9-2011

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VOLUME 29 · NUMBER 29 · OCTOBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study of Doxorubicin/Cyclophosphamide With Concomitant Versus Sequential Docetaxel As Adjuvant Treatment in Patients With Human Epidermal Growth Factor Receptor 2–Normal, Node-Positive Breast Cancer: BCIRG-005 Trial

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Submitted March 19, 2010; accepted January 12, 2011; published online ahead of print at www.jco.org on September 12, 2011.

Written on behalf of the Breast Cancer International Research Group 005 Investigators.

Presented in part at the 28th Annual San Antonio Breast Cancer Symposia, December 8-11, 2005, San Antonio, TX, and at the 31st Annual San Antonio Breast Cancer Symposia, December 10-14, 2008, San Antonio, TX.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/11/2929-3877/$20.00

DOI: 10.1200/JCO.2010.28.5437

ABSTRACT

Purpose
Anthracyclines, taxanes, and alkylating agents are among the most active agents in treatment of adjuvant breast cancer (BC), but the optimal schedule for their administration is unknown. We performed an adjuvant trial to compare the sequential regimen of doxorubicin with cyclophosphamide (AC) followed by docetaxel (ie, AC>T) with the combination regimen of TAC.

Patients and Methods
Women with node-positive, human epidermal growth factor receptor 2–nonamplified, operable BC were stratified by number of axillary nodes and hormone receptor status and were randomly assigned to adjuvant chemotherapy with six cycles of TAC (75/50/500 mg/m^2 every 3 weeks) or four cycles of AC (60/600 mg/m^2 every 3 weeks) followed by four doses of docetaxel at 100 mg/m^2 every 3 weeks (AC>T). After completion of chemotherapy, radiation therapy was given as indicated, and patients with hormone receptor (HR) –positive disease received adjuvant hormonal therapy with tamoxifen and/or aromatase inhibitors.

Results
In 30 months, 3,298 patients were enrolled (n = 1,649 in each arm). The major baseline characteristics were well balanced between the groups. At a median follow-up of 65 months, estimated 5-year disease-free survival rates were 79% in both groups (log-rank $P = .98$; hazard ratio [HR], 1.0; 95% CI, 0.86 to 1.16), and 5-year overall survival rates for both arms were 88% and 89%, respectively (log-rank $P = .37$; HR, 0.91; 95% CI, 0.75 to 1.11). TAC was associated with more febrile neutropenia and thrombocytopenia, and AC>T was associated with more sensory neuropathy, nail changes, and myalgia. The incidence of neutropenic infection was similar in both groups.

Conclusion
The sequential and combination regimens incorporating three drugs were equally effective but differed in toxicity profile.

J Clin Oncol 29:3877-3884. © 2011 by American Society of Clinical Oncology

INTRODUCTION

In the 1990s, the taxane microtubule poisons, docetaxel and paclitaxel, emerged as highly effective new agents in the treatment of metastatic breast cancer with single-agent activity that proved to be comparable or even superior to doxorubicin.[1,2] After taxane-anthracycline combinations, such as doxorubicin with docetaxel (AT) and docetaxel with doxorubicin and cyclophosphamide (TAC), had achieved promising results in advanced disease, particularly with poor prognostic features,[3,4,5] and after substantial activity was apparent in the neoadjuvant setting as well,[6,7,8] evaluation of docetaxel in the adjuvant setting seemed justified. After the docetaxel-anthracycline regimen TAC proved superior to anthracycline-based combination of fluorouracil, doxorubicin, and cyclophosphamide (FAC),[9] we sought to determine whether sequential or combination usage of anthracycline, taxane, and alkylators differed in their risk-to-benefit ratios.

The Breast Cancer International Research Group (BCIRG) –005 trial was designed to compare a sequential protocol—four cycles of doxorubicin/cyclophosphamide (AC) followed by four cycles of docetaxel—with six cycles of the triple combination TAC, in which all three agents were administered on the same day, in patients with node-positive early breast cancer. Because the adjuvant BCIRG-006 trial running in parallel to BCIRG-005 evaluated docetaxel combinations with trastuzumab in patients with human epidermal growth factor receptor 2 (HER2) –positive disease, accrual to BCIRG-005 was restricted to women with HER2-nonamplified breast cancer.

PATIENTS AND METHODS

Study Design

This was a multicenter, international, open-label, randomized, phase III study in women with operable node-positive, HER2-nonamplified breast cancer. Patients were centrally randomly assigned to receive adjuvant treatment with either four cycles AC followed by four cycles of docetaxel (AC>T) or six cycles of TAC, with stratification for center, number of involved axillary lymph nodes (1 to 3 $v \geq 4$), and hormone receptor status (estrogen and/or progesterone receptor status positive v negative). Random assignment was performed centrally. The primary end point was disease-free survival (DFS). Secondary end points included overall survival (OS) and safety.

Patients provided written informed consent before enrollment. The study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by institutional review boards, and conduct and analysis of the study were supervised by an independent data monitoring committee.

Patient Eligibility

Eligible women were 18 to 70 years old with a Karnofsky performance status ≥ 80% and with operable, histologically confirmed, invasive adenocarcinoma of the breast (T1-3, clinically N0-1, M0) without HER2 amplification of the primary tumor assessed by central fluorescence in situ hybridization (FISH; Pathvision; Vysis, Des Plaines, IL). Patients required mastectomy or a breast-conserving procedure with tumor-free margins (R0) and axillary lymph node dissection, with at least one involved axillary lymph node (pN1) from a minimum of six resected lymph nodes; with adequate hematologic, hepatic, and renal function, normal left ventricular ejection fraction (LVEF); and with an ECG without significant abnormalities. No prior systemic therapy or radiation therapy for breast cancer was allowed.

Treatment

Patients in the AC>T arm received doxorubicin 60 mg/m^2 as an intravenous (IV) bolus over 15 minutes and cyclophosphamide 600 mg/m^2 IV over 5 to 60 minutes on day 1 every 3 weeks for four cycles, followed by four cycles of docetaxel 100 mg/m^2 IV over 1 hour every 3 weeks. In the TAC arm, chemotherapy consisted of six cycles of doxorubicin at 50 mg/m^2, cyclophosphamide at 500 mg/m^2 and docetaxel at 75 mg/m^2, infused in this order every 3 weeks. In both arms, docetaxel was given with routine corticosteroid premedication for 3 days, starting the day before administration. Antibiotic prophylaxis with oral ciprofloxacin 500 mg twice per day for 10 days, starting on day 5 of each cycle, was mandatory in the TAC arm but was permitted in AC>T arm only after a grade 3 or 4 infection occurred. Antiemetic prophylaxis was given routinely in both arms. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) from the first cycle was allowed and was recommended for secondary prophylaxis after an episode of febrile neutropenia or infection or for inadequate neutrophil recovery on day 21.

Dose reductions were required for severe hematologic and/or nonhematologic toxicities, and dose re-escalation of doses in subsequent cycles was not allowed except for transient transaminase elevations. Treatments were stopped for withdrawal of consent; for severe or unacceptable toxicity that persisted despite adequate dose reduction; for chemotherapy delays exceeding 2 weeks that resulted from drug-related toxicities; or in the event of breast cancer relapse or second primary malignancy other than nonmelanoma skin cancer, in situ carcinoma of the uterine cervix, or in situ carcinoma of the breast.

Patients undergoing breast-conserving surgery were required to receive postoperative radiation therapy after completion of chemotherapy. Postmastectomy nodal or boost radiation was at the investigator's discretion. All patients with positive estrogen and/or progesterone receptor status received adjuvant hormonal therapy with tamoxifen or aromatase inhibitors, or the sequence, starting 3 to 4 weeks after completion of chemotherapy. Patients who received anticancer therapy other than that defined in the protocol during the course of the study were considered to have experienced treatment failure, and DFS was censored at the time of the initiation of the new anticancer therapy.

Assessments

Baseline examinations included the following: complete history, physical examination, hematology and clinical chemistry, ECG and LVEF determination, and pregnancy test when applicable. Imaging studies included contralateral mammography, chest x-ray and/or computed tomography (CT) and/or magnetic resonance imaging (MRI), abdominal ultrasound and/or CT and/or MRI, a bone scan, and bone x-ray in case of abnormal bone scan. Estrogen and/or progesterone receptor were assessed locally on tissue samples from the primary tumor.

Clinical and laboratory baseline examinations were repeated, and adverse events were documented, before each new chemotherapy cycle and within 3 to 4 weeks after completion of chemotherapy. Patients were observed for relapse and survival every 3 months for the first 2 years, every 6 months for years 3 to 5, and annually for years 6 to 10. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Statistical Analysis

The sample size was calculated to detect a 5% difference in 5-year DFS between arms. To detect this difference with a two-sided .05 significance level with statistical power of 80%, and assuming that 3% of the patients would be found ineligible after random assignment, 3,130 patients were needed (1,565 patients per treatment arm). A planned interim analysis was performed at a median follow-up of 30 months, after 392 DFS events and 175 deaths occurred. Safety data obtained in this analysis were previously reported.[10] This final protocol-specified analysis was triggered by 708 DFS events.

Survival data were analyzed for all patients and patient subgroups by using the Kaplan-Meier method, and the resulting curves were compared between groups with log-rank tests. DFS was measured from the date of random assignment to the date of first evidence of breast cancer relapse (local or distant), second primary cancer, initiation of anticancer therapy not permitted in the protocol, death, or last contact. OS was measured from the date of random assignment to the date of death as a result of any cause. Toxicities were compared between arms by using two-tailed χ^2 tests or, for rare adverse events, Fisher's exact tests. The efficacy analysis (DFS and OS) was performed on the intent-to-treat population (all randomly assigned patients). Toxicity was evaluated on safety population (ie, all patients who received at least one infusion of a study drug). All statistical analyses were performed by using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients and Treatment

Between August 2000 and February 2003, 335 centers in 37 countries enrolled 3,298 participants. The women were randomly assigned to adjuvant chemotherapy with AC>T (n = 1,649) or TAC (n = 1,649). Patient characteristics were well balanced between the treatment arms (Table 1). Median age was 50 years (range, 22 to 74 years). Nearly 60% of patients had a primary tumor of greater than 2 cm, and nearly 40% had four or more lymph nodes involved (11% had > 10 positive nodes).

Table 1. Baseline Demographic and Clinical Characteristics of All Randomly Assigned Patients From Intent-to-Treat Population

Characteristic	Patients by Regimen					
	AC>T (n = 1,649)		TAC (n = 1,649)		Total (N = 3,298)	
	No.	%	No.	%	No.	%
Age, years						
Median	50		50		50	
Range	22-74		24-72		22-74	
Premenopausal	787	48	782	47	1,569	48
Hormone receptor positive	1,348	82	1,346	82	2,694	82
Karnofsky performance status						
Median	100		100		100	
Primary tumor size and type, cm						
≤ 2 (pT1)	692	42	668	41	1360	41
> 2 to ≤ 5 (pT2)	824	50	844	51	1668	51
> 5 (pT3)	131	8	135	8	266	8
pT4	1	< 1	2	< 1	3	< 1
pTis	1	< 1	0	0	1	< 1
No. of positive nodes						
0	0	0	1	< 1	1	< 1
1-3	1,010	61	1,005	61	2,015	61
4-10	462	28	456	28	918	28
> 10	177	11	187	11	364	11
Grading						
Well differentiated	154	9	151	9	305	9
Moderately differentiated	780	47	758	46	1538	47
Poorly differentiated	564	34	596	36	1,160	35
Undifferentiated	3	< 1	2	< 1	5	< 1
Unassessable	147	9	139	8	286	9
Missing	1	< 1	3	< 1	4	< 1
Treatment						
Mastectomy	955	58	973	59	1,928	58
Breast-conserving surgery	694	42	676	41	1,370	42
Postoperative radiotherapy*	1,072	66	1,091	67	2,167	66
Adjuvant tamoxifen and/or aromatase inhibitor†	1,286	96	1,287	96	2,582	96

Abbreviations: AC>T, doxorubicin and cyclophosphamide followed by docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide.
*Among all patients who actually received chemotherapy (n = 1,634 in the AC>T group and n = 1,635 in the TAC group).
†Among all hormone receptor–positive patients who actually received chemotherapy (n = 1,339 in the AC>T group and n = 1,334 in the TAC group).

Approximately 99% of the randomly assigned patients received at least one cycle of the assigned chemotherapy (Fig 1), and the majority of patients in both arms received the full number of cycles as per protocol (ie, eight cycles of AC>T [1,478 patients, 90%] or six cycles of TAC [1,528 patients, 93%]). Of a total number of 12,615 cycles of AC>T and 9,475 cycles of TAC, 94% and 92%, respectively, were given at full doses, and 79% and 76% of the patients, respectively, were treated without delays or dose reductions. The median relative dose-intensity was 99% for all agents in both arms; 86% of the patients in the AC>T group and 89% of those in the TAC group had a relative dose-intensity of their chemotherapy ≥ 90%. Nearly all patients with hormone receptor–positive disease (96% in both groups) received adjuvant tamoxifen and/or aromatase inhibitors.

Outcome

At a median follow-up of 65 months, 708 events occurred, including 586 breast cancer relapses, 96 second primary malignancies, and 26 deaths. Table 2 summarizes the first observed DFS events in the intent-to-treat population. Kaplan-Meier curves of DFS are shown in Figure 2. The 5-year DFS rates were 78.6% in the AC>T group and 78.9% in the TAC group (hazard ratio [HR], 1.00; 95% CI, 0.86 to 1.16; log-rank $P = .98$). The OS curves are depicted in Figure 3. The 5-year OS rates were 88.9% and 88.1% in the AC>T and TAC arms, respectively (HR, 0.91; 95% CI, 0.75 to 1.11; log-rank $P = .37$). The efficacy of both regimens was equivalent in all subgroups, including number of involved axillary lymph nodes and hormone receptor status (Fig 4). In this HER2-nonamplified node-positive adjuvant population treated with aggressive and standardized adjuvant therapies, the outcome of patients with hormone-sensitive (luminal) breast cancers differed significantly from those with triple receptor–negative disease. The 5-year DFS was 81% in the hormone receptor–positive patient population, and it was 68.6% in the triple-negative group (HR, 0.535; 95% CI, 0.453 to 0.632; log-rank $P < .001$; Appendix Figs A1 and A2, online only).

Toxicity

Treatment-emergent grades 3 to 4 adverse events are listed in Table 3 As expected, the predominant toxicity was hematologic with either regimen. Although incidence of grade 3 or 4 neutropenia was similar between the groups, incidence of febrile neutropenia was significantly higher during chemotherapy with TAC

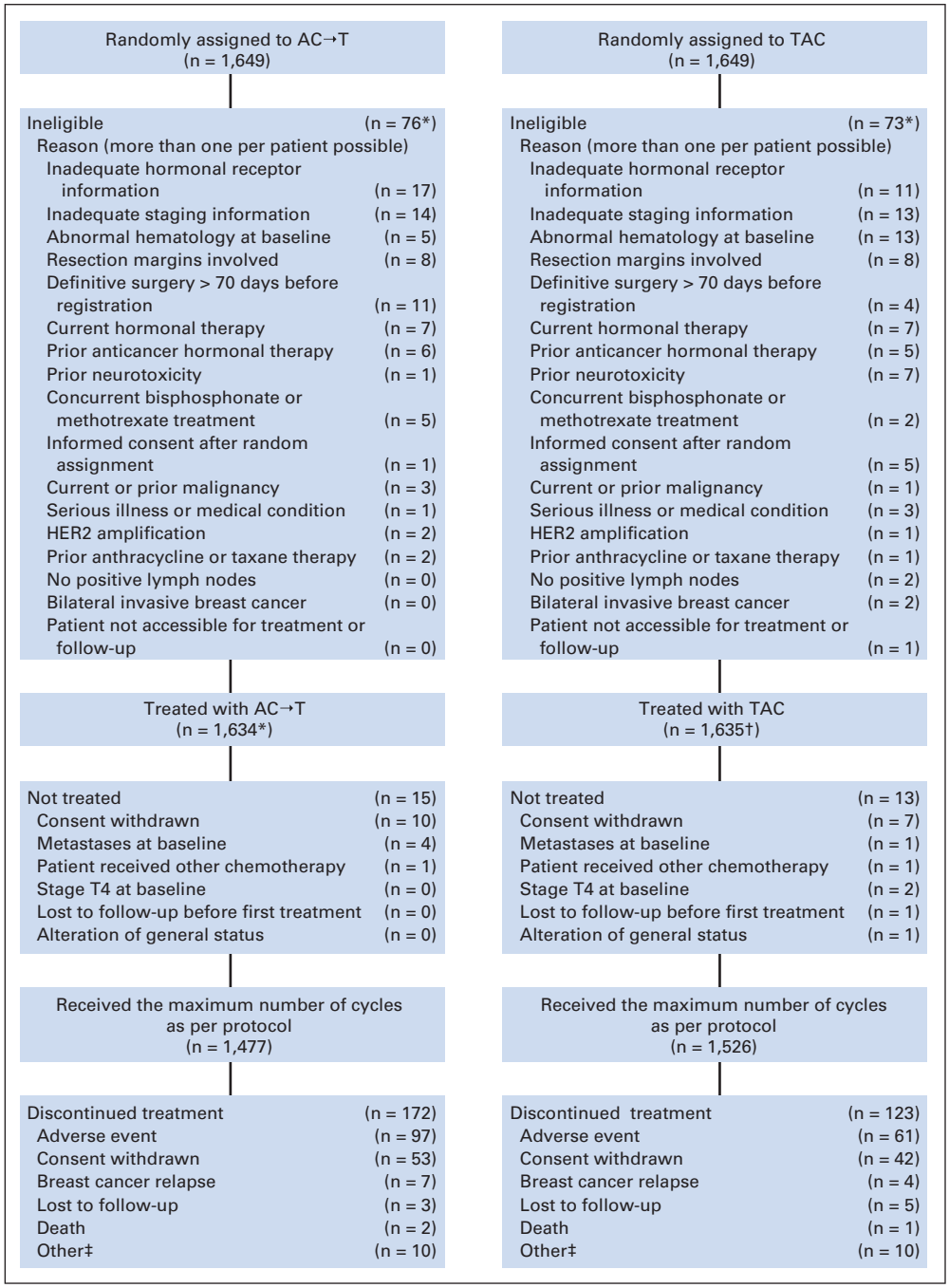

Fig 1. CONSORT diagram for patients in Breast Cancer International Research Group (BCIRG) –005 trial. AC→T, doxorubicin/cyclophosphamide followed by docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2. (*) Three patients received one cycle of paclitaxel instead of docetaxel; two patients received four cycles and one patient one cycle of epirubicin instead of doxorubicin. (†) Two patients received three and six cycles, respectively, of epirubicin instead of doxorubicin. (‡) Including protocol deviations and unspecified reasons.

compared with AC>T (17.4% *v* 7.7%; $P < .001$). However, there was a higher rate of infections with unknown absolute neutrophil count in the AC>T arm, and the rate of other infections was similar in both arms. Primary prophylaxis with G-CSF was not a protocol requirement but was given to 17% of patients in the TAC arm beginning with the first cycle. Any G-CSF usage was more frequent in the TAC group (44% of patients and 33% of cycles) compared with the AC>T group (28% of patients and 15% of cycles). Antibiotic prophylaxis was protocol mandated during TAC, and 96% of patients in the TAC group received antibiotics compared with 24% of patients in the AC>T group. Severe nonhematologic toxicities were uncommon with either treatment, with few differences between the groups. When nonhematologic toxicities of any grade were considered in the AC>T and TAC groups, incidences of sensory neuropathy (42.8% *v* 27.5% and 8.6% *v* 3.3% when referring to grade 2 only), myalgia (50.9% *v* 35.8%), and nail changes (44.5% *v* 22.1%) were significantly higher in the AC>T group (all $P < .001$), whereas incidence of thrombocytopenia was higher in the TAC group (25.6% *v* 41.0%; $P < .001$). There were five deaths attributable to chemotherapy; two were in the AC>T group, including one occurrence of congestive heart failure, and three were in the TAC group, including one septic death.

Table 2. First Observed DFS Events in the Intent-to-Treat Population

Event	Patients by Regimen: AC>T (n = 1,649) No.	%	TAC (n = 1,649) No.	%	Total (N = 3,298) No.	%
Any event	356	22	352	21	708	21
Breast cancer relapse	300	18	286	17	586	18
Local	58	3.5	46	2.8	104	3.2
Regional	29	1.8	22	1.3	51	1.5
Distant	248	15	240	15	488	15
Second primary malignancy	45	2.7	51	3.1	96	2.9
Left breast cancer	6	0.4	13	0.8	19	0.6
Right breast cancer	2	0.1	3	0.2	5	0.2
Endometrial cancer	2	0.1	6	0.4	8	0.2
Ovarian cancer	2	0.1	1	0.1	3	0.1
Leukemia	2	0.1	4	0.2	6	0.2
Other	31	1.9	24	1.5	55	1.7
Death	11	0.7	15	0.9	26	0.8
Septic	0	0.0	1	0.1	1	< 0.1
Non-septic	2	0.1	2	0.1	4	0.1
Anticancer treatment	0	0.0	0	0.0	0	0.0
After BCR/SPM						
Breast cancer	0	0.0	1	0.1	1	< 0.1
Malignant disease other than BCR	0	0.0	1	0.1	1	< 0.1
Other	8	0.5	10	0.6	18	0.5

Abbreviations: DFS, disease-free survival; AC>T, doxorubicin and cyclophosphamide followed by docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide; BCR, breast cancer relapse; SPM, second primary malignancy.

Study medication was discontinued because of toxicity in 97 patients in the AC>T group and 61 patients in the TAC group. Adverse events contributing most often to discontinuation of chemotherapy included sensory neuropathy (n = 14), hypersensitivity reactions (n = 10), diarrhea (n = 8), myalgia (n = 7), and neutropenia (n = 7) in the AC>T group, and hypersensitivity reactions (n = 7), febrile neutropenia (n = 7), neutropenic infection (n = 6), and nausea (n = 6) in the TAC group.

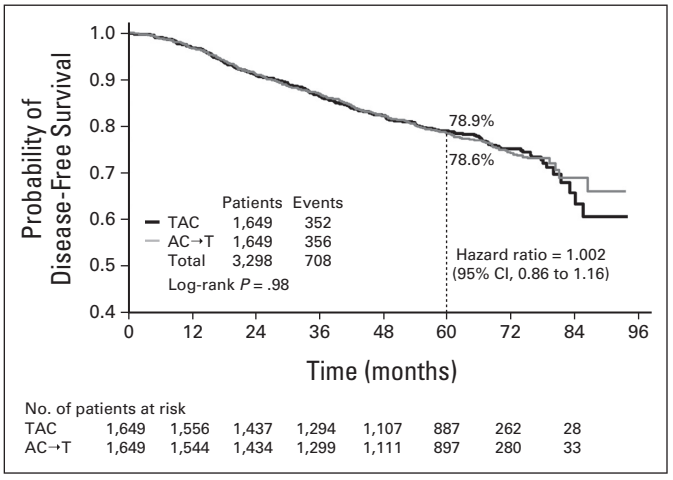

Fig 2. Kaplan-Meier curves of disease-free survival. TAC, docetaxel, doxorubicin, and cyclophosphamide; AC→T, doxorubicin and cyclophosphamide followed by docetaxel.

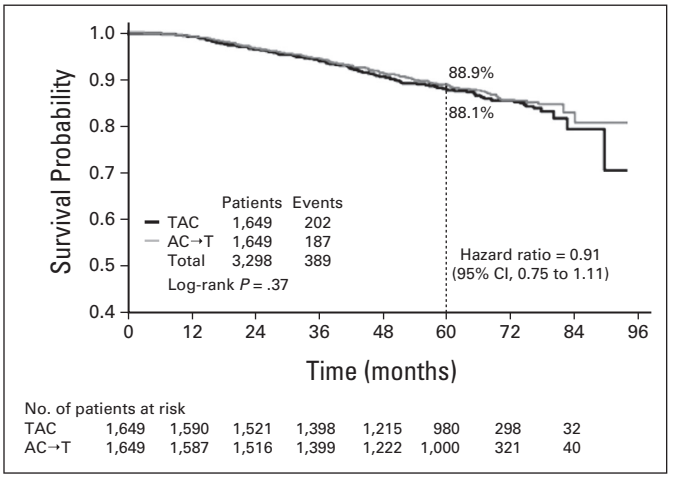

Fig 3. Kaplan-Meier curves of overall survival. TAC, docetaxel, doxorubicin, and cyclophosphamide; AC→T, doxorubicin and cyclophosphamide followed by docetaxel.

DISCUSSION

BCIRG-005 was designed to demonstrate a 5% difference in DFS between combination and sequential anthracycline-taxane chemotherapy in the adjuvant HER2-nonamplified breast cancer population. We compared the efficacy and safety of two docetaxel-containing adjuvant regimens in patients with operable, node-positive, HER2-nonamplified breast cancer and found that 5-year DFS and OS rates were indistinguishable after six cycles of TAC and four cycles of AC followed by four doses of docetaxel. The efficacy of the regimens was also comparable in subgroups defined by endocrine responsiveness and the number of involved nodes. The toxicity of both regimens was manageable. TAC was associated with more febrile neutropenia and thrombocytopenia, whereas more sensory neuropathy, nail changes, and myalgia occurred during treatment with AC>T. The incidence of neutropenic infection was similar between the treatment arms. In this study, only 17% of patients in the TAC arm received primary prophylactic G-CSF beginning with the first cycle; we now know that systematic administration of prophylactic G-CSF beginning with the first cycle reduces the rate of febrile

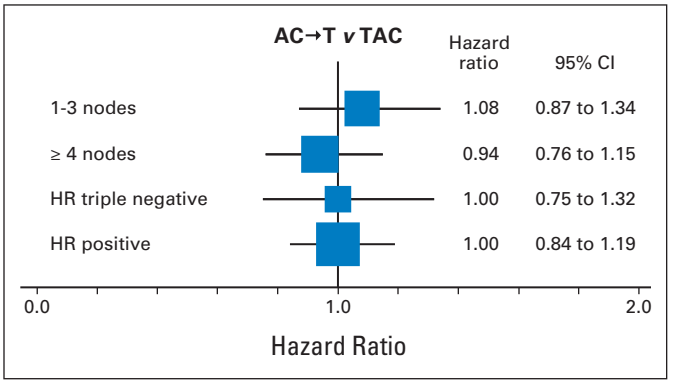

Fig 4. Hazard ratio plot of the effect of chemotherapy on survival by number of involved lymph nodes and hormone receptor status. Size of squares represents relative weight in the analysis. HR hormone receptor; AC→T, doxorubicin and cyclophosphamide followed by docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide.

Table 3. Grades 3 to 4 Adverse Events Among Treated Patients

Adverse Event*	% of Patients by Regimen: AC>T (n = 1,634)	TAC (n = 1,635)	P
Hematologic toxicity and infection			
Neutropenia	57.8	59.9	.22
Febrile neutropenia†	7.7	17.4	< .0001
Infection			
Neutropenic infection	8.5	9.7	.25
Infection with unknown ANC	11.1	6.9	< .0001
Infection without neutropenia	3.6	2.9	.23
Anemia	2.0	2.9	.07
Thrombocytopenia	1.3	2.5	.01
Leukemia/myelodisplastic syndrome	0.24	0.18	.99
Nonhematologic toxicity			
Diarrhea	3.1	2.9	.75
Dyspnea	1.5	1.3	.65
Fatigue	6.3	5.1	.15
Fluid retention	1.5	0.6	.01
Hand-foot skin reaction	1.8	0	< .0001
Hyperglycemia	1.4	1.3	.88
Irregular menses	19.6	18.8	.59
Myalgia	4.9	0.9	< .0001
Sensory neuropathy	1.5	0.3	.0004
Pain other than neuropathic	1.0	1.0	.99
Stomatitis	2.9	2.6	.59
Syncope	1.9	2.9	.07
Thrombosis/embolism	1.3	1.3	.88
Nausea	3.9	4.4	.49
Vomiting	5.2	4.1	.13
Congestive heart failure	0.4	0.1	.06

Abbreviations: AC>T, doxorubicin and cyclophosphamide followed by docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide; ANC, absolute neutrophil count.

*Adverse events with an incidence of 1% or more in at least one treatment group are shown, as well as important long-term toxicities.

†ANC $< 1.0 \times 10^9$/L and fever $\geq$ 38.5°C.

neutropenia from 24.6% to 6.5% ($P < .001$).[11] In accordance with current American Society of Clinical Oncology guidelines,[12] we believe that G-CSF should be systematically given as primary prophylaxis for patients receiving TAC.

The results of this study do not support the concept that sequential administration of an anthracycline and docetaxel is superior to combination treatment in the adjuvant setting. Rather, we found equivalent efficacy in both arms, despite the fact that AC>T delivered a higher absolute dose-intensity (defined as milligrams per square meter per week of administration) for each of the three agents, that AC>T was given for more cycles (eight *v* six), and that patients received chemotherapy for a longer duration (24 *v* 18 weeks).

When put into the context of reported adjuvant chemotherapy studies, it becomes evident that both TAC for six cycles and AC for four cycles followed by docetaxel for four cycles are among the most active regimens currently available for the adjuvant treatment of early, HER2-nonamplified breast cancer. Because paclitaxel cannot be safely combined with full-dose anthracycline chemotherapy as a result of a pharmacokinetic interaction and unacceptably high levels of cardiotoxicity,[13] the published experience with adjuvant taxane-anthracycline combination chemotherapy is confined to studies with docetaxel. In the BCIRG-001 study, adjuvant chemotherapy with six cycles of the TAC regimen as used in this trial was more effective than six cycles of the standard FAC regimen (ie, fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2).[9] Conversely, the regimen of sequential AC for four cycles followed by docetaxel for four cycles proved to be more effective than four cycles of TAC and also more effective than four cycles of AT, whereas the two latter regimens were similarly effective, according to the results of the National Surgical Adjuvant Breast and Bowel Project B-30 trial presented at the San Antonio Breast Cancer Symposium in 2008, at San Antonio, TX.[14] The summation of the BCIRG-005 results with National Surgical Adjuvant Breast and Bowel Project NSABP B-30, which have in common an identical regimen of AC for four cycles followed by docetaxel for four cycles, strongly suggests that four cycles of TAC is inferior to the standard six-cycle TAC regimen in this study. The Reposant sur des Arguments Pronostiques et Prédictifs-01 (RAPP-01)[15] and Eastern Cooperative Oncology Group 2197[16] studies demonstrated comparable efficacy for four cycles of AT (doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 in RAPP-01 trial and doxorubicin 60 mg/m^2 + docetaxel 60 mg/m^2 in Intergroup trial) and four cycles of AC (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 in both trials).

Two recent, large studies reported significant advantages of sequential epirubicin-docetaxel regimens over six cycles of fluorouracil, epirubicin, cyclophosphamide, with epirubicin given at 100 mg/m^2 ($FE_{100}C$). The sequential regimen in the Programme d'Actions Concertées Sein (PACS-01) trial consisted of three cycles of $FE_{100}C$ followed by three doses of docetaxel at 100 mg/m^2 every 3 weeks.[17] DFS improved from 65.8% to 70.2% ($P = .03$), and OS improved from 78% to 83.2% ($P = .006$) at 8 years. The patients in this study had one to three involved nodes (62% of patients) or $\geq$ 4 involved nodes (38% of patients), which was similar to our study. In the Epirubicin and Cyclophosphamide Followed by Docetaxel (EC-Doc) trial, the experimental regimen consisted of four cycles of epirubicin and cyclophosphamide (90/600 mg/m^2) followed by four doses of docetaxel 100 mg/m^2.[18] Only patients with one to three positive nodes were included. Event-free survival and OS rates at 5 years were higher in the sequential arm than in patients treated with $FE_{100}C$ (90% *v* 86% [$P = .004$] and 95% *v* 90% [$P = .03$], respectively).

The BIG02-98 trial[19] randomly assigned 2,887 node-positive patients (including 46% with $\geq$ four involved nodes) to four sequential regimens, with or without docetaxel: doxorubicin 75 mg/m^2 for four cycles followed by cyclophosphamide, methotrexate, and fluorouracil (CMF) for three cycles (A×4>CMF×3); doxorubicin and cyclophosphamide 60/600 mg/m^2 for four cycles followed by CMF for three cycles (AC×4>CMF×3), doxorubicin 75 mg/m^2 for three cycles followed by docetaxel 100 mg/m^2 for three cycles followed by CMF for three cycles (A×3>T×3>CMF×3); or doxorubicin and docetaxel 50/75 mg/m^2 for four cycles followed by CMF for three cycles (AT×4>CMF×3). When all docetaxel-treated patients were compared with all control patients, the addition of docetaxel improved 5-year DFS, though statistical significance was not achieved (HR, 0.86; 95% CI, 0.74 to 1.00; $P = .051$). However, comparison of the single-docetaxel arms with their respective control arms revealed that only the sequential addition of docetaxel prolonged 5-year DFS (A×3>T×3>CMF×3 *v* A×4>CMF×3; HR, 0.79; 95% CI, 0.64 to 0.98; $P = .035$), whereas combination doxorubicin and docetaxel did not (AT×4>CMF×3 *v* AC×4>CMF×3; HR, 0.93; 95% CI, 0.75 to

1.14; $P = .48$). It is interesting to note that, in each of the four trials discussed here, the two-drug combination of doxorubicin plus docetaxel was not shown to be more effective than the comparator regimens, which suggests that cyclophosphamide has an important contribution to the activity of the TAC regimen. The contribution of doxorubicin to the efficacy of the TAC regimen in the HER2-normal adjuvant population will be formally evaluated in the ongoing US Oncology Network study, in which six cycles of standard TAC will be compared with six cycles of docetaxel/cyclophosphamide 75/600 mg/m^2. Evaluation of the relative merits of TAC and of AC×4>paclitaxel 175 mg/m^2 every 2 weeks for four cycles await the results of the ongoing National Surgical Adjuvant Breast and Bowel Project NSABP B-38 study, in which these two regimens are directly compared.

When our results are put into the context of reported adjuvant chemotherapy studies, it becomes evident that both TAC for six cycles and AC for four cycles followed by docetaxel for four cycles are among the most active regimens currently available for the adjuvant treatment of HER2-nonamplified breast cancer. Because TAC for six cycles and AC for four cycles followed by docetaxel for four cycles have equivalent efficacy, the choice of regimen requires balancing the differences in toxicity and treatment duration. When used with primary prophylactic G-CSF to reduce hematologic complications, the TAC regimen provides an acceptable global safety profile and allows a substantially shorter duration of treatment, and it remains an appropriate standard adjuvant chemotherapy regimen for women with early-stage, HER2-nonamplified breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Marc Buyse, IDDI (C) **Consultant or Advisory Role:** Wolfgang Eiermann, Roche (C), AstraZeneca (C), sanofi-aventis (C), Novartis (C); Tadeusz Pienkowski, Roche (C), sanofi-aventis (C); Miguel Martin, sanofi-aventis (C); Arlene Chan, sanofi-aventis (C); Louise Provencher, sanofi-aventis (C); Michael Press, GlaxoSmithKline (C), sanofi-aventis (C) **Stock Ownership:** Marc Buyse, IDDI **Honoraria:** Wolfgang Eiermann, Roche, AstraZeneca, sanofi-aventis, Novartis, Cephalon; John Crown, sanofi-aventis; Saeed Sadeghi, sanofi-aventis; Miguel Martin, sanofi-aventis; Sandeep Sehdev, sanofi-aventis; Louise Provencher, sanofi-aventis; Guido Sauter, Abbott, Roche; John R. Mackey, sanofi-aventis **Research Funding:** Tadeusz Pienkowski, sanofi-aventis; John Crown, sanofi-aventis; Arlene Chan, sanofi-aventis; Mansoor Saleh, sanofi-aventis; Louise Provencher, sanofi-aventis; Michael Press, Genetech, Ventana Medical Systems, GlaxoSmithKline; Guido Sauter, Abbott, Roche **Expert Testimony:** None **Other Remuneration:** Arlene Chan, sanofi-aventis

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