ORIGINAL ARTICLE

Adjuvant Docetaxel for Node-Positive Breast Cancer

Miguel Martin, M.D., Tadeusz Pienkowski, M.D., John Mackey, M.D., Marek Pawlicki, M.D., Jean-Paul Guastalla, M.D., Charles Weaver, M.D., Eva Tomiak, M.D., Taher Al-Tweigeri, M.D., Linnea Chap, M.D., Eva Juhos, M.D., Raymond Guevin, M.D., Anthony Howell, M.D., Tommy Fornander, M.D., John Hainsworth, M.D., Robert Coleman, M.D., Jeferson Vinholes, M.D., Manuel Modiano, M.D., Tamas Pinter, M.D., Shou C. Tang, M.D., Bruce Colwell, M.D., Catherine Prady, M.D., Louise Provencher, M.D., David Walde, M.D., Alvaro Rodriguez-Lescure, M.D., Judith Hugh, M.D., Camille Loret, Ph.D., Matthieu Rupin, M.Sc., Sandra Blitz, M.Sc., Philip Jacobs, Ph.D., Michael Murawsky, M.Sc., Alessandro Riva, M.D., and Charles Vogel, M.D., for the Breast Cancer International Research Group 001 Investigators*

From Hospital Universitario San Carlos, Madrid (M. Martin); Maria Sklodowska-Curie Cancer Center, Warsaw, Poland (T. Pienkowski); Cross Cancer Institute, Edmonton, Canada (J.M., J. Hugh); Maria Sklodowska-Curie Memorial Institute, Krakow, Poland (M.P.); Centre Léon Bérard, Lyon, France (J.-P.G.); Response Oncology, Memphis, Tenn. (C.W.); Ottawa Regional Cancer Center, Ottawa (E.T.); Saskatoon Cancer Center, Saskatoon, Canada (T.A.-T.); UCLA School of Medicine, Los Angeles (L.C.); National Institute of Oncology, Budapest, Hungary (E.J.); Hôpital Saint Luc, Montreal (R.G.); Christie Hospital, Manchester, United Kingdom (A.H.); Onkologkliniken Södersjukhuset, Stockholm (T.F.); Cannon Cancer Center, Nashville (J. Hainsworth); Weston Park Hospital, Sheffield, United Kingdom (R.C.); Hospital Santa Casa de Misericordia, Porto Alegre, Brazil (J.V.); Arizona Clinical Research Center, Tucson (M. Modiano); Petz Aladár County Teaching Hospital, Gyor, Hungary (T. Pinter); Murphy Cancer Centre, Saint John, Canada (S.C.T.); Nova Scotia Cancer Center, Halifax, Canada (B.C.); Dumont Hospital, Moncton, Canada (C.P.); Hôpital du Saint Sacrement, Quebec, Canada (L.P.); Plummer Memorial Hospital, Sault Ste. Marie, Canada (D.W.); Hospital General, Elche, Spain (A.R.-L.); Breast Cancer International Research Group, Paris (C.L., M.R., S.B., A.R.); Institute of Health Economics, Edmonton, Canada (P.J.); Aventis Pharma, Antony, France (M. Murawsky); and Cancer Research Network, Plantation, Fla. (C.V.). Address reprint requests to Dr. Martin at Servicio de Oncologia Medica, Hospital Universitario San Carlos, 28040 Madrid, Spain, or at mmartin@geicam.org.

*Additional study investigators are listed in the Appendix.

N Engl J Med 2005;352:2302-13.

ABSTRACT

BACKGROUND

We compared docetaxel plus doxorubicin and cyclophosphamide (TAC) with fluorouracil plus doxorubicin and cyclophosphamide (FAC) as adjuvant chemotherapy for operable node-positive breast cancer.

METHODS

We randomly assigned 1491 women with axillary node-positive breast cancer to six cycles of treatment with either TAC or FAC as adjuvant chemotherapy after surgery. The primary end point was disease-free survival.

RESULTS

At a median follow-up of 55 months, the estimated rates of disease-free survival at five years were 75 percent among the 745 patients randomly assigned to receive TAC and 68 percent among the 746 randomly assigned to receive FAC, representing a 28 percent reduction in the risk of relapse (P=0.001) in the TAC group. The estimated rates of overall survival at five years were 87 percent and 81 percent, respectively. Treatment with TAC resulted in a 30 percent reduction in the risk of death (P=0.008). The incidence of grade 3 or 4 neutropenia was 65.5 percent in the TAC group and 49.3 percent in the FAC group (P<0.001); rates of febrile neutropenia were 24.7 percent and 2.5 percent, respectively (P<0.001). Grade 3 or 4 infections occurred in 3.9 percent of the patients who received TAC and 2.2 percent of those who received FAC (P=0.05); no deaths occurred as a result of infection. Two patients in each group died during treatment. Congestive heart failure and acute myeloid leukemia occurred in less than 2 percent of the patients in each group. Quality-of-life scores decreased during chemotherapy but returned to baseline levels after treatment.

CONCLUSIONS

Adjuvant chemotherapy with TAC, as compared with FAC, significantly improves the rates of disease-free and overall survival among women with operable node-positive breast cancer.

Adjuvant chemotherapy for breast cancer has undergone a major change over the past two decades. Chemotherapy with a regimen that includes an anthracycline or a combination of cyclophosphamide, methotrexate, and fluorouracil significantly decreases the risks of disease recurrence and death among women with early-stage breast cancer.[1] The overview analysis of the Early Breast Cancer Trialists' Collaborative Group demonstrated that, as compared with standard treatment with cyclophosphamide, methotrexate, and fluorouracil, regimens that contained doxorubicin or epirubicin reduced the annual risk of recurrence of breast cancer by 12 percent and the annual risk of death by 11 percent. Rates of disease-free and overall survival were similar among women treated with either six cycles (spanning 24 weeks) of cyclophosphamide, methotrexate, and fluorouracil or four cycles (12 weeks) of doxorubicin plus cyclophosphamide.[2]

Six cycles of fluorouracil, doxorubicin, and cyclophosphamide (FAC), given in various doses and according to various schedules, or fluorouracil, epirubicin, and cyclophosphamide appear superior to six cycles of cyclophosphamide, methotrexate, and fluorouracil in early-stage breast cancer,[1,3,4] and six cycles of adjuvant fluorouracil, epirubicin, and cyclophosphamide are better than three cycles in terms of disease-free and overall survival.[5] Therefore, at the time this trial was initiated, six cycles of FAC; cyclophosphamide, doxorubicin, and fluorouracil; or fluorouracil, epirubicin, and cyclophosphamide every three weeks were generally accepted as appropriate adjuvant regimens for the treatment of early breast cancer.[6] Although various regimens with fluorouracil, doxorubicin, and cyclophosphamide that differed in schedule and dose were developed,[7-10] no randomized, prospective, comparative trial has demonstrated the superiority of any one regimen.

Docetaxel, an active agent in the treatment of breast cancer,[11] is not cross-resistant with anthracyclines,[12,13] appears to be more active than doxorubicin,[14] and does not interfere with the pharmacokinetics of doxorubicin,[15,16] indicating that, unlike paclitaxel,[17-19] it may not exacerbate doxorubicin-related cardiotoxicity.[20,21] Three large randomized trials involving treatments for metastatic breast cancer found that regimens of docetaxel plus doxorubicin and of docetaxel, doxorubicin, and cyclophosphamide (TAC) have antitumor activity superior to that of doxorubicin plus cyclophosphamide and that of FAC, although survival was not significantly different between the treatment groups in two of the three studies.[21-23]

In 1997, the Breast Cancer International Research Group began a phase 3 trial to compare the docetaxel-containing regimen TAC with a regimen of FAC as adjuvant treatment for women with operable node-positive breast cancer. At a planned interim analysis at 33 months (August 2001), we reported a statistically significant improvement in the rate of disease-free survival among patients treated with TAC as compared with those treated with FAC (hazard ratio, 0.68; P=0.0011).[24] Because the results of this analysis did not meet the predefined P value of less than 0.001 to ascertain a statistically significant difference between TAC and FAC,[25] the independent data monitoring committee recommended that the protocol be amended to include a second interim analysis, to be conducted at the point at which there had been 400 events, in addition to the protocol-specified final analysis after 590 disease-free survival events. The comparison was to be performed at the level of P=0.001 for the primary end point of disease-free survival. We report the results of the second interim analysis, which was performed after a median follow-up period of 55 months (after 399 disease-free survival events).

METHODS

STUDY POPULATION

Women eligible for the study were between 18 and 70 years of age, had a score on the Karnofsky performance scale of 80 percent or more, and had undergone primary surgery (i.e., mastectomy, tumorectomy, or lumpectomy) with axillary-node dissection (sentinel-node biopsy was not routine practice) for unilateral, operable carcinoma of the breast. Patients were randomly assigned to a study group within 60 days after surgery. All patients had at least one axillary lymph node that was positive for cancer on histologic examination. The margins of resected specimens had to be histologically free of invasive adenocarcinoma and ductal carcinoma in situ. A complete staging workup within three months before registration — including bilateral mammography; chest radiography; abdominal ultrasonography, computed tomography, or both; and bone scanning — and an assessment of the left ventricular ejection fraction with the use of multiple gated acquisition scanning or echocardiography were mandatory.

Criteria for exclusion included advanced disease (i.e., T4, N2 or N3, or M1), a history of other cancers, motor or sensory neuropathy of grade 2 or more according to the National Cancer Institute Common Toxicity Criteria, pregnancy, lactation, and any serious illness or medical condition other than breast cancer. Prior therapy with anthracyclines or taxanes was not allowed.

The study was approved by the ethics committees or institutional review boards of all participating institutions. All patients provided written informed consent. The trial was conducted according to Good Clinical Practice and International Conference on Harmonization rules, including verification of source data.

STUDY DESIGN

In this phase 3, multicenter, prospective trial, randomization was stratified according to institution and number of involved axillary lymph nodes per patient (one to three vs. four or more). On day 1 of each of six 21-day cycles, eligible patients received either TAC (50 mg of doxorubicin per square meter of body-surface area in an intravenous infusion for 15 minutes, followed by 500 mg of cyclophosphamide per square meter administered intravenously for 1 to 5 minutes and then, after a 1-hour interval, 75 mg of docetaxel per square meter in an intravenous infusion for 1 hour) or FAC (50 mg of doxorubicin per square meter followed by 500 mg of fluorouracil per square meter, each as an intravenous infusion for 15 minutes, and then 500 mg of cyclophosphamide per square meter in an intravenous infusion for 1 to 5 minutes).

The primary end point was disease-free survival, defined as the time from randomization to the date of a clinical relapse (with histopathologic confirmation or radiologic evidence of tumor recurrence), a second cancer (with the exception of skin cancer other than melanoma, ductal or lobular carcinoma in situ of the breast, or in situ carcinoma of the cervix), or death, whichever occurred first. Secondary end points included overall survival (i.e., the time from randomization until death from any cause), toxic effects, and quality of life.

STUDY PROCEDURES

Concomitant Therapy and Dose Modifications

Patients randomly assigned to receive TAC received dexamethasone premedication (8 mg orally every 12 hours six times beginning the day before treatment started) to prevent docetaxel-related hypersensitivity and fluid retention. All patients were to receive a prophylactic antibiotic (500 mg of ciprofloxacin twice daily on days 5 to 14 of each cycle). Patients in the FAC group received prophylactic antibiotics only after an episode of febrile neutropenia or infection. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was not permitted. However, among patients who had one episode of febrile neutropenia or infection in subsequent cycles, administration of G-CSF was mandatory (150 μg of lenograstim per square meter per day or 5 μg of filgrastim per kilogram of body weight per day on days 4 to 11).

On completion of chemotherapy, tamoxifen (20 mg daily for five years) was administered to patients with estrogen-receptor–positive tumors, progesterone-receptor–positive tumors, or both. Radiotherapy was mandatory after breast-conserving surgery and was administered after mastectomy according to each institution's guidelines.

Dose modifications were planned according to standard toxicity criteria. Discontinuation of treatment was required for patients in whom there were nonhematologic grade 4 toxic effects according to the National Cancer Institute Common Toxicity Criteria, grade 3 toxic effects despite a dose reduction, or clinically significant cardiac events.

Evaluations

Blood counts and general biochemical and clinical assessments, including those for toxic effects, were performed on day 21 of each cycle and then every six months for the first five years of follow-up, after which they were performed annually. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 1.0. Chest radiography was repeated every 12 months for the first 5 years of follow-up. Mammography was repeated annually during follow-up.

Estrogen-receptor and progesterone-receptor status in the tumor was evaluated by immunohistochemical analysis.[26] *HER2/neu* gene amplification was evaluated by fluorescence in situ hybridization, with a positive result defined as a ratio of *HER2/neu* to chromosome 17 of greater than 2.0.[27-30] Assessments of hormone receptors and *HER2/neu* status were performed at the Cross Cancer Institute in Edmonton, Alberta, Canada.

Quality of Life

Quality of life was assessed with the use of the European Organisation for Research and Treatment

of Cancer Quality of Life Questionnaire (QLQ-C30, version 2.0) and the breast-cancer–specific QLQ-BR23 (version 1.0). The QLQ-C30 includes nine multiple-item scales pertaining to symptoms, five to function, and one to overall health — the global health status and quality-of-life scale. The QLQ-BR23 includes 23 questions regarding disease symptoms, treatment-related side effects, body image, sexuality, and future perspective. Patients were asked to complete both questionnaires on seven occasions: at baseline; before cycles 3 and 5; 3 to 4 weeks after the last cycle; and 6, 12, and 24 months after the last cycle.

Statistical Analysis

The trial was designed to have an overall power of 97 percent to detect a 27 percent reduction in the risk of relapse among patients treated with TAC as compared with those treated with FAC, regardless of nodal status. In addition, the study had 90 percent power to detect a 33 percent reduction in the risk of death. At the final analysis (i.e., at the point at which there were 590 patients), the sample size of 1491 patients would allow the detection, with 90 percent power, of a 27 percent reduction in the risk of relapse in favor of treatment with TAC among patients who had one to three positive lymph nodes. For the subgroup of patients with four or more positive nodes, the sample size would provide 80 percent power to detect a 29 percent reduction in the risk of relapse in favor of treatment with TAC.

The primary analysis was conducted according to the intention-to-treat principle, and a stratified log-rank test was used to compare TAC with FAC with respect to both disease-free and overall survival. The number of positive nodes (one to three or four or more) was the only stratification variable in the analysis. Analyses of subgroups according to hormone-receptor status and *HER2/neu* status were prospectively defined but were not powered. Unadjusted analyses and analyses according to the Cox proportional-hazards model (adjusted for age, tumor size, nodal status, hormone-receptor status, and *HER2/neu* status) were performed to estimate disease-free and overall survival. The Kaplan–Meier method was used to calculate probability estimates of disease-free and overall survival. Hypothesis testing was two-sided. Hazard ratios and 95 percent confidence intervals were obtained from the Cox proportional-hazards model. The primary quality-of-life analysis was performed with the use of the scores from the global health status and quality-of-life scale. A repeated-measures mixed-effect analysis of variance was performed to analyze the evolution of the scores on the global health status subscale over time.

The protocol was designed by the study chairs of the Breast Cancer International Research Group in collaboration with Aventis personnel. The data were collected and maintained by the Breast Cancer International Research Group. All analyses were conducted according to the protocol. The efficacy analyses were performed by the independent data monitoring committee; other analyses were conducted by Aventis personnel. Submission of the results for publication was mandated by the independent data monitoring committee. The manuscript was drafted by Dr. Martin and modified after review by the cochairs and other coauthors. A reviewer at Aventis evaluated the manuscript but did not participate in writing it. The final content of the manuscript was determined entirely by the investigators.

RESULTS

PATIENTS

Between June 1997 and June 1999, 1491 women from 20 countries were enrolled in the study. Eleven women (1 who had been randomly assigned to receive TAC and 10 assigned to receive FAC) did not receive any treatment, for the following reasons: 8 withdrew consent, 1 was lost to follow-up, and 2 did not receive treatment for other reasons. In total, 1480 patients (744 in the TAC group and 736 in the FAC group) were treated and were included in the safety analysis. Efficacy analyses were based on the intention-to-treat principle (1491 patients) and on populations of patients who were eligible according to the protocol (1421 patients). Seventy patients (4.7 percent of all those enrolled) — 36 in the TAC group and 34 in the FAC group — were ineligible. The most common reason for ineligibility in both groups was indeterminate hormone-receptor status at randomization (21 women in the TAC group and 19 in the FAC group). The groups were well balanced in terms of demographic and tumor characteristics (Table 1).

TREATMENT

Six treatment cycles were completed by 91.3 percent of the patients in the TAC group and by 96.6 percent of those in the FAC group. Overall, the median relative dose intensities were 99 percent in the TAC group and 98 percent in the FAC group. Treatment

Table 1. Characteristics of the Patients and the Tumors at Baseline.*

Characteristic	TAC Group (N=745)	FAC Group (N=746)
Age — yr		
Median	49	49
Range	26–70	23–70
Menopausal status — no. of women (%)		
Premenopausal†	421 (56.5)	409 (54.8)
Postmenopausal‡	324 (43.5)	337 (45.2)
Primary tumor size — no. of women (%)		
T1, ≤2 cm	296 (39.7)	320 (42.9)
T2, 2–5 cm	392 (52.6)	383 (51.3)
T3, >5 cm	57 (7.7)	43 (5.8)
Nodal status — no. of women (%)		
N1, N2, or N3	467 (62.7)	459 (61.5)
N4 or higher	278 (37.3)	287 (38.5)
Positive estrogen-receptor or progesterone-receptor status — no. of women (%)§	567 (76.1)	565 (75.7)
HER2/neu status — no. of women (%)¶		
Positive	155 (20.8)	164 (22.0)
Unknown	115 (15.4)	114 (15.3)
Breast-conserving surgery — no. of women (%)‖	300 (40.3)	303 (41.2)
With radiotherapy	285 (38.3)	293 (39.8)
Without radiotherapy	15 (2.0)	10 (1.4)
Mastectomy — no. of women (%)‖	444 (59.7)	433 (58.8)
With radiotherapy	227 (30.5)	236 (32.1)
Without radiotherapy	217 (29.2)	197 (26.8)

* TAC denotes docetaxel plus doxorubicin and cyclophosphamide, and FAC fluorouracil plus doxorubicin and cyclophosphamide.
† Premenopausal women were those in whom the last menses had occurred within the previous six months and who had not previously had bilateral ovariectomy or estrogen-replacement therapy (including women of unknown status less than 50 years of age).
‡ Postmenopausal women were those who had had a prior bilateral ovariectomy or in whom more than 12 months had passed since the last menses, with no prior hysterectomy (including women of unknown status 50 years of age or older).
§ For the central review, estrogen-receptor status was assessed with clone 6F11; progesterone-receptor status was assessed with clone 636 with the use of tumor blocks or unstained slides.
¶ *HER2/neu* status was determined by fluorescence in situ hybridization for 1250 patients. Immunohistochemistry with clone CB11 was used for 12 patients. The status of the remaining patients was not assessed owing to a lack of tumor specimens.
‖ Women who had surgery were among the treated patients (744 in the TAC group and 736 in the FAC group).

was modified (by a delay, a dose reduction, or both) for 250 patients in the TAC group (33.6 percent) and 293 in the FAC group (39.8 percent). The most frequent reason for delaying a cycle of treatment was the occurrence of hematologic toxic effects.

Adjuvant radiotherapy[31] was administered to 68.8 percent of the patients in the TAC group and 71.9 percent of those in the FAC group. Among women with hormone-receptor–positive tumors, the rates of compliance with tamoxifen treatment, as planned according to the protocol, were 94.9 percent in the TAC group and 93.7 percent in the FAC group.

EFFICACY

The efficacy analysis was performed after it had been documented that 399 events had been recorded (172 in the TAC group and 227 in the FAC group) as of July 15, 2003, representing a median follow-up period of 55 months (Table 2). Ninety-seven per-

cent of the patients in the study completed at least 45 months of follow-up.

The estimated rates of disease-free survival at five years were 75 percent in the TAC group and 68 percent in the FAC group (P=0.001). This difference was due mainly to the greater number of patients in the FAC group who had relapses of breast cancer at distant sites (Table 2). Similar results were observed in the eligible population as well as in the unadjusted and multivariate analyses (Fig. 1A). After adjustment for nodal status, treatment with TAC, as compared with FAC, was associated with a 28 percent reduction in the risk of relapse (hazard ratio, 0.72; 95 percent confidence interval, 0.59 to 0.88) (Fig. 1A).

The superiority of TAC over FAC was also observed in all planned subgroup analyses, which included the number of involved axillary lymph nodes, hormone-receptor status, and *HER2/neu* status, and was independent of menopausal status (a factor in the sensitivity analysis) (Fig. 2). In the subgroup of patients with one to three positive nodes, treatment with TAC reduced the risk of relapse by 39 percent (hazard ratio, 0.61; 95 percent confidence interval, 0.46 to 0.82; P<0.001). Among women with four or more positive nodes, treatment with TAC reduced the risk of relapse by 17 percent (hazard ratio, 0.83; 95 percent confidence interval, 0.63 to 1.08; P=0.17). Analysis with the Cox model did not detect any difference in the treatment effect between the two nodal-status strata (ratio of hazard ratios, 1.34; P=0.15), suggesting that TAC was superior to FAC, regardless of the number of lymph nodes involved.

Of the 221 deaths, 91 were in the TAC group and 130 in the FAC group; TAC was associated with a 30 percent lower risk of death than was FAC (hazard ratio, 0.70; 95 percent confidence interval, 0.53 to 0.91; P=0.008) (Fig. 1B). The estimated overall survival rates at five years were 87 percent in the TAC group and 81 percent in the FAC group.

Table 2. Analysis of Events According to the Intention-to-Treat Principle.*

Event	TAC Group (N=745)	FAC Group (N=746)
	no. of patients (%)	
None	573 (76.9)	519 (69.6)
Any event	172 (23.1)	227 (30.4)
Relapse of breast cancer	144 (19.3)	197 (26.4)
Local only, regional only, or both	29 (3.9)	39 (5.2)
Distant (with or without local or regional)	115 (15.4)	158 (21.2)
Second primary cancer	20 (2.7)	26 (3.5)
Contralateral breast cancer	7 (0.9)	8 (1.1)
Other cancers	13 (1.7)	18 (2.4)
Death (without evidence of cancer)	8 (1.1)	4 (0.5)
Due to toxic effects, with sepsis	0	0
Due to toxic effects, without sepsis	2 (0.3)	1 (0.1)
Other causes	6 (0.8)	3 (0.4)

* Events are those included in the analysis of disease-free survival. TAC denotes docetaxel plus doxorubicin and cyclophosphamide, and FAC fluorouracil plus doxorubicin and cyclophosphamide.

TOXIC EFFECTS

Overall, the incidence of grade 3 or 4 or severe nonhematologic adverse events, regardless of type, was 36.3 percent in the TAC group and 26.6 percent in the FAC group (P<0.001). The incidence of grade 3 or 4 neutropenia was 65.5 percent in the TAC group and 49.3 percent in the FAC group (P<0.001); febrile neutropenia was observed in 24.7 percent of the patients in the TAC group and 2.5 percent of those in the FAC group (P<0.001) (Table 3). Grade 3 or 4 infections occurred in 3.9 percent of patients treated with TAC and 2.2 percent of those treated with FAC (P=0.05); no deaths occurred as a result of infection (Table 4). The overall incidence of congestive heart failure (including that during follow-up) was 1.6 percent among patients treated with TAC and 0.7 percent for those treated with FAC (P=0.09). As of the cutoff date for this analysis, the only secondary hematologic cancer was acute myeloid leukemia, which developed in two patients in the TAC group and one patient in the FAC group.

QUALITY OF LIFE

All baseline quality-of-life values were similar between the two treatment groups, with a mean score of 72 (on a scale of 0 to 100, with higher scores representing a better quality of life) in both groups on the global health status subscale of the Quality of Life Questionnaire. The mean scores at the end of treatment were 62 in the TAC group (95 percent confidence interval, 61 to 64) and 69 in the FAC group (95 percent confidence interval, 67 to 70). At the first follow-up visit, the quality-of-life scores either returned to or were higher than those at baseline in both groups, with scores of 76 in the TAC group (95 percent confidence interval, 74 to 77) and 75 in the FAC group (95 percent confidence in-

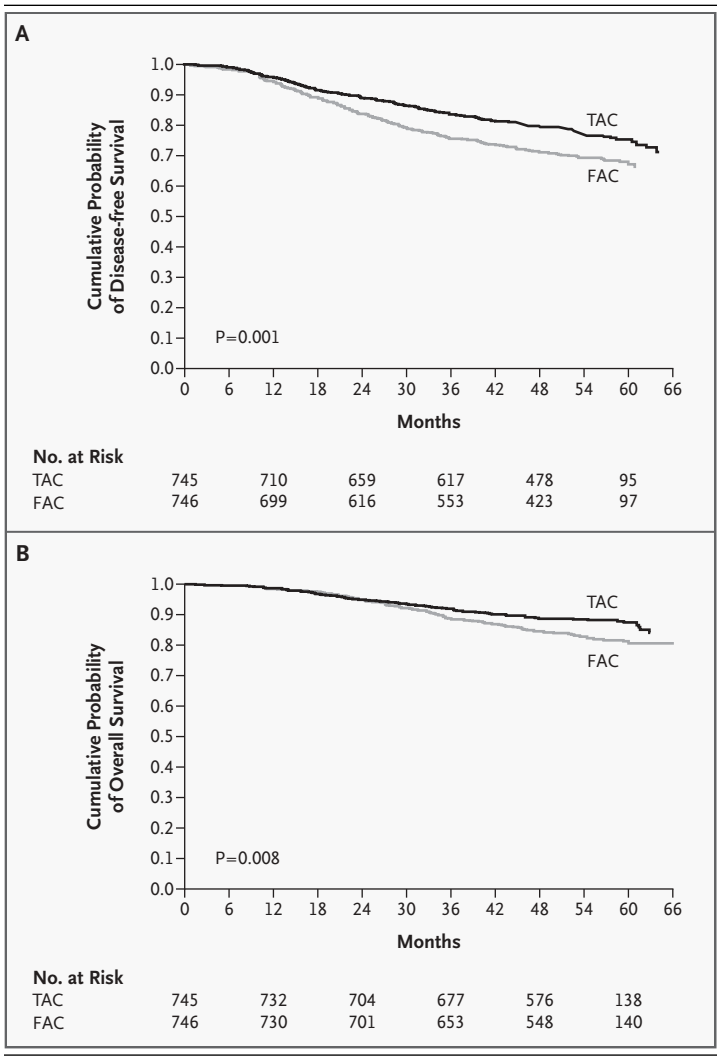

Figure 1. Analysis of Survival Rates in the Two Study Groups.

Panel A shows the rates of disease-free survival. For the 1491 randomly assigned patients included in the intention-to-treat analysis, the hazard ratio, adjusted for nodal status, was 0.72 (95 percent confidence interval, 0.59 to 0.88; P=0.001); unadjusted for nodal status, 0.71 (95 percent confidence interval, 0.59 to 0.87; P<0.001); and with the Cox proportional-hazards model — adjusted for number of positive nodes, age, tumor size, histologic grade, and hormone-receptor and *HER2/neu* status — 0.70 (95 percent confidence interval, 0.58 to 0.86; P<0.001). For the 1421 patients eligible for treatment, the hazard ratio, adjusted for nodal status, was 0.72 (95 percent confidence interval, 0.59 to 0.89; P=0.002). Events occurred in 172 patients (23 percent) in the TAC group and 227 (30 percent) in the FAC group. Data were censored for 573 patients (77 percent) in the TAC group and 519 (70 percent) in the FAC group. Panel B shows the rates of overall survival. For the 1491 randomized patients included in the intention-to-treat analysis, the hazard ratio, adjusted for nodal status, was 0.70 (95 percent confidence interval, 0.53 to 0.91; P=0.008); unadjusted for nodal status, 0.69 (95 percent confidence interval, 0.52 to 0.90; P=0.005); and with the Cox proportional-hazards model, adjusted for the same variables as those listed for Panel A, 0.68 (95 percent confidence interval, 0.52 to 0.89; P=0.004). For the 1421 patients eligible for treatment, the hazard ratio, adjusted for nodal status, was 0.70 (95 percent confidence interval, 0.53 to 0.93; P=0.01). Events occurred in 91 patients (12 percent) in the TAC group and 130 (17 percent) in the FAC group. Data were censored for 654 patients (88 percent) in the TAC group and 616 (83 percent) in the FAC group. P values and confidence intervals are nominal. TAC denotes docetaxel plus doxorubicin and cyclophosphamide, and FAC fluorouracil plus doxorubicin and cyclophosphamide.

terval, 73 to 77). Follow-up quality-of-life measurements were similar between the two groups and similar to baseline values: at six months, the scores were 77 in the TAC group (95 percent confidence interval, 75 to 78) and 75 in the FAC group (95 percent confidence interval, 73 to 77); at the end of two years, they were 78 in the TAC group (95 percent confidence interval, 76 to 79) and 76 in the FAC group (95 percent confidence interval, 74 to 78).

DISCUSSION

This randomized, phase 3 trial of adjuvant chemotherapy in women with operable node-positive breast cancer showed that, at a median follow-up of 55 months, the estimated rate of disease-free survival at 5 years was 75 percent in the TAC group and 68 percent in the FAC group (P=0.001). The relative risk of death was 30 percent lower among women in the TAC group than among those in the FAC group.

Moreover, treatment with TAC, as compared with FAC, was associated with a 28 percent relative reduction in the risk of relapse. The reduction in the risk of relapse did not seem to be driven by nodal status or by hormone-receptor or *HER2/neu* status. A final analysis of this trial at 590 events will be required to confirm and extend the findings of the main and subgroup analyses. Although amenorrhea occurred more frequently among women in the TAC group (61.7 percent) than among those in the FAC group (52.4 percent) (P=0.007), the superior efficacy of TAC over FAC in terms of disease-free survival was independent of menopausal sta-

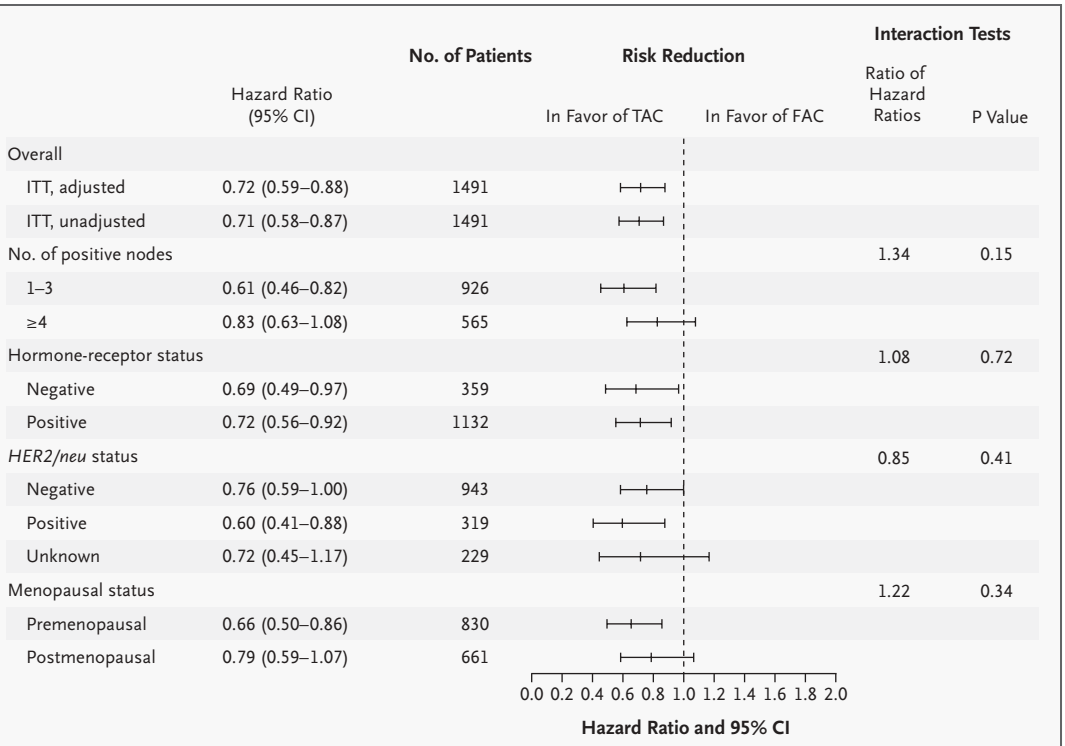

Figure 2. Risk Reduction for Disease-free Survival in the Main Subgroups.

Premenopausal patients included those whose menopausal status was unknown but who were less than 50 years of age; postmenopausal patients included those whose menopausal status was unknown but who were 50 years of age or older. TAC denotes docetaxel plus doxorubicin and cyclophosphamide, FAC fluorouracil plus doxorubicin and cyclophosphamide, ITT intention to treat, and CI confidence interval.

tus. The observation that the benefits of treatment with docetaxel are independent of hormone-receptor status are consistent with the findings of the National Surgical Adjuvant Breast and Bowel Project trial B-27,[32] in which patients with breast cancer who were treated with presurgical doxorubicin plus cyclophosphamide followed by docetaxel had higher rates of complete pathological response than did those treated with doxorubicin plus cyclophosphamide alone, regardless of hormone-receptor status.

The symmetrical design of this trial — in which patients underwent six cycles of treatment with either FAC or TAC, followed by tamoxifen therapy, radiation therapy, or both, as indicated — demonstrates a benefit with the replacement of fluorouracil by docetaxel. Six cycles of three-drug, anthracycline-based regimens are considered among the most effective treatments for node-positive breast cancer.[6] The FAC regimen generally used in North America (two doses of fluorouracil per cycle) was not directly compared with the FAC regimen we selected, and there is no evidence that the omission of a dose of fluorouracil would influence the patients' outcomes. At the dose and schedule used in this trial, FAC is an appropriate control chemotherapeutic regimen. The TAC combination in this trial was also administered at a feasible dose and schedule. In both groups, the dosage of doxorubicin was 50 mg per square meter for six cycles (for a total of 300 mg per square meter).

The Cancer and Leukemia Group B trial 9344 did not demonstrate a benefit with an escalation of the doxorubicin dosage (240, 300, or 360 mg per square meter, delivered over four cycles).[33] Another study of adjuvant therapy[34] showed that administering chemotherapy at shorter intervals (every two weeks vs. every three weeks) significantly improved

Table 3. Adverse Events in the Two Treatment Groups.*

Toxic Effect	TAC Group (N=744)		FAC Group (N=736)		P Value†	
	Overall	Grade 3 or 4 or Severe	Overall	Grade 3 or 4 or Severe	All	Grade 3 or 4
	percent					
Hematologic						
Anemia						
Any	91.5	4.3	71.7	1.6	<0.001	0.003
Need for blood transfusions	4.6	—	1.5	—	<0.001	—
Neutropenia	71.4	65.5	82.0	49.3	<0.001	<0.001
Thrombocytopenia	39.4	2.0	27.7	1.2	<0.001	0.23
Febrile neutropenia‡						
Protocol definition	24.7	—	2.5	—	<0.001	—
NCI CTC definition 2.0	28.8	—	4.4	—	<0.001	—
Neutropenic infection						
Protocol definition§	12.1	—	6.3	—	<0.001	—
NCI CTC definition 2.0	20.4	—	10.8	—	<0.001	—
Nonhematologic						
Alopecia	97.8	—	97.1	—	0.39	—
Asthenia	80.8	11.2	71.2	5.6	<0.001	<0.001
Nausea	80.5	5.1	88.0	9.5	<0.001	0.001
Stomatitis	69.4	7.1	52.9	2.0	<0.001	<0.001
Amenorrhea¶	61.7	—	52.4	—	0.007	—
Vomiting	44.5	4.3	59.2	7.3	<0.001	0.013
Infection	39.4	3.9	36.3	2.2	0.22	0.05
Diarrhea	35.2	3.8	27.9	1.8	0.002	0.02
Peripheral edema	33.7	0.5	12.6	0.1	<0.001	0.37‖
Myalgia	26.7	0.8	9.9	0	<0.001	0.03‖
Skin	26.5	0.8	17.7	0.4	<0.001	0.51‖
Neurosensory effects**	25.5	0	10.2	0	<0.001	—
Anorexia	21.6	2.2	17.7	1.2	0.05	0.17
Arthralgia	19.4	0.5	9.0	0.3	<0.001	0.69‖
Nail disorder	18.5	0.4	14.4	0.1	0.03	0.62‖
Allergy	13.4	1.3	3.7	0.1	<0.001	0.007
Abdominal pain	10.9	0.7	5.3	0	<0.001	0.06‖
Mild-to-severe congestive heart failure	1.6	0.1	0.7	0.1	0.09	1.0‖

* TAC denotes docetaxel plus doxorubicin and cyclophosphamide, and FAC fluorouracil plus doxorubicin and cyclophosphamide.
† P values were calculated with the use of the chi-square test unless otherwise specified.
‡ The study protocol defined febrile neutropenia as fever of grade 2 or more concomitant with grade 4 neutropenia requiring intravenous antibiotics, hospitalization, or both. The National Cancer Institute Common Toxicity Criteria (NCI CTC) definition 2.0 is fever of 38°C or more concomitant with grade 3 or 4 neutropenia.
§ The study protocol defined neutropenic infection as that of grade 2 or more concomitant with grade 3 or 4 neutropenia. The NCI CTC definition 2.0 is infection of any grade concomitant with grade 3 or 4 neutropenia.
¶ Amenorrhea was defined as the absence of menses for at least three months. Percentages were calculated among premenopausal patients (420 in the TAC group and 403 in the FAC group) who could be evaluated for safety and were treated with study drugs.
‖ P values were calculated according to Fisher's exact test.
** Grade 2 neurosensory effects occurred in 3.6 percent of patients in the TAC group and 1.4 percent in the FAC group.

clinical outcomes, raising the possibility that alternative schedules and durations of treatment may further improve outcomes in this setting. A comparison of a dose-dense regimen (treatment administered every two weeks) and the TAC regimen used in the current trial will be part of the National Surgical Adjuvant Breast and Bowel Project trial B-38.

The toxic effects associated with the TAC regimen we used are consistent with those reported in association with TAC in women with advanced breast cancer[20,22] and were manageable with standard supportive measures. Grade 3 or 4 neutropenia was common in both groups (65.5 percent in the TAC group and 49.3 percent in the FAC group, P<0.001). Although the incidence of febrile neutropenia was higher among women treated with TAC (despite the administration of prophylactic ciprofloxacin) than among those treated with FAC (24.7 percent and 2.5 percent), grade 3 or 4 infection was seen in only 3.9 percent of patients in the TAC group, and no deaths due to sepsis occurred. Considering that the rates of febrile neutropenia did not reach the recommended threshold for routine prophylactic administration of G-CSF,[35] the administration of primary prophylaxis with G-CSF should be left to the discretion of the treating physician. However, on the basis of good practice, after an episode of febrile neutropenia, prophylaxis with G-CSF is recommended for all subsequent cycles.

Most patients completed all six treatment cycles (91.3 percent in the TAC group and 96.6 percent in the FAC group), and one third required a delay in or adjustment of treatment (33.6 percent in the TAC group and 39.8 percent in the FAC group). The incidence of congestive heart failure was 1.6 percent among patients treated with TAC, which is consistent with the incidence associated with anthracycline-based adjuvant chemotherapy.[4,33,34]

The tolerability of adjuvant chemotherapy and the magnitude of deterioration in quality of life are important considerations in a woman's decision to undergo treatment. It is reassuring to note that although both chemotherapy regimens in our trial were associated with transient, statistically significant reductions in quality-of-life scores, these scores returned to baseline levels at the first follow-up visit after treatment and were similar between the treatment groups.

In conclusion, this interim analysis of the Breast Cancer International Research Group trial 001 demonstrates a therapeutic advantage of TAC over FAC, but at the expense of increased toxic effects. Furthermore, chemotherapeutic treatment with TAC led to only a transient reduction in quality-of-life scores, which subsequently returned to pretreatment baseline values.

Table 4. Deaths Due to Causes Other Than Breast Cancer or a Second Cancer.*

Deaths	TAC Group (N=745)	FAC Group (N=746)
	no. of patients	
All	10	9
Deaths ≤30 days after last treatment cycle	2	2
Due to toxic effects		
Pulmonary embolism	1†	1†
Due to other causes (unrelated to study drug)		
Pulmonary embolism	1†	0
Hypovolemic shock (hemorrhage during catheter placement)	0	1†
Deaths >30 days after last treatment cycle	8	7
Due to toxic effects		
Sudden cardiac arrest	0	1
Adverse effects on cardiac function	1†	1
Due to other causes (unrelated to study drug)	6‡	4§
Due to additional chemotherapy	1	1

* TAC denotes docetaxel plus doxorubicin and cyclophosphamide, and FAC fluorouracil plus doxorubicin and cyclophosphamide.
† Death occurred before a relapse or second cancer.
‡ Five deaths occurred before a relapse or second cancer.
§ Two deaths occurred before a relapse or second cancer.

Supported by Aventis.

Dr. Martin reports having served as a consultant for and having received speakers' honoraria from Bristol-Myers Squibb and Aventis; Dr. Mackey, having served as a consultant for and having received speakers' honoraria from Aventis, AstraZeneca, Amgen, and Roche and grant support from AstraZeneca, Roche, Amgen, and the Canadian Breast Cancer Research Alliance; Dr. Guastalla, having served as a consultant for and having received speakers' honoraria from Aventis; Dr. Chap, having received speakers' honoraria from AstraZeneca, Pfizer, and Novartis; Dr. Howell, having served as a consultant for and having received speakers' honoraria from AstraZeneca, Pfizer, and Novartis; Dr. Coleman, having served as a consultant for and having received speakers' honoraria from Novartis and grant support from Roche, AstraZeneca, Novartis, the National Cancer Research Network, and the Association of Medical Research Charities; Dr. Modiano, having served as a consultant for Aventis and Amgen; Dr. Pinter, having served as a consultant for and having received speakers' honoraria from Pfizer, Eli Lilly, and Aventis; Dr. Tang, having served as a consultant for and having received speakers' honoraria from Pfizer, Novartis, and Aventis; Dr. Prady, having served as a consultant for Aventis; Dr. Provencher, having served as a consultant for Aventis; Dr. Rodriguez-Lescure, having received speakers' honoraria from Aventis; Dr. Jacobs, having received grant support from Aventis; Dr. Vogel, having served as a consultant for and having received speakers' honoraria from AstraZeneca, Aventis, Novartis, Genentech, GlaxoSmithKline, Ortho Biotech, Pfizer, and

Roche; Drs. Fornander and Modiano, holding equity in Pfizer; Dr. Weaver, holding equity in Cancer Consultants; Dr. Riva, holding stock options for Aventis and having received speakers' honoraria from Aventis and Roche; and Dr. Loret, holding equity in Aventis. Mr. Murawsky is employed by Aventis and reports holding equity in the company.

We are indebted to the 1491 women who agreed to participate in this trial.

APPENDIX

Additional investigators participating in the Breast Cancer International Research Group trial 001 were as follows: — H. Guixa, E. Mickiewicz, and J. Martinez (Argentina), J. Schuller (Austria), L. Teixeira (Brazil), K. Gelmon, S. Sehdev, Y. Drolet, J. Dufresne, L. Yelle, L. Zibdawi, B. Lesperance, S. Verma, J. Cantin, D. Holland, M. Trudeau, J. Chang, S. Rubin, and S. Allan (Canada), J. Abrahamova and J. Finek (Czech Republic), H. Abd-El-Azim and N. Gad-El-Mawla (Egypt), C. Oberhoff (Germany), V. Georgoulias (Greece), K. Szanto (Hungary), H. Lurie, O. Merimsky, and M. Steiner (Israel), H. Karnicka (Poland), I. Goncalves and M. Chumbo (Portugal), I. Koza (Slovak Republic), P. Ruff (South Africa), A. Pelegri, E. Alba, I. Alvarez, E. Aranda, B. Munarriz, A. Anton, F. Lobo, J.M. Lopez-Vega, M.D. Menendez, A. Murias, J. Cassinello, and J.L. Garcia-Puche (Spain), U. Nylen (Sweden), E. Whipp, and J. Le Vay (United Kingdom), J. Erban, B. Graham, L. Harris, M. O'Rourke, T. Beck, S. Limentani, N. Robert, J. Tongol, F. Schnell, A. Begas, R. Kerns, A. Rosenberg, L. Campos, J. Foster, T. Beeker, N. Iannotti, C. George, and B. Avery (United States), and A. Viola and C. Garbino (Uruguay); design of quality-of-life analyses — H.J. Au (Canada); data-center team of the Breast Cancer International Research Group — V. Bée, D. Borrits, F. Dabbouz-Harrouche, S. de Ducla, S. Gazel, and M.A. Lindsay; study managers — J.P. Aussel, N. Domege, and S. Dumont; statisticians — L. Hatteville and E. Brunel; clinical directors — M. Alakl and A. Yver, who were key Aventis personnel; and independent data monitoring committee — A. Efremidis (Greece), M. Aapro (Switzerland), J. Bryant, E. Mamounas, and E. Perez (United States).

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 1998;352:930-42.
2. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin–cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8:1483-96.
3. Hutchins L, Green S, Ravdin P, et al. CMF versus CAF with and without tamoxifen in high-risk node-negative breast cancer patients and a natural history follow-up study in low-risk node-negative patients: first results of Intergroup Trial INT 0102. Proc Am Soc Clin Oncol 1998;17:1a. abstract.
4. Martin M, Villar A, Sole-Calvo A, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol 2003;14:833-42.
5. Fumoleau P, Kerbrat P, Romestaing P, et al. Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positive breast cancer patients: 10-year follow-up results of the French Adjuvant Study Group 01 trial. J Clin Oncol 2003;21:298-305.
6. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003;21:3357-65.
7. Parnes HL, Cirrincione C, Aisner J, et al. Phase III study of cyclophosphamide, doxorubicin, and fluorouracil (CAF) plus leucovorin versus CAF for metastatic breast cancer: Cancer and Leukemia Group B 9140. J Clin Oncol 2003;21:1819-24.
8. Aisner J, Weinberg V, Perloff M, et al. Chemotherapy versus chemoimmunotherapy (CAF v CAFVP v CMF each +/– MER) for metastatic carcinoma of the breast: a CALGB study: Cancer and Leukemia Group B. J Clin Oncol 1987;5:1523-33.
9. Smalley RV, Carpenter J, Bartolucci A, Vogel C, Krauss S. A comparison of cyclophosphamide, adriamycin, 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone (CMFVP) in patients with metastatic breast cancer: a Southeastern Cancer Study Group project. Cancer 1977;40:625-32.
10. Buzdar AU, Singletary SE, Valero V, et al. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial. Clin Cancer Res 2002;8:1073-9.
11. Nabholtz JM, Riva A, Lindsay MA, Reese DM, Tonkin K. The taxanes: paclitaxel and docetaxel. In: Nabholtz J-M, Tonkin K, Reese DM, Aapro M, Buzdar AU, eds. Breast cancer management: application of clinical and translational evidence to patient care. Philadelphia: Lippincott Williams & Wilkins, 2003:147-68.
12. Valero V, Holmes F, Walters RS, et al. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. J Clin Oncol 1995;13:2886-94.
13. Ravdin PM, Burris HA III, Cook G, et al. Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. J Clin Oncol 1995;13:2879-85.
14. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999;17:2341-54.
15. Schüller J, Czejka M, Kletzl H, et al. Doxorubicin (DOX) and Taxotere (TXT) — a pharmacokinetic (PK) study of the combination in advanced breast cancer. Proc Am Soc Clin Oncol 1998;17:205a. abstract.
16. Bellot R, Robert J, Dieras V, et al. Taxotere (T) does not change the pharmacokinetic (PK) profile of doxorubicin (dox) and doxorubicinol (Dx-ol). Proc Am Soc Clin Oncol 1998;17:221a. abstract.
17. Gianni L, Munzone E, Capri G, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995;13:2688-99.
18. Gehl J, Boesgaard M, Paaske T, et al. Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic. Ann Oncol 1996;7:687-93.
19. Gianni L, Vigano L, Locatelli A, et al. Human pharmacokinetic characterization and in vitro study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. J Clin Oncol 1997;15:1906-15.
20. Nabholtz JM, Mackey JR, Smylie M, et al. Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. J Clin Oncol 2001;19:314-21.
21. Nabholtz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003;21:968-75. [Erratum, J Clin Oncol 2003;21:2048.]

22. Mackey JR, Paterson A, Dirix LY, et al. Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2002;21:35a. abstract.
23. Bontenbal M, Braun JJ, Creemers GJ, et al. Phase III study comparing AT (adriamycin, docetaxel) to FAC (fluorouracil, adriamycin, cyclophosphamide) as first-line chemotherapy (CT) in patients with metastatic breast cancer (MBC). Eur J Cancer Suppl 2003;1:S201.
24. Nabholtz JM, Pienkowski T, Mackey J, et al. Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of the BCIRG 001 study. Proc Am Soc Clin Oncol 2002;21:36a. abstract.
25. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1976;34:585-612.
26. Elledge RM, Green S, Pugh R, et al. Estrogen receptor (ER) and progesterone receptor (PgR), by ligand binding assay compared with ER, PgR, and pS2, by immunohistochemistry in predicting response to tamoxifen in breast cancer: a Southwest Oncology Group Study. Int J Cancer 2000; 89:111-7.
27. Jacobs TW, Gown AM, Yaziji H, Barnes MJ, Schnitt SJ. HER-2/*neu* protein expression in breast cancer evaluated by immunohistochemistry: a study of interlaboratory agreement. Am J Clin Pathol 2000;113:251-8.
28. Mass RD, Sanders C, Kasian C, Johnson L, Everett T, Anderson S. The concordance between the clinical trials assay (CTA) and fluorescence in situ hybridization in the Herceptin pivotal trials. Proc Am Soc Clin Oncol 2000;19:75a. abstract.
29. Pauletti G, Godolphin W, Press MF, Slamon DJ. Detection and quantitation of HER-2/*neu* gene amplification in human breast cancer archival material using fluorescence in situ hybridization. Oncogene 1996;13:63-72.
30. Persons DL, Borelli KA, Hsu PH. Quantitation of HER-2/*neu* and c-myc gene amplification in breast carcinoma using fluorescence in situ hybridization. Mod Pathol 1997;10:720-7.
31. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995;333: 1456-61.
32. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003;21:4165-74.
33. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21: 976-83.
34. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9. [Erratum, J Clin Oncol 2003;21:2226.]
35. Ozer H, Armitage JO, Bennett CL, et al. 2000 Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 2000;18:3558-85.