figure 2) and 5-year overall survival was 92.3% (95% CI.88·5–94.9) for patients with pathological complete response versus 78.6% (75.3–81.6) for those without (HR 0.34, 95% CI 0.23–0.51; p<0.0001; figure 2). When considering pathological complete response for breast plus nodes (data not shown), 5-year disease-free survival was 87.8% (95% CI 82.7–91.4) for patients with pathological complete response versus 68.2% (95% CI 64.6–71.5) for those without (HR 0.33, 95% CI 0.23–0.48, p<0.0001) and 5-year overall survival was 95.5% (95% CI

91.8–97.6) for those with pathological complete response versus 78.5% (75.3–81.4) for those without (HR 0.20, 95% CI 0.12–0.35, p<0.0001).

Among 201 patients in the T→AC group, 19 did not complete four cycles of docetaxel and another 21 had dose reduction in docetaxel; among 197 patients in the T plus bevacizumab→AC plus bevacizumab group, 12 did not complete four cycles of docetaxel and another 32 had dose reduction in docetaxel; among 204 patients in the TX→AC group, 20 did not complete four cycles of docetaxel plus capecitabine and another 102 had dose reduction in docetaxel plus capecitabine; among 199 patients in the TX plus bevacizumab→AC plus bevacizumab group, 22 did not complete four cycles of docetaxel plus capecitabine and another 117 had dose reduction in docetaxel plus capecitabine; among 196 patients in the TG→AC group, 11 did not complete four cycles of docetaxel and gemcitabine and another 147 had dose reduction in docetaxel and gemcitabine; and among 204 patients in the TG plus bevacizumab→AC plus bevacizumab group, 15 did not complete four cycles of docetaxel and gemcitabine and another 159 had dose reduction in docetaxel and gemcitabine. There were no statistically significant differences in 5-year disease-free survival or overall survival among the three chemotherapy regimens (5-year disease-free survival: 72.8% [95% CI 67.9–77.1] for T, 72.6% [67.4–77.1] for TX, 73.9% [68.3–78.7] for TG [p=0.70] and 5-year overall survival: 80.9% [95% CI 76.2–84.8] for T, 81.5% [76.8–85.3] for TX, 85.7% [81.3–89.1] for TG [p=0.21]; appendix pp 47, 48. For disease-free survival, comparing with T, the hazard ratio associated with TX was 1.01 (95% CI 0.77−1.33) and the hazard ratio associated with TG was 0.90 (95% CI 0.67–1.19; appendix p 47). For overall survival, comparing with T, the hazard ratio associated with TX was 0.95 (95% CI 0.68–1.32) and the hazard ratio associated with TG was 0.73 (95% CI 0.51–1.04; appendix p 48).

Preoperative bevacizumab and chemotherapy were completed (all doses given, complete per protocol criteria) in 80% of patients assigned to the bevacizumab groups. Among 587 patients who were assigned to bevacizumab and for whom we had treatment data, 430 (73%) began post-operative bevacizumab. 157 patients (27%) did not start postoperative bevacizumab for the following reasons: adverse events (47 patients), alternative therapy (nine patients), new lesions or other signs of progression (15 patients), and other reasons (86 patients). All ten doses of postoperative bevacizumab were completed by 289 (67%) of the 430 patients who initiated post-operative therapy, whereas 48 (11%) received one to three doses, 57 (13%) received four to six doses, and 36 (8%) received seven to nine doses. Of 430 patients who began post-operative bevacizumab, 74 (17%) discontinued because of adverse events, side-effects, or complications, one (<1%) discontinued because of change to alternative therapy, 11 (3%) discontinued because of new lesions or other signs of progression, and 55 (13%) discontinued for other reasons. Completion of all planned post-operative bevacizumab doses was similar between patients who achieved a breast pathological complete response (108 [54%] of 200) and those who did not (190 [50%] of 383). Disease-free survival was not significantly different between groups treated with bevacizumab compared with those who did not receive bevacizumab (figure 3A), but there was a statistically significant improvement in overall survival for those who received bevacizumab compared to those who did not (figure 3B). As shown in figure 4, an exploratory subset analysis showed that the subset of patients with hormone-receptor-

positive tumours seemed to derive a greater benefit from bevacizumab (disease-free survival: HR 0.73 [95% CI 0.53–1.00]; p=0.05; overall survival: HR 0.63 [95% CI 0.42–0.96]; p=0.03), consistent with the drug's greater impact on pathological complete response in this subset.[1] However, tests for interaction between HR status and bevacizumab effect on outcomes were not statistically significant (disease-free survival: p=0.23; overall survival: p=0.51).

The effect of adding bevacizumab was especially noteworthy for reduction in distant metastatic first events, rather than for local or regional recurrences (table 3). Sites of distant metastases for the bevacizumab and non-bevacizumab arms are shown in the appendix p 45; most differences are accounted for by bone, lung, and CNS metastases. In the exploratory analysis of distant recurrence-free interval, the addition of bevacizumab significantly decreased the risk of developing distant metastasis overall (HR 0.70, 95% CI 0.54–0.92; p=0.01; appendix p 49) and the risk of developing distant metastasis in patients with hormone-receptor-positive tumours (HR 0.68, 95% CI 0.47–0.97, p=0.03; appendix p 50). The effect of bevacizumab was greater in the groups in which patients received gemcitabine or capecitabine with docetaxel (appendix p 46). However, the p-value for interaction was significant only for distant recurrence-free interval, but not for disease-free survival or overall survival. In a further exploratory analysis, patients with hormone-receptor-positive tumours who were assigned to bevacizumab and did not achieve a pathological complete response after neoadjuvant chemotherapy had better disease-free survival than those who were in non-bevacizumab groups and did not achieve a pathological complete response. The effect of bevacizumab was smaller in those patients who achieved a pathological complete response (appendix p 51). This must be interpreted with caution, because pathological complete response and bevacizumab treatment are not independent factors.

Aside from assignment to bevacizumab treatment, other significant variables associated with disease-free survival and overall survival in Cox proportional hazards models with multiple covariates were clinical tumour size (>4 cm vs 2–4 cm; disease free survival: HR 1.51 [95% CI 1.19–1.92]; p=0.0007; overall survival: HR 1.55 [95% CI 1.16–2.08]; p=0.003), clinical nodal status (disease-free survival: HR 1.60 [95% CI 1.27–2.02]; p<0.0001; overall survival: HR 1.62 [95% CI 1.22–2.15]; p=0.0009), HR status (overall survival: HR 0.72 [95% CI 0.52–0.99]; p=0.04), and tumour grade (disease-free survival: intermediate *vs* low HR 2.04 [95% CI 1.03–4.05], high *vs* low HR 2.37 [1.18–4.73]; p=0.05; table 4). Although the proportional hazard assumption was violated in tumour grade (intermediate vs low and high vs low) and hormone receptor status, there was no consistent pattern over time and we did not pursue to fit a time-dependent effect of tumour grade or hormone receptor status in the Cox model reported in table 4.

Discussion

Neither gemcitabine nor capecitabine added to neoadjuvant docetaxel followed by doxorubicin and cyclophosphomide had significant effect on disease-free survival or overall survival. Neoadjuvant and postoperative bevacizumab marginally increased disease-free survival overall, particularly in the hormone-receptor-positive subset. Addition of bevacizumab significantly improved overall survival for the entire cohort of women with

operable HER2-negative breast cancer, particularly for those with hormone-receptor-positive cancers. The main effect of adding bevacizumab was a reduction in the incidence of distant metastases. The addition of bevacizumab to adjuvant chemotherapy has been shown to be of no benefit for disease-free survival or overall survival in three large, randomised clinical trials (ECOG 5103, BEATRICE, BETH).[34–36] One large neoadjuvant study, GeparQuinto, in which bevacizumab was given with chemotherapy only during the neoadjuvant period, showed a significant increase in pathological complete response with the addition of bevacizumab but did not show improvement in disease-free survival or overall survival.[43,44] By contrast with the results of B-40, in GeparQuinto the beneficial effect of adding bevacizumab to neoadjuvant chemotherapy was predominantly in patients with triple-negative disease. Similar to GeparQuinto and by contrast with B-40, the ARTEMIS, S0800, and CALGB 40603 trials reported that bevacizumab had the greatest effect on pathological complete response in patients with triple-negative breast cancers or ER-low tumours.[45–47] Although NSABP B-40 showed an increase in pathological complete response with the addition of bevacizumab to neoadjuvant chemotherapy, unlike other studies in which bevacizumab administraton was limited to either the metastatic, adjuvant, or neoadjuvant settings,[31–36,43,44] administration of neo adjuvant plus adjuvant bevacizumab in the B-40 trial resulted in a non-statistically significant increase in disease-free survival and statistically significantly increased overall survival. These somewhat unexpected results suggest that the biology of angiogenesis could result in complex interactions among the primary tumour, clinically occult metastatic foci, and the timing of administration of bevacizumab. The effect of bevacizumab on gross tumor in the breast and lymph nodes, which have acquired an adequate blood supply by the time of diagnosis, could differ from the mechanisms that might prevent the growth and survival of micrometastases. Key elements of the effect of bevacizumab on the primary tumour could include sensitising tumour endothelial cells to chemotherapy[48–50] or normalisation of blood vessels and increased delivery of chemotherapy drugs.[51] For occult micrometastases, anti-VEGF therapy could arrest capillary ingrowth by so-called sprouting,[52] and prevent the growth of tumour cells in premetastatic niches.[50] Averting the induction of angiogenesis in dormant micrometastases might be the key to preventing them from becoming clinically evident at a later time.[50,53] Neoadjuvant administration of bevacizumab plus chemotherapy begins VEGF inhibition at micrometastatic sites concurrently with cytotoxic effects on the cancer cells and before removal of the primary tumour, both of which could result in loss of factors from the primary tumor that inhibit angiogenesis.[6–8,49] If the neoadjuvant systemic therapy was sufficient to achieve a pathological complete response, then resumption of VEGF targeting post-operatively would be unlikely to be beneficial, because these patients already achieve excellent outcomes. However, if the surgical specimen contains residual disease, it is likely also to remain in micrometastatic sites, and neovascularisiation that was inhibited by bevacizumab in the neoadjuvant period could be initiated by continued VEGF production from the residual foci of cancer within a short time. Resumption of bevacizumab in the postoperative period could continue the critical inhibition of VEGF-driven neovascularisation crucial for surviving deposits of cancer cells in micrometastatic sites.

The addition of neoadjuvant plus adjuvant bevacizumab in NSABP B-40 led to a significant increase in overall survival, especially for hormone-receptor-positive cancers. The pattern of

the bevacizumab effect seen here, with the greatest effect being on distant metastases and being proportionately greater beyond 2 years of follow-up also suggests a predominant effect on occult micro-metastases present at the time of diagnosis. This also fits with the preferential effect of bevacizumab in women with hormone-receptor-positive cancers, whose recurrences tend to be later than for patients with triple-negative breast cancer. As in other studies, pathological complete response correlated with improved disease-free survival and overall survival in this trial. The observed improvement in overall survival with addition of bevacizumab, despite a non-significant increase in disease-free survival, could result from the inclusion of local recurrence, contralateral breast cancer, and new cancers at other sites as disease-free survival events; such events are less likely to be affected by anti-angiogenic therapy and would also be less likely to affect overall survival than distant metastases.

Although our results can only be considered hypothesis-generating in view of the consistently negative results in adjuvant trials of bevacizumab, there are biologically plausible explanations for the beneficial effect of administering bevacizumab with neoadjuvant chemotherapy and after surgery. The preferential effect of bevacizumab on disease-free survival and overall survival in hormone-receptor-positive cancers noted in the B-40 trial is consistent with the previously reported selectivity for pathological complete response in this trial, despite the contradictory results from GeparQuinto.[44] The differences between the results reported here and those from GeparQuinto could be related to the inclusion of patients with more advanced disease in the German trial, the addition of adjuvant bevaciziumab in B-40, and the withdrawal of patients who were early non-responders from the initial treatment in GeparQuinto. The last of these could have been particularly important if, as suggested by an exploratory analysis, bevacizumab has the most benefit in women with HR+ tumours and residual disease after neoadjuvant chemotherapy. A careful molecular analysis of the tissue and blood samples obtained before therapy from B-40 patients could help to explain these results based on tumour or patient biology, but in view of the negative adjuvant trials with bevacizumab and the contradictory results from GeparQuinto, it would be premature to depend on the results of this trial to change practice. It is likely that the only way to determine if these findings reflect identification of important new biology or if these are spurious results would be to conduct another prospective, randomised trial evaluating neoadjuvant and adjuvant administration of VEGF inhibitor in combination with neoadjuvant chemotherapy. Although the preferential effect of bevacizumab in patients who received neoadjuvant antimetabolites might make it tempting to add gemcitabine or capecitabine to baseline chemotherapy in such a trial, the fact that the interactions were not statistically significant except for distant recurrence-free interval and the absence of any statistically significant benefit from adding these drugs would make such a design doubtful. One approach might be to randomly assign non-pathological complete response patients after neoadjuvant chemotherapy plus bevacizumab to continue bevacizumab after surgery, or to omit adjuvant bevacizumab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

This protocol was undertaken starting in 2007, before which, all relevant data from trials of adding gemcitabine, capecitabine, and bevavicizumab to chemotherapy in the metastatic, adjuvant, and neoadjuvant settings for breast cancer were reviewed using the PubMed database, personal files, and meeting presentations. However, no specific records of literature reviews were kept during the time this trial was developed during 2005–06. As noted in detail in our previous publication on the proportion of patients achieving a response, the decision to test capecitabine and gemcitabine was based on previous reports that these compounds added to taxane-based chemotherapy increased progression-free survival in patients with metastatic breast cancer. Likewise, previous trials had shown that bevacizumab added to chemotherapy increased response rates and progression-free survival in patients with advanced breast cancer. The potential benefit of addition of bevacizumab to treatment of breast cancer has also been reviewed not only by us but also by others. The previous results suggested that adding each of these compounds to chemotherapy in either adjuvant or neoadjuvant settings would increase the benefits in terms of response and patient outcomes. Those data are summarised in this paper and in the paper showing the proportion of patients achieving a response, published in 2012.

Added value of this study

The results reported here agree with the final results of neoadjuvant and adjuvant trials, which have shown that neither gemcitabine nor capecitabine improves on the efficacy of chemotherapy for early stage breast cancer. The results reported here on the effect of adding neoadjuvant and adjuvant bevacizumab, on the other hand, contradict other reports in which addition of either adjuvant or neoadjuvant bevacizumab to chemotherapy for breast cancer did not significantly improve the proportion of patients achieving a response or patient outcomes. We noted a significant increase in pathological complete response as well as disease-free survival and overall survival with bevacizumab given with neoadjuvant chemotherapy and continued postoperatively. We also noted a preferential effect in hormone-receptor-positive breast cancer, whereas others have suggested a greater benefit for triple-negative breast cancer. However, this is the only study in which bevacizumab was added to neoadjuvant chemotherapy and added to postoperative adjuvant therapy.

Implications of all the available evidence

Although it would be premature to apply the results of B-40 reported here to routine practice, there are biologically plausible explanations for the results reported here, despite the contradictory results from other trials. Based on these results in the context of other studies, we cannot recommend routine use of bevacizumab for neoadjuvant or adjuvant treatment of operable breast cancer. However, with the correlative science studies that will be done with the tumour tissue and blood collected in advance from the patients in this trial, a more refined selection of patients who might benefit most from adding bevacizumab might be possible. Moreover, additional trials could be appropriate

to clarify and refine these results to obtain more actionable information about the use of bevacizumab in this setting, with possible emphasis on patients who do not achieve a pathological complete response with neoadjuvant chemotherapy plus bevacizumab.

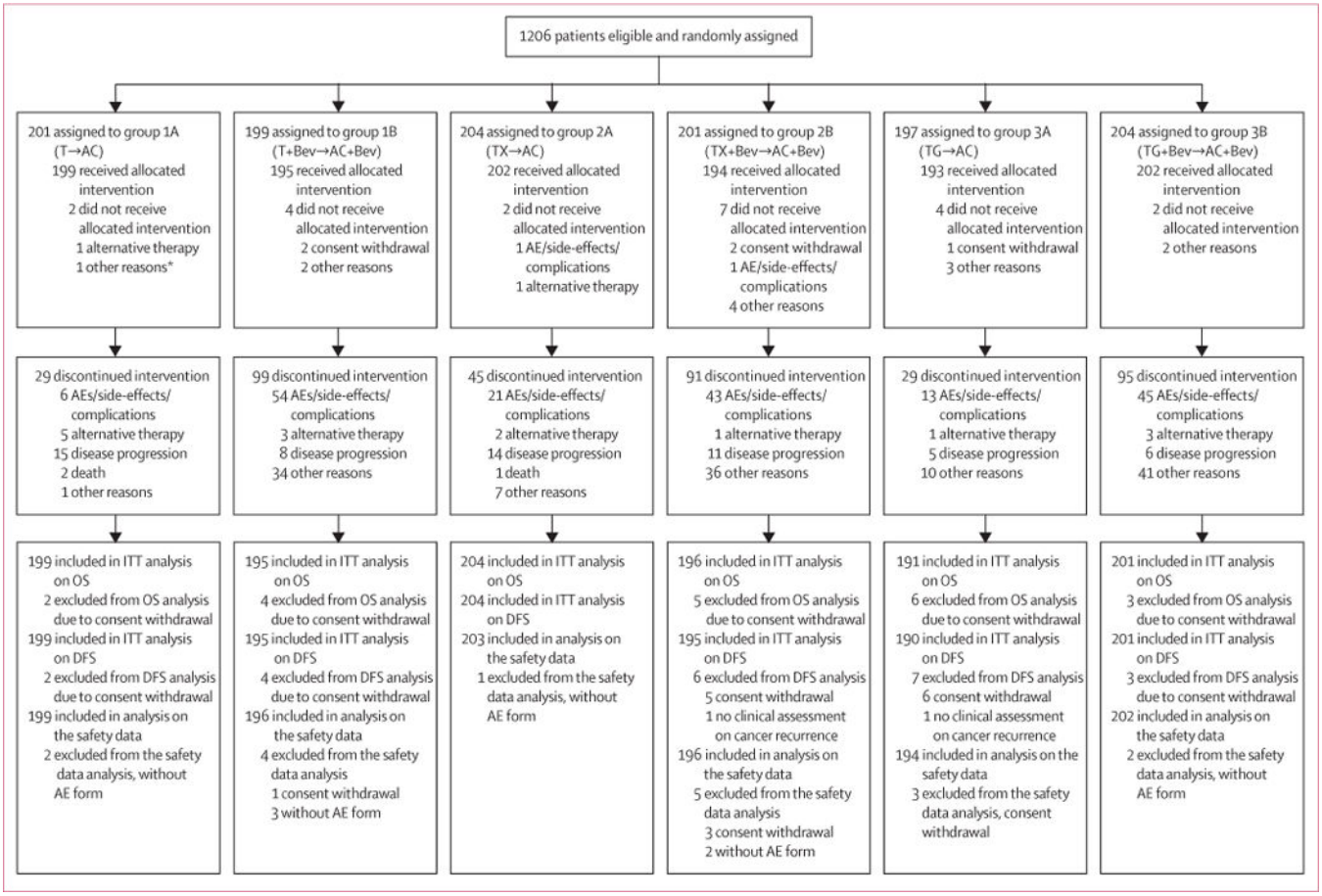

Figure 1. Trial profile

T→AC=docetaxel followed by doxorubicin and cyclophosphamide. TX→AC=docetaxel and capecitabine followed by doxorubicin and cyclophosphamide. TG→AC=docetaxel and gemcitabine followed by doxorubicin and cyclophosphamide. Bev=bevacizumab. ITT=intent-to-treat. OS=overall survival. DFS=disease-free survival. AE=adverse event. *Other reasons imply not adverse event, side-effects, or complications, alternative therapy, disease progression, or death.

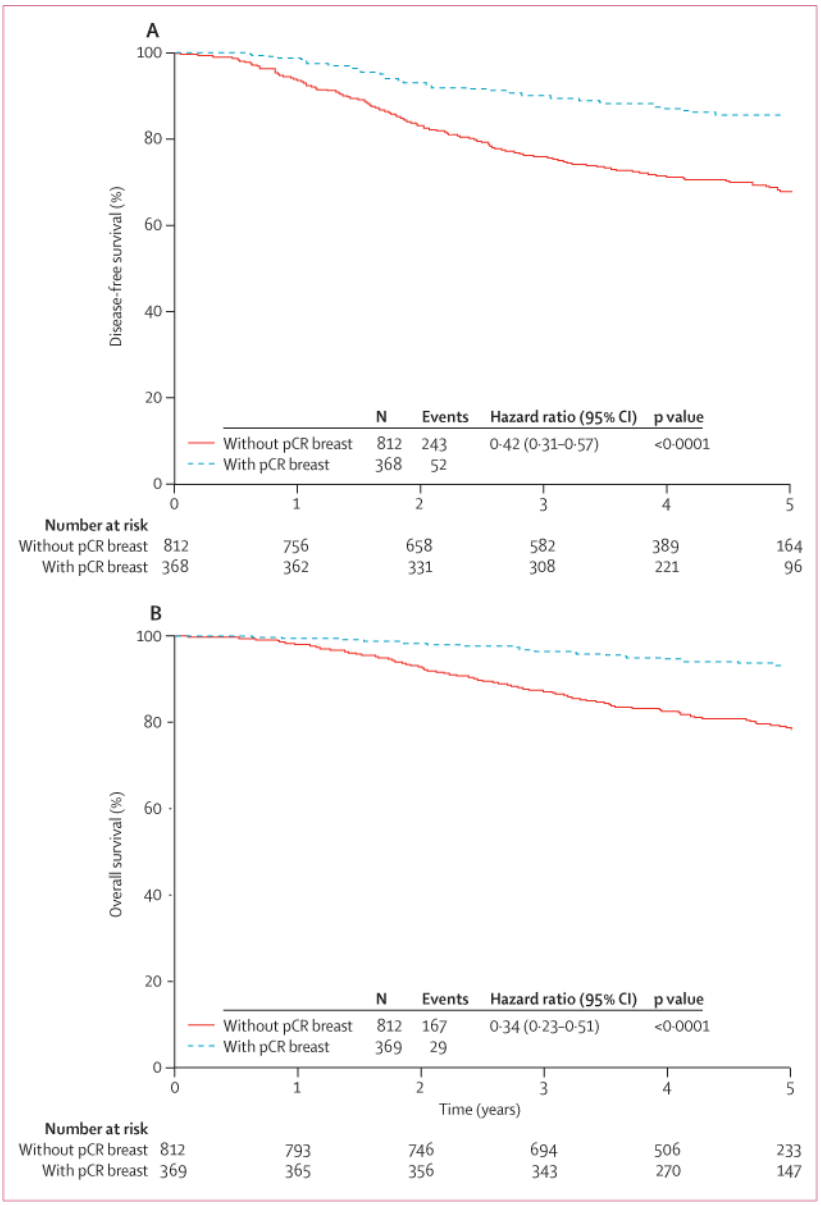

Figure 2. Kaplan-Meier estimates of (A) disease-free survival and (B) overall survival comparing those with pCR in breast and those without pCR in breast

The p value is for the log-rank test. The hazard ratio (HR) and its 95% CI are obtained from a Cox proportional hazards model. pCR=pathological complete response.

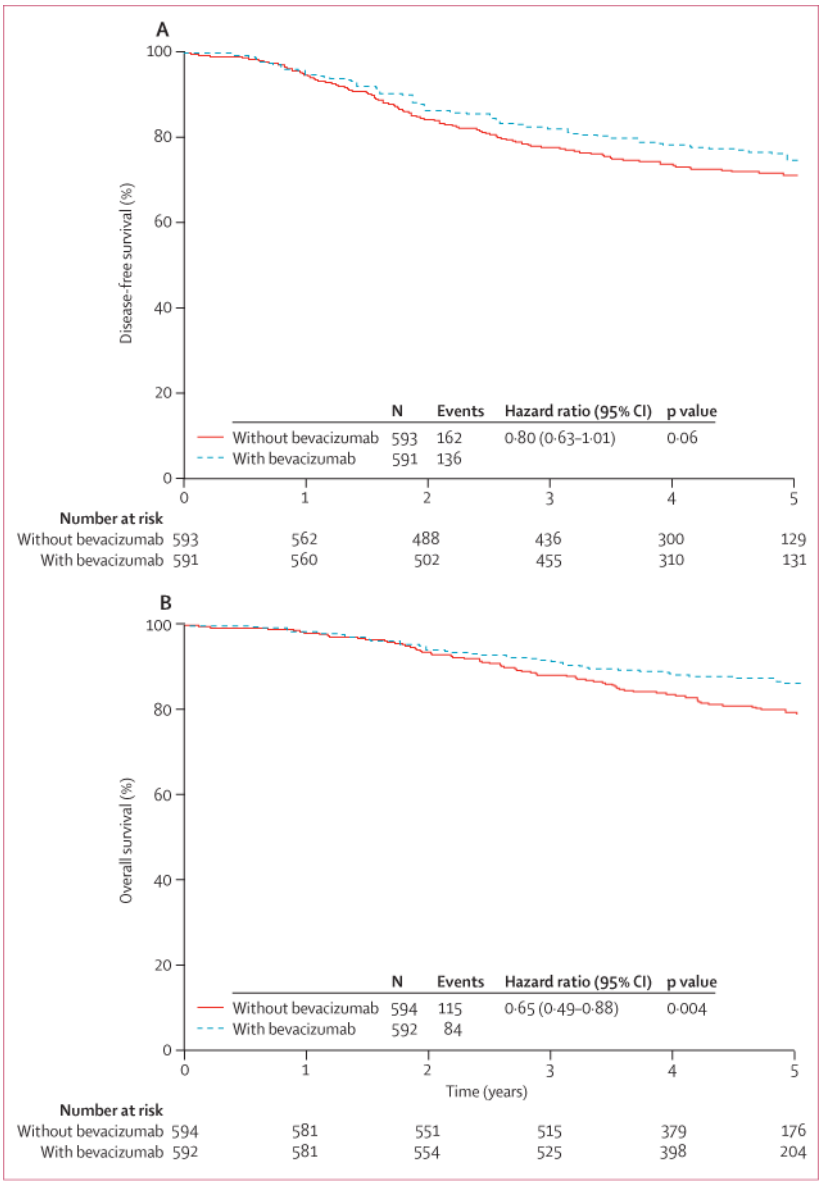

Figure 3. Kaplan-Meier estimates of (A) disease-free survival and (B) overall survival comparing the groups with bevacizumab and those without bevacizumab

The p value is for the stratified log-rank test with clinical tumour size, clinical nodal status, hormone receptor status, age, and chemotherapy as stratification factors. The hazard ratio (HR) and its 95% CI are obtained from a stratified Cox proportional hazards model with clinical tumour size, clinical nodal status, hormone receptor status, age, and chemotherapy as stratification factors.

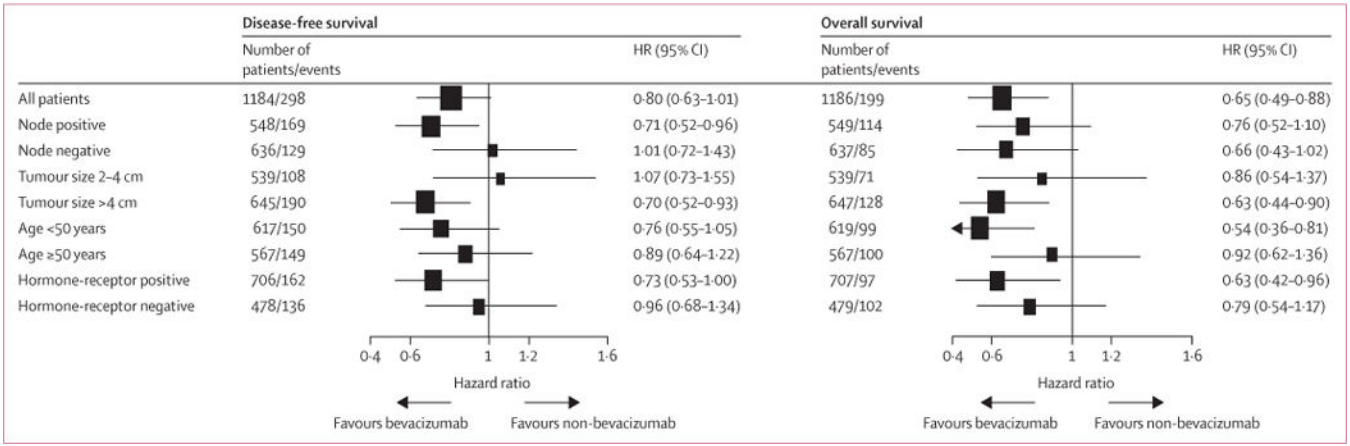

Figure 4. Forest plots comparing groups with bevacizumab and those without bevacizumab within various subsets in disease-free survival and overall survival

The hazard ratios (HR) and their 95% CIs are obtained from the corresponding Cox proportional hazards models. HR<1 implies benefit from the addition of bevacizumab.

Table 1

Patient characteristics of the intent-to-treat population

	T→AC	T+ Bev→AC + Bev	TX→AC	TX+ Bev→AC + Bev	TG→AC	TG+ Bev→AC + Bev
Patients with follow-up	199	195	204	196	191	201
Age at entry (years)						
≤49	107 (54%)	101 (52%)	101 (50%)	105 (54%)	100 (52%)	105 (52%)
50–59	63 (32%)	64 (33%)	66 (32%)	55 (28%)	65 (34%)	62 (31%)
≥60	29 (15%)	30 (15%)	37 (18%)	36 (18%)	26 (14%)	34 (17%)
Clinical tumour size						
2–4 cm	89 (45%)	84 (43%)	97 (48%)	92 (47%)	84 (44%)	93 (46%)
>4 cm	110 (55%)	111 (57%)	107 (52%)	104 (53%)	107 (56%)	108 (54%)
Clinical nodal status						
Positive	96 (48%)	91 (47%)	93 (46%)	90 (46%)	88 (46%)	91 (45%)
Negative	103 (52%)	104 (53%)	111 (54%)	106 (54%)	103 (54%)	110 (55%)
Hormone receptor status						
Positive	118 (59%)	117 (60%)	117 (57%)	117 (60%)	116 (61%)	122 (61%)
Negative	81 (41%)	78 (40%)	87 (43%)	79 (40%)	75 (39%)	79 (39%)
Ethnic origin						
White	167 (84%)	169 (87%)	164 (80%)	170 (87%)	145 (76%)	172 (86%)
African–American	25 (13%)	20 (10%)	34 (17%)	20 (10%)	34 (18%)	28 (14%)
Other	7 (4%)	6 (3%)	6 (3%)	6 (3%)	12 (6%)	1 (<1%)
Histological tumour grade						
Low	15 (8%)	11 (6%)	14 (7%)	15 (8%)	15 (8%)	13 (6%)
Intermediate	72 (36%)	70 (36%)	67 (33%)	75 (38%)	63 (33%)	78 (39%)
High	109 (55%)	112 (57%)	120 (59%)	105 (54%)	109 (57%)	108 (54%)
Unknown	3 (2%)	2 (1%)	3 (1%)	1 (<1%)	4 (2%)	2 (1%)

Data are n (%). T→AC=docetaxel followed by doxorubicin and cyclophosphamide. Bev=bevacizumab. TX→AC=docetaxel and capecitabine followed by doxorubicin and cyclophosphamide. TG→AC=docetaxel and gemcitabine followed by doxorubicin and cyclophosphamide.

Table 2

Overall and selected toxicities between groups without bevacizumab and those with bevacizumab

	Non-bevacizumab (N=596)			Bevacizumab (N=594)		
	Grade 2	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Overall (grades 2–4)	111 (18%)	293 (49%)	51 (9%)	91 (15%)	372 (63%)	63 (11%)
Leucopenia	0	34 (6%)	8 (1%)	0	35 (6%)	2 (<1%)
Neutropenia	0	98 (16%)	36 (6%)	0	99 (17%)	37 (6%)
Hypertension	7 (1%)	2 (<1%)	0	81 (14%)	60 (10%)	2 (<1%)
Left ventricular systolic dysfunction	0	1 (<1%)	0	0	7 (1%)	1 (<1%)
Fatigue	0	53 (9%)	0	0	60 (10%)	0
Hand–foot syndrome	67 (11%)	43 (7%)	NA	93 (16%)	63 (11%)	NA
Rash	62 (10%)	4 (<1%)	NA	83 (14%)	6 (1%)	NA
Diarrhoea	76 (13%)	42 (7%)	1 (<1%)	82 (14%)	30 (5%)	0
Symptomatic mucositis	95 (16%)	21 (4%)	0	153 (26%)	40 (7%)	1 (<1%)
Nausea	0	25 (4%)	0	0	27 (5%)	0
Vomiting	0	30 (5%)	1 (<1%)	0	18 (3%)	0
Febrile neutropenia	0	34 (6%)	1 (<1%)	0	56 (9%)	2 (<1%)
Infection in wound	0	2 (<1%)	0	0	16 (3%)	0
Sensory neuropathy	65 (11%)	16 (3%)	0	72 (12%)	22 (4%)	0
Bone pain	0	17 (3%)	0	0	26 (4%)	0
Headache	0	5 (<1%)	0	0	25 (4%)	0
Dyspnoea	22 (4%)	5 (<1%)	0	25 (4%)	7 (1%)	3 (<1%)
Thrombosis, thrombus, embolism	4 (<1%)	8 (1%)	3 (<1%)	7 (1%)	9 (2%)	6 (1%)

Data are n (%). Fewer than 1% of patients died in all groups (with or without bevacizumab during the treatment period). Deaths: vascular disorder (T→AC group, <1%), infective endocarditis (T+Bev→AC +Bev group, <1%), visceral arterial ischaemia (T→AC group, <1%), and sudden death (TX→AC group, <1%). For a list of other grade 3–4 toxicities, see appendix p 44. Bev=bevacizumab.

Table 3

Disease-free survival events for groups with bevacizumab and those without bevacizumab

	Without bevacizumab (N=593)	With bevacizumab (N=591)
Ipsilateral breast	8 (1%)	15 (3%)
Local recurrence	12 (2%)	6 (1%)
Regional recurrence	9 (1%)	14 (2%)
Distant metastasis	106 (18%)	80 (14%)
Opposite breast	5 (<1%)	9 (1%)
Other second primary cancer	12 (2%)	7 (1%)
Dead, no evidence of disease	10 (2%)	5 (<1%)
Total	162 (27%)	136 (23%)

Table 4

Results from Cox proportional hazards models with multiple covariates

	Disease-free survival		Overall survival	
	Hazard ratio (95% CI)	**p value**	**Hazard ratio (95% CI)**	**p value**
Bevacizumab	0.83 (0.66–1.05)	0.11	0.74 (0.55–0.98)	0.03
TX→AC *vs* T→AC	1.02 (0.77–1.34)	0.89	0.98 (0.70–1.36)	0.88
TG→AC *vs* T→AC	0.89 (0.67–1.18)	0.42	0.78 (0.55–1.10)	0.16
Age (≥50 years vs <50 years)	1.08 (0.86–1.36)	0.51	1.17 (0.88–1.55)	0.27
Tumour size (>4 cm *vs* 2–4 cm)	1.51 (1.19–1.92)	0.0007	1.55 (1.16–2.08)	0.003
Clinical nodal status (positive *vs* negative)	1.60 (1.27–2.02)	<0.0001	1.62 (1.22–2.15)	0.0009
Hormone receptor status (positive *vs* negative)	0.79 (0.61–1.04)	0.09	0.72 (0.52–0.99)	0.04
Tumour grade (intermediate *vs* low)	2.04 (1.03–4.05)	0.05*	2.18 (0.87–5.44)	0.06*
Tumour grade (high *vs* low)	2.37 (1.18–4.73)		2.79 (1.11–7.01)	

T→AC=docetaxel followed by doxorubicin and cyclophosphamide. TX→AC=docetaxel and capecitabine followed by doxorubicin and cyclophosphamide. TG→AC=docetaxel and gemcitabine followed by doxorubicin and cyclophosphamide.

*p value for global test of significance for tumour grade.