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Neoadjuvant Chemotherapy and Bevacizumab for HER2-Negative Breast Cancer

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ABSTRACT

BACKGROUND

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, has shown clinical efficacy in patients with human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer. We evaluated the efficacy, measured according to the rate of pathological complete response (absence of invasive and intraductal disease in the breast and the axillary lymph nodes), and the safety of adding bevacizumab to neoadjuvant chemotherapy in patients with early-stage breast cancer.

METHODS

We randomly assigned 1948 patients with a median tumor size of 40 mm on palpation to receive neoadjuvant epirubicin and cyclophosphamide followed by docetaxel, with or without concomitant bevacizumab. Patients with untreated HER2-negative breast cancer were eligible if they had large tumors, hormone-receptor–negative disease, or hormone-receptor–positive disease with palpable nodes or positive findings on sentinel-node biopsy, and no increased cardiovascular or bleeding risk.

RESULTS

Overall, the rates of pathological complete response were 14.9% with epirubicin and cyclophosphamide followed by docetaxel and 18.4% with epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab (odds ratio with addition of bevacizumab, 1.29; 95% confidence interval, 1.02 to 1.65; P=0.04); the corresponding rates of pathological complete response were 27.9% and 39.3% among 663 patients with triple-negative tumors (P=0.003) and 7.8% and 7.7% among 1262 patients with hormone-receptor–positive tumors (P=1.00). Breast-conserving surgery was possible in 66.6% of the patients in both groups. The addition of bevacizumab, as compared with neoadjuvant therapy alone, was associated with a higher incidence of grade 3 or 4 toxic effects (febrile neutropenia, mucositis, the hand–foot syndrome, infection, and hypertension) but with a similar incidence of surgical complications.

CONCLUSIONS

The addition of bevacizumab to neoadjuvant chemotherapy significantly increased the rate of pathological complete response among patients with HER2-negative early-stage breast cancer. Efficacy was restricted primarily to patients with triple-negative tumors, in whom the pathological complete response is considered to be a reliable predictor of long-term outcome. (Funded by Sanofi-Aventis and Roche, Germany; ClinicalTrials.gov number, NCT00567554.)

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The efficacy of neoadjuvant chemotherapy, as measured by the rate of pathological complete response (the absence of invasive and intraductal disease in the breast and the axillary lymph nodes), varies according to breast-cancer subtype.[1] When anthracyclines, taxanes, and agents directed against anti–human epidermal growth factor receptor 2 (HER2) (if indicated) are used, approximately 30 to 40% of all breast cancers that are HER2-positive or triple-negative (estrogen-receptor–negative, progesterone-receptor–negative, and no overexpression of HER2) are completely eradicated locally at the time of surgery.[2-6] Long-term follow-up studies have shown a consistent correlation between pathological complete response and low rates of relapse and death among patients with these two subtypes of breast cancer.[4,7,8]

The GeparQuinto phase 3 study was initiated to investigate subtype-specific treatment approaches for patients with HER2-negative primary breast cancer (group 1), HER2-negative primary breast cancer that did not have a response to four cycles of neoadjuvant chemotherapy as confirmed by ultrasonography (group 2), or HER2-positive primary breast cancer (group 3) (see the figure in the Supplementary Appendix, available with the full text of this article at NEJM.org). This article focuses on patients in group 1 — patients with HER2-negative, operable or locally advanced tumors who were treated with anthracycline- and taxane-based neoadjuvant chemotherapy and were randomly assigned to either simultaneous treatment with bevacizumab or no additional therapy.

Data from the phase 3 GeparTrio trial (Clinical Trials.gov number, NCT00544765) showed that patients without an early tumor response rarely achieved a pathological complete response to conventional chemotherapy.[9] Therefore, in the GeparQuinto study, an interim response assessment was performed after 12 weeks of treatment to identify patients with treatment failure and to administer the drug-resistance modulating agent everolimus in group 2 of the study.

Bevacizumab was chosen as a candidate treatment to further increase the rate of pathological complete response in patients with the HER2-negative subtypes. The use of this antibody, directed against vascular endothelial growth factor A, was associated with significant but moderate improvements in overall response and progression-free survival when added to chemotherapy in three studies of first-line treatments for metastatic, HER2-negative breast cancer.[10-12] However, the investigation of bevacizumab in the treatment of nonmetastatic breast cancer might be more suitable for showing potential improvements in survival, because fewer proangiogenic factors and pathways are activated in early-stage disease than in late-stage disease.[13]

Methods

Primary and Secondary End Points

The primary objective of the HER2-negative component of this study was to compare the rates of pathological complete response after neoadjuvant chemotherapy with or without bevacizumab among patients with HER2-negative primary breast cancer. The secondary end points included toxic effects, adherence to treatment, the response rates of breast tumors and axillary nodes as assessed by physical examination and imaging tests (ultrasonography, mammography, or magnetic resonance imaging) before surgery, the rates of pathological stage T0 and Tis tumors (with "is" denoting in situ and referring to residual intraductal disease) after neoadjuvant therapy irrespective of nodal status, the rate of pathological stage T0 or TisN0 (no invasive residual disease in the breast and lymph nodes) tumors after neoadjuvant therapy, and the rate of breast conservation. Efficacy was assessed in predefined subgroups according to tumor stage (operable [clinical stage T1–T3, N0–N2] vs. locally advanced [clinical stage T4 or N3]) and hormone-receptor status (hormone-receptor invasive and intraductal–positive [estrogen receptor, progesterone receptor, or both ≥10%] vs. hormone-receptor–negative [both receptors <10%]).

Study Oversight

The study was designed and the protocol (available at NEJM.org) was written by the first author and by members of the neoadjuvant subcommittee of the German Breast Group and Arbeitsgemeinschaft Gynäkologische Onkologie–Breast study groups and was reviewed by the sponsors, Sanofi-Aventis and Roche, Germany. The sponsors had no access to the study data, which were collected at the German Breast Group headquarters. The data were analyzed by a member of the German Breast Group, and the first draft of the manuscript was written by the first author; both vouch for the correctness of the data and for the fidelity of the study to the protocol. The decision to sub-

mit the manuscript for publication was made by all the authors. No persons other than the listed authors contributed to the writing of the manuscript. The protocol was reviewed by the responsible ethics committee at each participating site. The conduct of the trial was supervised by an independent data and safety monitoring committee.

PATIENTS

Women with previously untreated, unilateral or bilateral, primary invasive breast carcinoma were enrolled in the study if they provided written informed consent. The diagnosis of breast cancer had to be confirmed histologically by means of a core biopsy. The HER2 status of the tumor had to be negative according to the HercepTest (Dako) (a score of 0 or 1+, in a possible range from 0 to 3+, with higher values indicating increased overexpression) or in situ hybridization (a score of 2+ on the HercepTest and no gene amplification), as assessed by the local pathologist. Tumor lesions were required to have a size of 2 cm or more on palpation or 1 cm or more in maximum diameter on ultrasonographic examination and had to be measurable in two dimensions, preferably by means of ultrasonography. In cases of inflammatory disease, the clinical extent of inflammation was considered to be a measurable lesion.

Patients were eligible if they had any stage of disease that was deemed to be appropriate for adjuvant chemotherapy (e.g., clinical stage T4 or T3 tumors, hormone-receptor–negative tumors, or hormone-receptor–positive tumors with clinical stage N+ disease [in the case of clinical stage T2 tumors] or sentinel-node–positive disease [in the case of clinical stage T1 tumors]). Further relevant criteria for eligibility were normal cardiac function (left ventricular ejection fraction ≥55%), no evidence of distant disease or known or suspected cardiac disease, no previous thromboembolic event, no known hemorrhagic diathesis or coagulopathy, no disease with a clinically significant effect on gastrointestinal function, no major surgery within the past 28 days or anticipation of the need for major surgery during study treatment, and no concurrent treatment with other anticancer or investigational agents.

TREATMENT

All patients were scheduled to receive epirubicin (at a dose of 90 mg per square meter of body-surface area) plus cyclophosphamide (at a dose of 600 mg per square meter), both administered on day 1, every 3 weeks for four cycles, followed by four cycles of docetaxel at a dose of 100 mg per square meter on day 1, every 3 weeks. Patients were randomly assigned to receive eight cycles of bevacizumab (at a dose of 15 mg per kilogram of body weight intravenously every 3 weeks starting on day 1 of the first epirubicin–cyclophosphamide cycle) or no additional treatment. In patients who did not have an ultrasonographically confirmed or clinical response to four cycles of epirubicin–cyclophosphamide, study treatment was discontinued and the patients were randomly assigned to weekly paclitaxel therapy with or without everolimus (group 2). In cases of tumor progression, the study treatment was discontinued and further local or systemic treatment was permitted at the discretion of the investigator. Patients could not undergo surgery for at least 28 days after the last chemotherapy or bevacizumab infusion.

ASSESSMENT OF END POINTS

Hematologic and biochemical measures were assessed weekly; the target lesion and regional lymph nodes were examined by palpation at every cycle. Breast ultrasonographic examination was repeated after every second cycle; ultrasonographic examination and mammography were performed before breast surgery. Cardiac ultrasonographic examination was repeated after four cycles of therapy and before surgery.

Pathological response of the breast tumor and of the infiltration of regional lymph nodes was assessed by the local pathologist. Pathological reports were reviewed at a central location by two pathologists who were unaware of the treatment assignments, and response was staged according to the tumor–node–metastasis (TNM) system.[14] A pathological complete response was defined as pathological stage T0 and N0 after neoadjuvant therapy. The presence of noninvasive residual disease only (pathological stage T0N0 or TisN0) or no invasive residual disease (pathological stage T0N0/+ or TisN0/+) in the breast after neoadjuvant therapy was reported as a secondary end point to allow for comparison with other studies.

Clinical complete response was defined as the absence of evidence of disease in the breast on ultrasonographic examination, or, if ultrasonographic examination was not possible, on mammographic or physical examination. A partial response was defined as a reduction in the product of the two largest perpendicular diameters of the primary tumor by 50% or more; progressive dis-

ease was defined as an increase in tumor size (the product of the two largest perpendicular dimensions) by 25% or more or the presence of a new lesion. All remaining scenarios were categorized as no change.

Patients were considered to have had breast-conserving surgery if the final surgical procedure was tumorectomy, segmentectomy, or quadrantectomy. Toxic effects were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

All patients who received at least one cycle of epirubicin and cyclophosphamide were included in the efficacy and safety analyses (Fig. 1). Treatment groups were compared with the use of a continuity-corrected two-sided Pearson's chi-square test and Fisher's exact test, and 95% confidence intervals are provided for the efficacy end points. Patients with missing data on response were counted as having had no response. Multivariate logistic regression was used to adjust for the baseline factors. Univariate logistic regression was performed in subgroups; a Breslow–Day test[15] was used for testing the homogeneity of odds ratios across subgroups. All statistical analyses were performed with the use of SAS software, version 9.2.

On the basis of the findings of the GeparDuo study (NCT00793377),[16] we assumed that the rate of pathological complete response with epirubicin and cyclophosphamide followed by docetaxel would be 14%; we expected that the rate of pathological complete response with epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab would be 18.9% (odds ratio, 1.43). With these assumptions, we estimated that we would need to enroll 1876 patients, according to a two-sided continuity-corrected Pearson's chi-square test with an alpha level of 0.05 and a beta level of 0.20. An interim safety analysis involving the first 30 patients who received at least two cycles of epirubicin–cyclophosphamide was performed to make recommendations regarding supportive treatment.[17]

Randomization was performed in a 1:1 ratio, at a central location, according to dynamic allocation, and was stratified according to participating site, hormone-receptor status (negative or positive), and extent of disease (clinical stage T1–T3 N0–N2 vs. T4 or N3). The minimization method of Pocock and Simon[18] was used for randomization. P values calculated from the chi-square test and Fisher's exact test for baseline variables are to be considered descriptive only, since they do not account for the dynamic allocation.

RESULTS

PATIENTS

From November 2007 through June 2010, a total of 1948 patients were enrolled in the HER2-negative component of this study at 126 centers in Germany and 1 center in Switzerland (Fig. 1). The baseline characteristics of the patients were equally balanced between the two groups (Table 1, and Table 1 in the Supplementary Appendix). The median tumor size in patients in both groups was 40 mm as assessed by palpation and 29 mm as assessed by ultrasonography.

EFFICACY

A total of 144 patients who received epirubicin and cyclophosphamide followed by docetaxel (14.9%) and 176 patients treated with epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab (18.4%) had a pathological complete response (pathological stage T0N0) (odds ratio with the addition of bevacizumab, 1.29; 95% confidence interval [CI], 1.02 to 1.65; P=0.04) (Table 2). After adjustment for age, clinical tumor and nodal stage, hormone-receptor status, tumor grade, and histologic type as covariates, the odds ratio with the addition of bevacizumab was 1.36 (95% CI, 1.05 to 1.77; P=0.02) (Table 2 in the Supplementary Appendix). The rates of pathological complete response with the addition of bevacizumab increased to 20.5% if nodal involvement (pathological stage T0N0/+) was included in the definition, 21.7% if noninvasive residual disease in the breast (pathological stage T0/isN0) was included in the definition, and 24.6% if both nodal involvement and noninvasive residual disease in the breast (pathological stage T0/isN0/+) were included in the definition; these rates were higher than the corresponding rates of pathological complete response with epirubicin and cyclophosphamide followed by docetaxel (Table 2).

A total of 371 patients with no change in tumor size or with tumor progression after four cycles of epirubicin–cyclophosphamide were switched to group 2 and were assessed as having not achieved

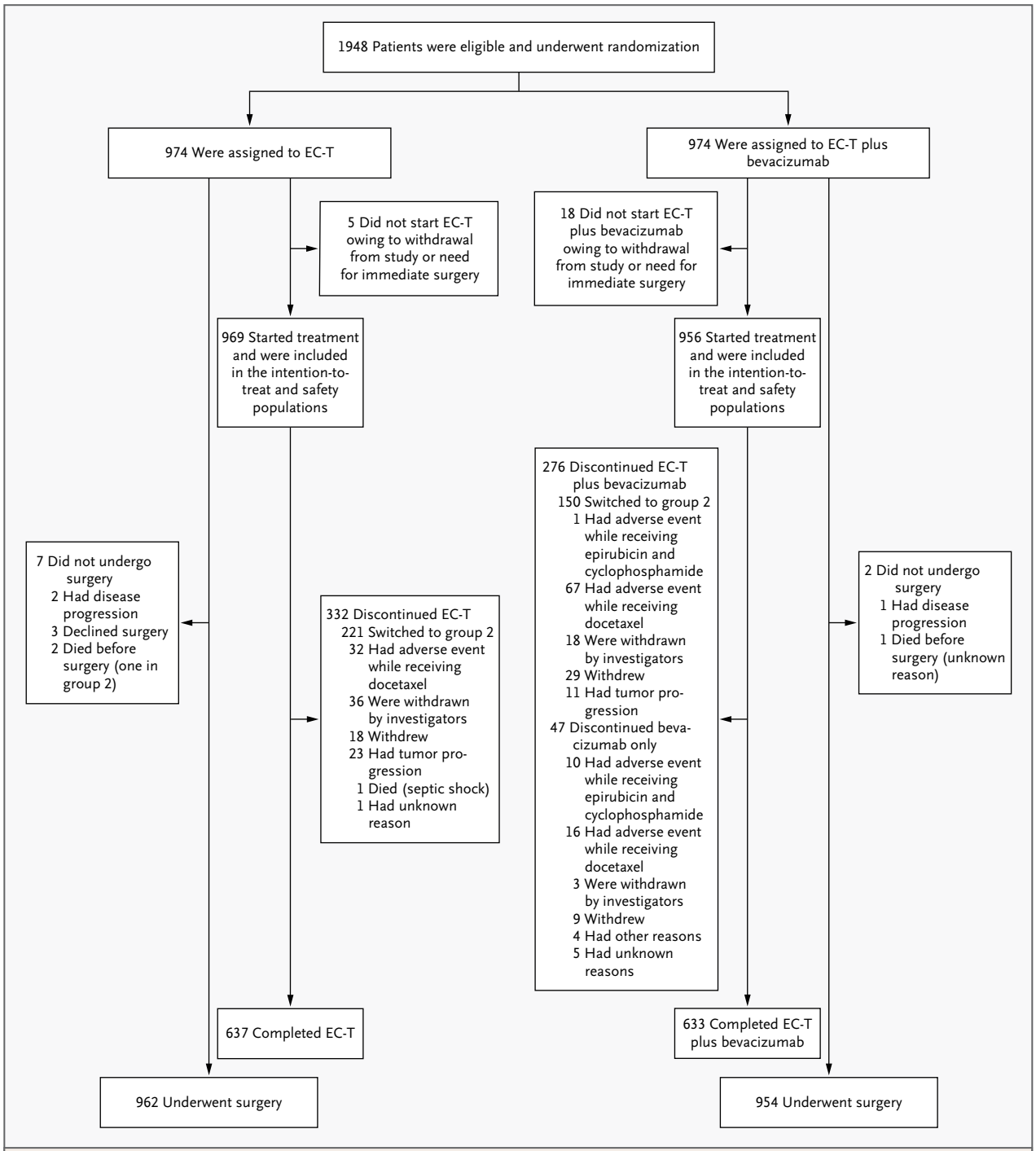

Figure 1. Enrollment and Outcomes.
EC-T denotes epirubicin and cyclophosphamide followed by docetaxel.

a pathological complete response. Seven of these patients who were initially randomly assigned to epirubicin and cyclophosphamide followed by docetaxel and 12 who were randomly assigned to epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab later had a pathological complete response. If these pathological complete responses had been included in the cal-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Epirubicin–Cyclophosphamide followed by Docetaxel (N=969)	Epirubicin–Cyclophosphamide followed by Docetaxel plus Bevacizumab (N=956)	P Value†
Age — yr			
Median	48	49	
Range	24–78	21–75	
Clinical tumor stage — no. of patients (%)			0.83
T1–T3	852 (87.9)	838 (87.7)	
T4a–T4c	57 (5.9)	53 (5.5)	
T4d	60 (6.2)	65 (6.8)	
Disease stage — no. of patients (%)			0.78
Operable	859 (88.6)	843 (88.2)	
Locally advanced: clinical stage T4 or N3	110 (11.4)	113 (11.8)	
Clinical nodal status — no. of patients (%)			0.54
N0	391 (40.4)	376 (39.3)	
N1	542 (55.9)	554 (57.9)	
Unknown	36 (3.7)	26 (2.7)	
Tumor type — no. of patients (%)			0.84
Ductal invasive	773 (79.8)	770 (80.5)	
Lobular invasive	106 (10.9)	102 (10.7)	
Other	89 (9.2)	81 (8.5)	
Unknown	1 (0.1)	3 (0.3)	
Tumor grade — no. of patients (%)			0.45
1	43 (4.4)	32 (3.3)	
2	507 (52.3)	503 (52.6)	
3	412 (42.5)	417 (43.6)	
Unknown	7 (0.7)	4 (0.4)	
Hormone-receptor status — no. of patients (%)			0.56
Estrogen-negative and progesterone-negative	340 (35.1)	323 (33.8)	
Estrogen-positive, progesterone-positive, or both	629 (64.9)	633 (66.2)	

* Percentages may not sum to 100 because of rounding.
† P values for clinical nodal status, tumor type, and tumor grade were calculated without data from patients with unknown status.

culations, the overall rates of pathological complete response would have been 15.6% among patients who received epirubicin and cyclophosphamide followed by docetaxel and 19.7% among patients who received epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab (P=0.02).

Figure 2 shows the effect of bevacizumab on the rate of pathological complete response within clinically relevant subgroups. Variations in treatment effect appeared to be related predominantly to a potential differential activity of bevacizumab according to hormone-receptor status. Among 663 patients with triple-negative tumors, the rates of pathological complete response were 27.9% in the group that received epirubicin and cyclophosphamide followed by docetaxel and 39.3% in the group that received epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab (P=0.003), and among 1262 patients with hormone-receptor–positive tumors, the corresponding rates were 7.8% and 7.7% (P=1.00). However, the test for interaction only approximated significance (P=0.07).

Table 2. Efficacy of Treatment, According to Histologic, Surgical, and Clinical Outcome.

Outcome	Epirubicin–Cyclophosphamide followed by Docetaxel (N=969)	Epirubicin–Cyclophosphamide followed by Docetaxel plus Bevacizumab (N=956)	P Value*
	no. (% [95% CI])	*no. (% [95% CI])*	
Primary end point: absence of invasive and intraductal disease in breast and nodes			
No	825 (85.1)	780 (81.6)	
Yes	144 (14.9 [12.7–17.3])	176 (18.4 [16.0–21.0])	0.04
Absence of invasive and intraductal disease in breast, irrespective of nodes			
No	809 (83.5)	760 (79.5)	
Yes	160 (16.5 [14.2–19.0])	196 (20.5 [18.0–23.2])	0.03
Absence of invasive disease in breast and nodes			
No	792 (81.7)	749 (78.3)	
Yes	177 (18.3 [15.9–20.8])	207 (21.7 [19.1–24.4])	0.07
Absence of invasive disease in breast, irrespective of nodes			
No	769 (79.4)	721 (75.4)	
Yes	200 (20.6 [18.1–23.3])	235 (24.6 [21.9–27.4])	0.04
Clinical response			
Complete or partial response	767 (79.2 [77.0–82.1])	830 (86.8 [85.1–89.4])	<0.001
Complete	194 (20.0)	210 (22.0)	
Partial	573 (59.1)	620 (64.9)	
No change	151 (15.6)	103 (10.8)	
Progressive disease	45 (4.6)	17 (1.8)	
Unknown	6 (0.6)	6 (0.6)	
Breast-conserving surgery			
No	301 (31.1)	299 (31.3)	
Yes	600 (61.9 [63.4–69.7])	597 (62.4 [63.4–69.7])	1.00
Unknown	61 (6.3)	58 (6.1)	
No surgery	7 (0.7)	2 (0.2)	

* P values for clinical response and breast-conserving surgery were calculated without data from patients with unknown status.

The overall clinical response rate, determined by means of palpation and imaging tests, was higher in the group that received bevacizumab than in the group that did not (87.4% vs. 79.6%). The rate of breast-conserving surgery was identical (66.6%) in both treatment groups (Table 2).

ADHERENCE TO TREATMENT

Of 969 patients who started treatment with epirubicin–cyclophosphamide without bevacizumab, 221 (22.8%) were switched to group 2 because of a lack of a tumor response by cycle 4, and 111 other patients (11.5%) discontinued neoadjuvant treatment. Of 956 patients who started treatment with epirubicin–cyclophosphamide plus bevacizumab, 150 (15.7%) were switched to group 2 because of the lack of a tumor response by cycle 4, another 126 (13.2%) discontinued chemotherapy, and 47 (4.9%) discontinued bevacizumab treatment only (Fig. 1). Chemotherapy was delayed in 35.6% of the patients in the group that received epirubicin–cyclophosphamide followed by docetaxel and in 43.1% of the patients in the group that received epirubicin–cyclophosphamide followed by docetaxel plus bevacizumab (P=0.001); the dose was reduced in 12.5% and 20.8% of the patients in

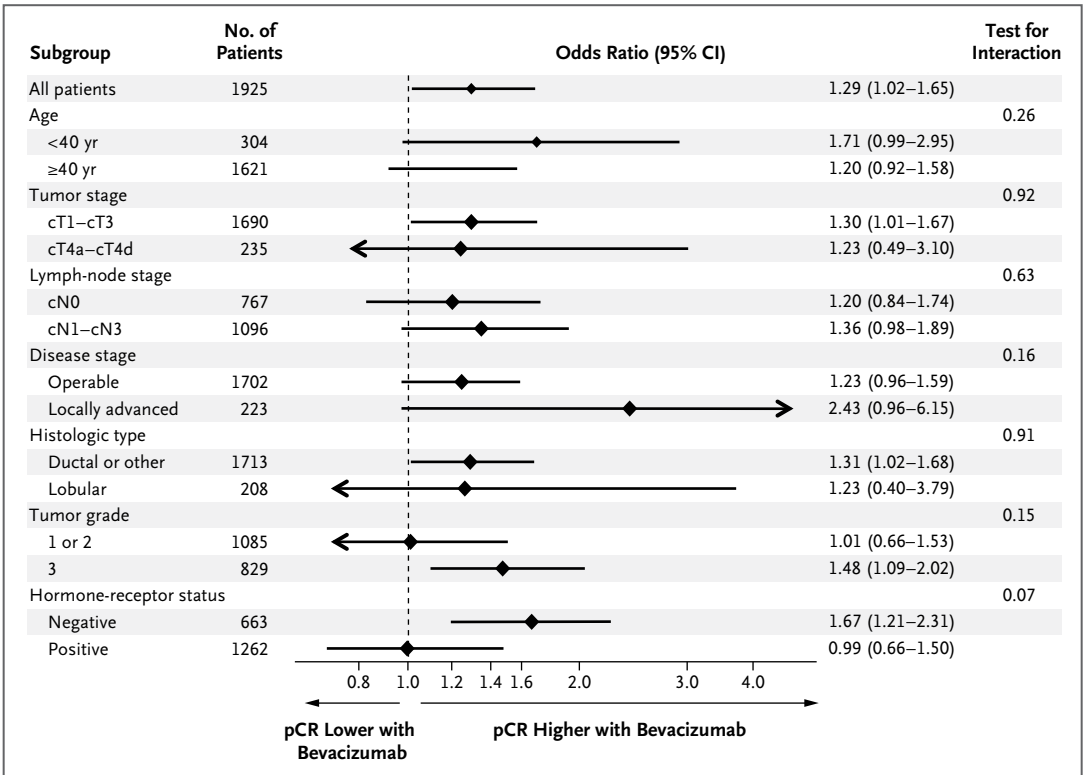

Figure 2. Pathological Complete Response (pCR), According to Subgroup.

The analyses of subgroups according to tumor and node stage and hormone-receptor status were prespecified and stratified.

the two groups, respectively (P<0.001). The doses of bevacizumab infusions were reduced in 1.2% and omitted in 7.6% of patients in the group receiving epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab; all eight cycles of bevacizumab were administered to 79.8% of patients.

SAFETY

Bevacizumab-specific toxic effects, such as bleeding and arterial hypertension, occurred more frequently in the group that received bevacizumab than in the group that did not (Table 3, and Table 3 in the Supplementary Appendix). The addition of bevacizumab to epirubicin and cyclophosphamide followed by docetaxel was associated with a higher rate of febrile neutropenia, infections, mucositis, and the hand–foot syndrome. The rate of surgical complications was generally low but was numerically higher in the group that received bevacizumab than in the group that did not. One death during therapy occurred in each group (Fig. 1).

DISCUSSION

Our study shows that the addition of bevacizumab to neoadjuvant anthracycline- and taxane-containing chemotherapy can increase the rate of pathological complete response in patients with operable or locally advanced HER2-negative breast cancer. The results from prespecified subgroup analyses suggest that the effect of bevacizumab derived mainly from patients with triple-negative breast cancer (odds ratio, 1.67). However, the test for interaction was not significant (P=0.07) in this study, which was not powered to show these differential effects.

Inhibiting angiogenesis might be a potential strategy for the treatment of triple-negative breast cancer because genes involved in angiogenesis are frequently activated in basal-like tumors.[19] Our findings suggest that bevacizumab has a higher level of activity in the triple-negative subtype than in the hormone-receptor–positive, HER2-negative subtype; none of the trials involving patients with

Table 3. Adverse Events.*

Event and Maximal Grade*	Epirubicin–Cyclophosphamide followed by Docetaxel (N=969)	Epirubicin–Cyclophosphamide followed by Docetaxel plus Bevacizumab (N=956)	P Value
	no. of patients/total no. (%)		
Anemia, 3–4	16/963 (1.7)	17/950 (1.8)	0.86
Neutropenia, 3–4	747/939 (79.6)	763/936 (81.5)	0.29
Febrile neutropenia, any	69/965 (7.2)	130/951 (13.7)	<0.001
Thrombocytopenia, 3–4	15/963 (1.6)	20/951 (2.1)	0.40
Mucositis, 3–4	26/965 (2.7)	157/951 (16.5)	<0.001
Edema, 3–4	8/965 (0.8)	7/951 (0.7)	1.0
Hand–foot syndrome, 3	33/965 (3.4)	52/951 (5.5)	0.04
Nail changes, 3	12/965 (1.2)	7/951 (0.7)	0.36
Infection, 3–4	66/964 (6.8)	97/951 (10.2)	0.01
Thromboembolic events, 3–4	18/965 (1.9)	26/951 (2.7)	0.22
Bleeding, 3–4	3/965 (0.3)	4/951 (0.4)	0.72
Surgical complications	38/349 (10.9)	58/394 (14.7)	0.13
Arterial hypertension, 3–4	4/965 (0.4)	25/951 (2.6)	<0.001
Cardiovascular disorders			
Any except congestive heart failure, 1–4	65/965 (6.7)	73/951 (7.7)	0.43
Any except congestive heart failure, 3–4	7/965 (0.7)	2/951 (0.2)	0.18
Congestive heart failure, 3–4	0/953 (0)	2/942 (0.2)	0.25
LVEF changes, any†	2/866 (0.2)	9/874 (1.0)	0
Proteinuria, any‡	NA	53/939 (5.6)	NA

* The grades of maximal severity per patient were based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0, except those for congestive heart failure, which were based on New York Heart Association classification, and surgical complications, which were not graded. NA denotes not available.
† Adverse changes with respect to left ventricular ejection fraction (LVEF) were an ejection fraction of <50% and at least a 10-percentage-point decrease from baseline.
‡ Proteinuria was defined as a urine-dipstick result of 2+ or 3+.

metastatic disease reported heterogeneous efficacy of bevacizumab according to hormone-receptor status.[10-12] The observed activity in patients with early-stage breast cancer is consistent with the findings of the National Surgical Adjuvant Breast and Bowel Project B-40 study (NSABP B-40; ClinicalTrials.gov number, NCT00408408, reported by Bear et al. elsewhere in this issue of the *Journal*[20]), which showed a significant improvement in the overall rate of pathological complete response with the addition of bevacizumab to neoadjuvant chemotherapy for HER2-negative disease.[20,21] In the NSABP B-40 study, a numerical but statistically nonsignificant increase in the rate of pathological complete response was reported with the use of bevacizumab in the subgroup of 490 patients with triple-negative breast cancer.[21] The nonsignificant result might be attributable to the smaller sample size in the NSABP B-40 study than in our study. In the subgroup of 735 patients with hormone-receptor–positive, HER2-negative tumors, however, bevacizumab-containing therapy was associated with a significantly higher rate of pathological complete response,[21] which is in contrast to the results in our study.

Despite many similarities in the NSABP B-40 and GeparQuinto trials, including the fact that the median tumor size at baseline was similar in the two trials, there were a number of differences that might have contributed to the divergent results. A total of 12% of the participants in our trial had clinical stage T4a–T4d disease, whereas patients with these disease stages were not eligible for the NSABP B-40 study. The NSABP B-40 study also

included patients with hormone-receptor–positive, HER2-negative, node-negative tumors; these patients were excluded from the GeparQuinto study. An anthracycline-containing regimen was administered before the docetaxel in our study, whereas this sequence was reversed in the NSABP B-40 study. Moreover, the NSABP B-40 study tested the additive effect of two antimetabolites with the use of a 2-by-3 factorial design and used a decreased dose of docetaxel (75 mg per square meter) in the experimental groups, which might have interacted with the efficacy of bevacizumab in the hormone-receptor subgroups; in addition, bevacizumab was administered during only six of the eight cycles. Finally, in our study, patients without a response after the first four cycles were considered not to have achieved a pathological complete response, which might have biased the efficacy results. However, a sensitivity analysis that included these patients according to the observed pathological response showed similar results.

The addition of bevacizumab to epirubicin and cyclophosphamide followed by docetaxel was associated with an increased number of grade 3 and 4 toxic effects. Drug-specific grade 3 or 4 toxic effects, such as arterial hypertension and bleeding, occurred infrequently. However, we observed an increased incidence of toxic effects typically associated with docetaxel in the group that received bevacizumab, a finding that is similar to the results from previous studies.[11,20] The protective effect of bevacizumab on chemotherapy-induced edema has been described previously.[22] In contrast to earlier, preliminary reports,[23] we did not observe a significantly increased rate of surgical complications after neoadjuvant bevacizumab therapy. A 4-week interval between the last bevacizumab infusion and surgery appeared to be sufficient to reduce the incidence of therapy-associated surgical complications. The incidence of congestive heart failure during the short observation period was low, but there were numerically more events of congestive heart failure in the group that received bevacizumab than in the group that did not.

Our study provides high-level evidence on the basis of the large number of patients and data that could be evaluated and the high quality of assessment of pathological complete response. Because of the short follow-up period, we cannot confirm that the observed increases in the rate of pathological complete response translate into a survival advantage. However, given that pathological complete response has been shown to be highly correlated with outcome, particularly in patients with triple-negative disease,[8] we speculate that the beneficial effect will be sustained. A recent meta-analysis of bevacizumab trials involving patients with metastatic breast cancer did not show a decreased time to disease progression, increased mortality, or an altered pattern of disease progression after the discontinuation of bevacizumab therapy[24]; consequently, we do not expect any detrimental effect to be seen after the completion of 24 weeks of neoadjuvant bevacizumab. Participants in our study provided numerous blood and tissue samples before, during, and after treatment, which may allow for the identification of a target population that will have maximum benefit from bevacizumab. In addition, the Bevacizumab Adjuvant Therapy in Triple Negative Breast Cancer study (Beatrice, NCT00528567) is evaluating adjuvant bevacizumab therapy in 2582 patients with early-stage triple-negative breast cancer.

In conclusion, adding bevacizumab to neoadjuvant chemotherapy significantly increased the rate of pathological complete response among patients with early-stage HER2-negative breast cancer, with the most notable and pronounced improvement seen in the subgroup of patients with triple-negative disease. Long-term follow-up data are needed before this treatment option can be fully understood.

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