JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Multicenter Trial of Doxorubicin Plus Cyclophosphamide Followed by Paclitaxel Compared With Doxorubicin Plus Paclitaxel Followed by Weekly Paclitaxel As Adjuvant Therapy for Women With High-Risk Breast Cancer

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See accompanying editorial doi:10.1200.JCO/2010/284653

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Submitted May 12, 2009; accepted January 19, 2010; published online ahead of print at www.jco.org on May 17, 2010.

Supported by by Bristol-Myers Squibb, Plainsboro, NJ.

Presented in part at the 29th Annual San Antonio Breast Cancer Symposium, December 14-17, 2006, San Antonio, TX; and at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL.

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

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0732-183X/10/2899-1/$20.00

DOI: 10.1200/JCO.2009.24.1000

ABSTRACT

Purpose
This study compared disease-free survival (DFS) obtained with two different regimens of adjuvant therapy in high-risk breast cancer.

Methods
Women (who had performance status [PS] of 0 to 1) with operable, histologically confirmed, stage I to III adenocarcinoma of the breast were eligible. Patients had undergone primary surgery with no residual tumor. Treatments were as follows: arm 1 was doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles followed by paclitaxel 175 mg/m^2 every 3 weeks for four cycles (ie, AC-P); and arm 2 was doxorubicin 50 mg/m^2 plus paclitaxel 200 mg/m^2 every 3 weeks for four cycles followed by paclitaxel 80 mg/m^2 weekly for 12 weeks.

Results
Overall, 1,830 patients were enrolled and 1,801 were treated: arm 1 (n = 906; AC→P) and arm 2 (n = 895; AP-WP). Overall, patients had a PS of 0 (88%), had estrogen receptor and progesterone receptor–positive disease (52%), had one to three positive nodes (46%), and were postmenopausal (57%); the median age was 52 years. Currently, 1,640 patients (90%) are alive. The 6-year DFS was 79% to 80% in both groups. Disease relapse was the cause of death for 83 patients in arm 1 and in 66 patients of arm 2. Overall 6-year survival rates were 82% and 87% in arms 1 and 2, respectively. Reasons for patients being taken off study treatment included toxicity (13% in arm 1 *v* 20% in arm 2), progressive disease or recurrence (7% *v* 5%), and consent withdrawn (9% *v* 8%), respectively. The most frequent toxicities were hematologic, including neutropenia and leukopenia followed by neuropathy, myalgia, nausea, fatigue, headache, arthralgia, and vomiting.

Conclusion
The results indicate that the AP-WP regimen is an equally effective and tolerable option for the adjuvant treatment of patients with high-risk breast cancer. The substitution of paclitaxel for cyclophosphamide results in comparable effectiveness of the regimen.

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INTRODUCTION

Despite extensive research in breast cancer, the incidence of this disease has increased steadily, and it is estimated that nearly 182,460 new occurrences were diagnosed in the United States in the year 2008.[1] Breast cancer accounts for approximately 26% of all new cancer diagnoses,[2] excluding basal and squamous cell skin cancers and in situ carcinoma of the uterine cervix. Breast cancer remains a major health concern for women.[3]

Adjuvant therapy became firmly established as effective in the treatment of breast cancer when the results of a meta-analysis of data collected worldwide were presented in 1995.[4] If the majority of tumor cells that remain postoperatively can be killed with adjuvant therapy, the time to disease progression (TTP), and thus overall survival (OS), can be

extended. More optimistically, if these tumor cells are totally eliminated, a cure is possible.

The primary focus of research today is improving adjuvant regimens that are currently in use. By incorporating newer, more effective drugs and by optimizing the dose and schedule of administration, improved outcomes are possible. Indeed, common themes in more recent studies of adjuvant therapy for breast cancer have been dose-intensity and sequential drug administration.

The combination of doxorubicin and paclitaxel has shown promise as therapy for advanced or metastatic breast cancer, as demonstrated by the substantial evidence in the literature.[5-13] Cyclophosphamide has been used in combination with docetaxel and/or paclitaxel in numerous studies. Doxorubicin and paclitaxel has produced the highest response rates in patients with metastatic breast cancer[14]; weekly paclitaxel has been used as salvage treatment for patients previously experiencing failure on anthracycline therapy.[15] This study was designed to determine if these approaches in the metastatic setting translate into improved efficacy in the adjuvant setting.

According to the design of this trial, the maximum cumulative doxorubicin dose that a patient could potentially receive in either treatment arm was 240 mg/m^2. This is well below the 360 mg/m^2 limit that has been suggested for minimizing cardiotoxicity in other trials.[16,17] Thus, in this study, investigators hypothesized that cardiotoxicity would be minimized with the planned regimen and dosing schedule, with the regimen used in Cancer and Leukemia Group B study CALGB 9344 as the comparator arm.[18]

PATIENTS AND METHODS

Study Design

This was an open label, randomized, phase III study of adjuvant chemotherapy in female patients with high-risk breast cancer (defined as one or more positive lymph nodes and tumors that are T1-3, N1-2, and M0 or as node-negative [ie, N0] disease with tumors that are $>$ 2 cm or as node-negative disease with tumors that are $>$ 1 cm and ER negative/PR negative). Staging of disease was based on American Joint Committee on Cancer guidelines (ed 5).[19] The protocol was approved by a central institutional review board with jurisdiction over specific sites that registered patients on study, and all patients were required to sign an informed consent form before being enrolled onto the study.

Patients

Patients with stages I to IIIA disease were eligible to participate on this study. Patients with T1 or T2 disease with one sentinel node or micrometastasis less than 2 mm were eligible without having had a complete axillary dissection; however, if there was more than one sentinel node with micrometastasis less than 2 mm, or one node greater than 2 mm and/or if tumor was greater than T1 or T2, then complete axillary dissection was required. Prior treatment by lumpectomy or mastectomy was permitted as long as surgery was done within the previous 84 days.

Patients were excluded from study participation if they had locally advanced disease at diagnosis (ie, T4 disease); evidence of residual gross or microscopic tumor noted, at the margin, in the final surgery or pathology reports; had previously received any prior therapy for any invasive breast cancer; had a history of any other malignancy within the last 5 years (except cured basal cell carcinoma of skin and carcinoma in situ of uterine cervix); or had received prior anthracyclines or anthracenes (for any prior disease). Individuals with cardiac dysrhythmia were considered for eligibility on a case-by-case basis by the principal investigator; however, patients could not have any uncontrolled severe cardiovascular disease (ie, myocardial infarction or congestive heart failure) within the previous 6 months; Fig 1, CONSORT diagram).

Treatment

The treatment schema for both study groups is listed in Table 1. All drugs were infused intravenously; doxorubicin was administered over 5 to 15 minutes, cyclophosphamide was infused over 15 to 30 minutes, and paclitaxel infusions were 1 to 3 hours. All patients were premedicated with the following medications, administered intravenously 30 minutes before paclitaxel: dexamethasone 20 mg, diphenhydramine 50 mg, and cimetidine 300 mg (or ranitidine 50 mg). No prophylactic hematopoietic growth factors were permitted in cycle 1; use in subsequent cycles was at the discretion of the treating physician.

After completion of the study regimens, premenopausal patients who were hormone receptor positive (ie, estrogen receptor [ER] –positive and/or progesterone receptor [PR] –positive) received tamoxifen for 2 to 3 years, which was later increased to 5 years. In postmenopausal patients, tamoxifen was given for 2 to 3 years and could be followed by an aromatase inhibitor at the discretion of the treating physician.

Patients who requested breast sparing procedures received standard radiation therapy beginning 3 to 6 weeks after the completion of chemotherapy. Patients who had a mastectomy received radiation if they had four or more positive nodes.

Assessments

Each patient gave informed consent before study registration. Prestudy (ie, baseline) evaluations included the following: medical history, complete physical examination with vital signs, pelvic exam with cytology, Eastern Cooperative Oncology Group performance status, ER/PR status, *HER2/neu* status, mammography, chest x-ray, bone scan, complete blood count (CBC), creatinine, liver function tests (LFTs), ECG, and left ventricular ejection fraction (LVEF). During treatment, CBCs and toxicity were assessed weekly, and physical exams, assessment of PS, creatinine, and LFTs were assessed before the start of each cycle. ECGs were done before cycle 5 (ie, single-agent paclitaxel), and LVEF was assessed after four cycles of the doxorubicin-based therapy. During radiotherapy, physical examinations and CBCs were done weekly; Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring was done at each visit.

Post-treatment assessment of performance status, mammography (except in patients who had undergone bilateral mastectomy), chest x-rays, CBCs, and creatinine were done annually; LFTs were assessed at progression and then annually. LVEF was assessed at the 1-year visit and then at the discretion of the treating physician. Follow-ups consisted of assessments every 3 months in year 1, every 6 months in year 2, and annually thereafter up to (and including) year 6.

Statistical Analysis

This was a randomized (1:1) study, stratified by ER status (positive or negative) and nodal status (0, 1 to 3, $\geq$ 4). Disease-free survival (DFS) was the primary end point of this study. If we assumed DFS duration followed exponential distribution, and with a desired 25% decrease of annual hazard rate from 9% per year, the accrual time was estimated to be 18 months, with 3 years as follow-up time. With a two-sided significance level .05, and with a desired power of 90% to detect such 25% difference, the accrual rate was evaluated to be approximately 100 patients per month. Therefore, the total sample size was calculated to be 1,810.

DFS, in which relapse or death as a result of any cause is considered as an event, was calculated from date of random assignment to date of first event, or to date of censoring if eventless. Overall survival (OS) was a secondary end point and was calculated from date of random assignment to date of death or date of censoring if alive. Both DFS and OS were analyzed by using the method by Kaplan and Meier[20] that is based on intent-to-treat population, and the log-rank test was used to test for differences between the curves.

All safety analyses were based on safety population and included patients who received at least one dose of study drug.

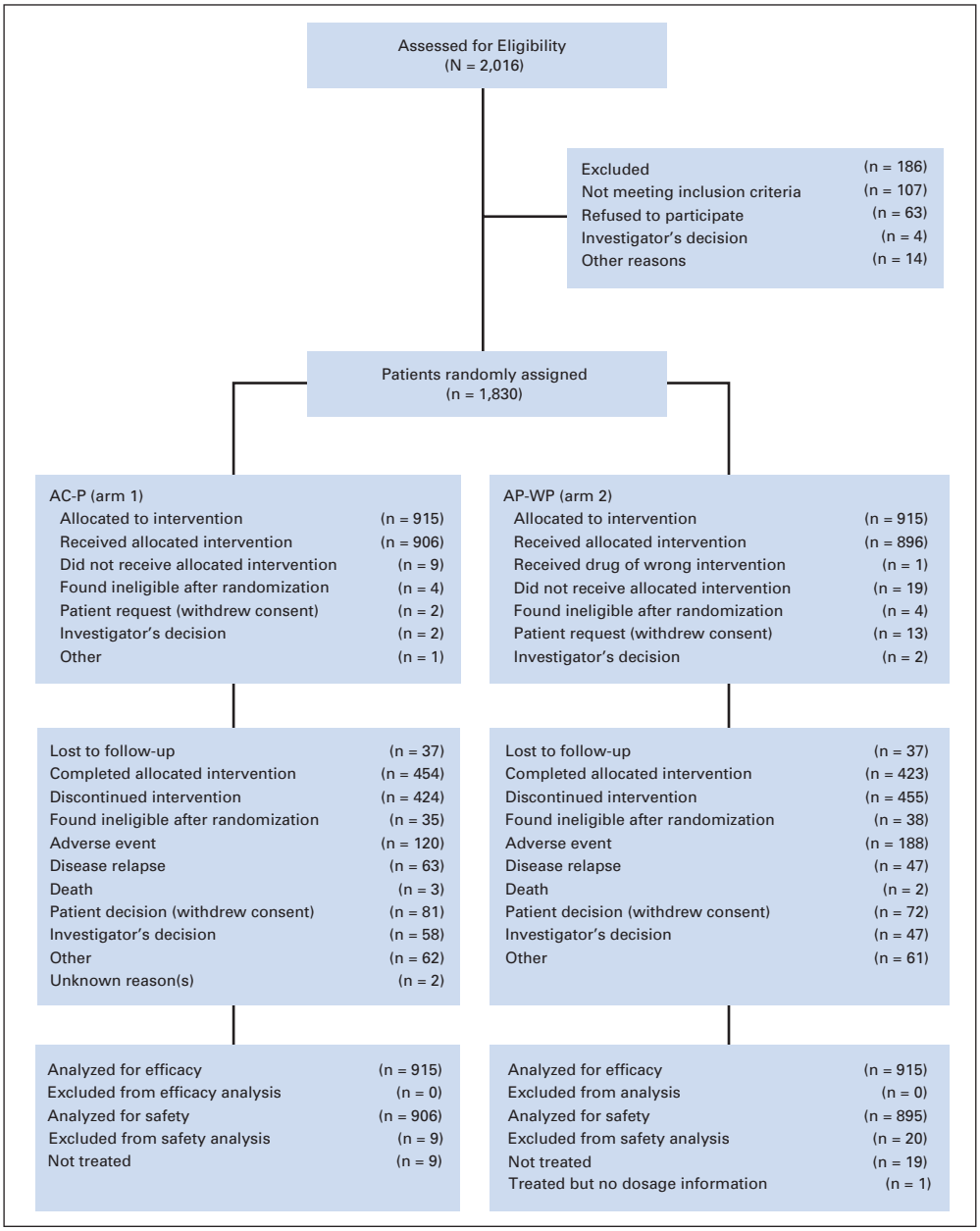

Fig 1. CONSORT diagram. AC-P, doxorubicin plus cyclophosphamide followed by paclitaxel every 3 weeks × 4 doses; AP-WP, doxorubicin plus paclitaxel followed by weekly paclitaxel × 12 doses.

RESULTS

Patient Characteristics

A total of 1,830 patients were enrolled from January 5, 2000 to March 28, 2002. Baseline demographics are listed in Table 2; 6-year survival is presented in Table 3, and reasons for discontinuation and causes of death are listed in Table 4.

Treatment Outcomes

Median follow-up for all patients was as follows: arm 1, 63.4 months (range, < 1 to 79.2 months) and arm 2, 64.0 months (range, < 1 to 85.0 months). Survival rates at 3 and 5 years were 93% and 94% for arm 1 compared with 86% and 89%, respectively, for arm 2. The median DFS (Fig 2A; Table 6), and median OS times had not been reached in either arms 1 or 2 (Fig 2B; Table 7).

There were no significant differences in 6-year survival between the two treatment arms; however, in an unplanned subgroup analysis, both ER-negative/PR-negative and triple-negative subgroups approached significance ($P = .06$ and .07, respectively) that favored arm 2. Overall survival has ranged up to 79.2 months for arm 1 patients and to 85.0 months in arm 2 ($P = .08$; hazard ratio, 1.29). Disease-free survival was similar, ranging up to 79.2 months for arm 1 and 84.3 months for arm 2 ($P = .35$; hazard ratio, 11.1).

Drug Delivery

Overall, the median number of cycles completed in arm 1 doxorubicin plus cyclophosphamide was four (range, one to four; 95.7% completed all four cycles) and four cycles for single-agent paclitaxel (range, one to four; 86.4% completed all four cycles of single-agent paclitaxel). The median cumulative doses (and median dose-intensities) of study drugs were as follows: doxorubicin 425 mg (100%;

Table 1. Dosing Schemas

Arm 1 (AC-P)	Arm 2 (AP-WP)
Doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by paclitaxel 175 mg/m^2 every 3 weeks for 4 cycles	Doxorubicin 50 mg/m^2 plus paclitaxel 200 mg/m^2 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 weekly for 12 weeks

Abbreviations: AC, doxorubicin plus cyclophosphamide; P, paclitaxel; AP, doxorubicin plus paclitaxel; WP, weekly paclitaxel.

Table 2. Patient Characteristics at Baseline

Characteristic	Patients by Arm			
	Arm 1		Arm 2	
	No.	%	No.	%
No. of patients enrolled	915		915	
Ethnicity				
White	758	82.8	764	83.5
Black	86	9.4	69	7.5
Hispanic	64	7.0	70	7.7
Other	7	0.8	12	1.3
Age, years				
Median	52.0		52.3	
Range*	23.8-83.4		20.3-81.1	
ECOG performance status				
0	794	86.8	816	89.2
1	121	13.2	99	10.8
Stage at diagnosis				
I	55	6.0	46	5.0
IIA	423	46.2	430	47.0
IIB	321	35.1	322	35.2
IIIA	114	12.5	116	12.7
IIIB†	2	0.2	1	0.1
Positive nodes				
0	251	27.4	243	26.6
1-3	406	44.4	428	46.8
4-9	189	20.7	167	18.3
≥ 10	69	7.5	77	8.4
Menopausal status				
Premenopausal	297	32.5	308	33.7
Perimenopausal	69	7.5	61	6.7
Postmenopausal	522	57.0	526	57.5
Unknown	27	3.0	20	2.2
Hormone receptor status				
ER positive/PR positive	491	53.7	460	50.3
ER positive/PR negative	78	8.5	111	12.1
ER negative/PR positive	21	2.3	24	2.6
ER negative/PR negative	323	35.3	317	34.6
ER/PR unknown	2	0.2	3	0.3
HER2 negative	583	63.7	557	60.9
HER2 positive	288	31.5	320	35.0
ER negative/PR negative/*HER2* negative	199	21.7	182	19.9
HER2 unknown	44	4.8	38	4.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.
*Minimum to maximum values.
†Found to be ineligible after random assignment.

range, 76% to 119%); cyclophosphamide 4,264 mg (100%; range, 76% to 107%); and paclitaxel 1,232 mg (100%; range, 70.5% to 117%).

In arm 2, the median number of cycles completed for doxorubicin plus paclitaxel was four (range, one to four; 92.3% completed all four cycles) and 12 weeks of weekly paclitaxel (range, one to 12; 81.6% completed all 12 weeks of weekly paclitaxel). The median cumulative doses (and median dose-intensities) of study drugs were as follows: doxorubicin 353 mg (100%; range, 61% to 120%); and paclitaxel 1,408 mg (100%; range, 62.5% to 137%) in cycles 1 to 4 and 1,662 mg (100%; range, 71% to 157%) in 12 weeks of single-agent paclitaxel.

The percentages of patients who had doses reduced or delayed were 3% and 14%, respectively, in arm 1 and 5% and 14%, respectively, in arm 2. Overall, these reductions and delays were largely attributed to toxicity, specifically neutropenia (16% in arm 1 *v* 11% in arm 2) and neuropathy (4% in arm 1 *v* 12% in arm 2); other contributing adverse events occurring in ≥ 2% of patients that contributed to delays or reductions were arthralgia, febrile neutropenia, myalgia, fever, nausea, and fatigue. In arm 1, 751 patients (83%) received the scheduled regimen without reduction; similarly, arm 2 had 724 patients (81%) without reduction.

Toxicity

Grade 3 to 4 treatment-related toxicities occurring in ≥ 1% are listed in Table 4. Grade 3 to 4 neuropathy was more frequent in arm 2 (6% in arm 1 *v* 14% in arm 2; $P < .01$); it was one of the few toxicities that were significantly different between treatment arms. Other significant toxicities were leukopenia, anemia, vomiting, and shortness of breath ($P < .01$ each) and nausea ($P = .03$). All other events related to chemotherapy, not listed in Table 5, were mild to moderate or occurred at grade 3 to 4 in less than 1% of patients. Grade 3 to 4 toxicities related to radiation were infrequent; events reported in ≥ 1% of patients in arms 1 and 2 were limited to radiation dermatitis (0.6% *v* 1.3%) and desquamation (1.0% *v* 0.6%). Only one death was possibly related to treatment; a patient in arm 1 developed pulmonary edema and sepsis, which resulted in death.

Review of toxicity data by the data safety monitoring board after treatment of 200 patients found that there were no toxicity concerns, and the study was permitted to continue. Cardiotoxicity was rare; only tachycardia (all grades) was reported in greater than 1% of patients (ie, six patients [0.7%] in arm 1 and 16 patients [1.8%] in arm 2).

DISCUSSION

The background for the research arm in this trial evolved from the best clinical pharmacotherapeutics of the day at the time the study was designed and initiated. It was comprised of the most active two-drug cytotoxic combination (ie, doxorubicin plus paclitaxel) for metastatic breast cancer in 1999,[17] and it was restricted to four cycles to limit the potential risk of cardiotoxcity. This was followed by weekly paclitaxel for 12 cycles, per the work of Seidman et al,[15] who demonstrated that the weekly schedule had the capacity to salvage patients with metastatic breast cancer who previously received paclitaxel therapy at 3-week intervals. Later, it became known that weekly paclitaxel had an antiangiogenic effect in addition to its antimicrotubule effects.[21,22]

Another consideration in the construct of this trial was to determine whether paclitaxel could be substituted for cyclophosphamide. After the initial report of data at the 1999 meeting of the American Society of Clinical Oncology by Pouilliart,[23,24] investigators designing

Table 3. Six-Year Survival in Subgroups

Subgroup	Arm 1 %	Arm 1 95% CI	Arm 2 %	Arm 2 95% CI	Log-Rank *P*	No. of Patients Arm 1	No. of Patients Arm 2
Overall*	81.7	72.0 to 88.3	87.0	81.3 to 91.1	.08	915	915
ER positive/PR positive	90.7	87.0 to 93.3	91.9	88.6 to 94.3	.59	491	460
ER positive/PR negative	—	—	73.2	27.6 to 92.7	.81	78	111
ER negative/PR positive	—	—	86.5	63.8 to 95.5	.81	21	24
ER negative/PR negative	72.9	59.4 to 82.6	84.6	79.5 to 88.5	.06	323	317
HER2 positive	71.7	37.2 to 89.4	87.5	82.8 to 91.0	.63	288	320
ER negative/PR negative/*HER2* negative	78.5	71.5 to 83.9	85.9	79.1 to 90.6	.07	199	182

NOTE. Arm 1 is doxorubicin plus cyclophosphamide followed by paclitaxel; Arm 2 is doxorubicin plus paclitaxel followed by weekly paclitaxel.
Abbreviations: ITT, intent-to-treat; ER, estrogen receptor; PR, progesterone receptor.
*ITT populations.

this study concluded that the issue of cardiotoxicity cannot be discounted when a combination regimen of doxorubicin and paclitaxel is used; however, its impact can be significantly lessened by careful monitoring of the total cumulative dose of doxorubicin. We did not observe increase cardiotoxicity in patients in arm 1.

The current experience is similar to the randomized, four-arm trial of weekly versus every-3-week taxane therapy after administering four cycles of upfront, standard doxorubicin and cyclophosphamide conducted by Sparano,[25] which favored the weekly paclitaxel arm along with demonstrating the highest levels of neurotoxicity (ie, 8% grade 3 to 4 neurotoxicity compared with 5% in the every-3-week arm). It is difficult to make therapeutic comparisons of this trial compared with the Sparano trial because not all patients received the same initial four cycles of therapy. It is possible that our trial may

Table 4. Reasons for Nonevaluability and Study Discontinuation

Variable	Patients by Arm: Arm 1 No.	Arm 1 %	Arm 2 No.	Arm 2 %
Total No. of patients enrolled	915		915	
Total No. of patients treated	906		895	
Reason for study discontinuation				
Normal protocol completion	454	49.6	423	46.2
Disease relapse/recurrence	63	6.9	47	5.1
Toxicity	115	12.6	183	20.0
Death	3	0.3	2	0.2
Unrelated complication	5	0.5	5	0.5
Physician request	58	6.3	47	5.1
Patient request/withdrew consent	81	8.9	72	7.9
Lost to follow-up	37	4.0	37	4.0
Failed entry	35	3.8	38	4.2
Screening failure	21		25	
Margins not clear	11		12	
Other	3		1	
Other*	64	7.0	61	6.7
Total patients surviving	811	88.6	829	90.6
Causes of death				
Total deaths	104		88	
Relapse/recurrence	83	79.8	66	76.7
Other malignancy	3	2.9	5	5.8
Cardiovascular	3	2.9	3	3.5
Respiratory/pulmonary	4	3.8	1	1.2
Renal/hepatic	3	2.9	2	2.3
Hemorrhage/heme disorder	0		2	2.3
Pneumonia/sepsis	2	1.9	2	2.3
Unknown	6	5.8	7	8.1

NOTE. Arm 1 is doxorubicin plus cyclophosphamide followed by paclitaxel; Arm 2 is doxorubicin plus paclitaxel followed by weekly paclitaxel.
*For example, lapses in insurance coverage or cost of drug prohibitive, patient relocation, protocol deviation, site closure, noncompliance.

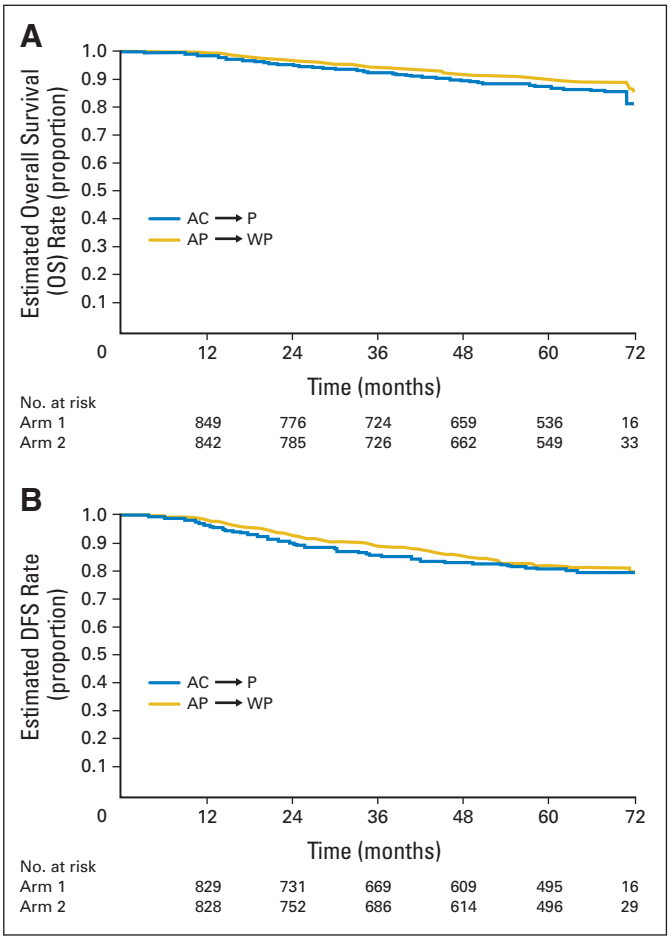

Fig 2. (A) Overall survival. (B) Disease-free survival (DFS). AC-P, doxorubicin plus cyclophosphamide followed by paclitaxel; AP-WP, doxorubicin plus paclitaxel followed by weekly paclitaxel.

Table 5. Treatment-Related Adverse Events Greater Than Grade 3

Event	Patients by Arm and Event Grade							
	Arm 1 (n = 906)				Arm 2 (n = 895)			
	Grade 3 (No.)	Grade 4 (No.)	Total		Grade 3 (No.)	Grade 4 (No.)	Total	
			No.	%			No.	%
Hematologic								
Neutropenia	194	515	709	78	196	509	705	79
Leukopenia*	165	63	228	25	138	22	160	18
Anemia*	24	2	26	3	8	0	8	0.9
Nonhematologic								
Neuropathy*†	55	3	58	6	114	7	121	14
Myalgia	81	1	82	9	60	3	63	7
Nausea‡	65	2	67	7	43	1	44	5
Fatigue	48	5	53	6	59	5	64	7
Arthralgia	61	1	62	7	55	1	56	6
Vomiting*	55	1	56	6	27	2	29	3
Bone pain	28	0	28	3	23	1	24	3
Diarrhea	17	0	17	2	17	1	18	2
Pain	15	1	16	2	11	1	12	1
Fever	9	0	9	1	12	2	14	2
Weakness	8	1	9	1	14	2	16	2
Shortness of breath*	4	0	4	0.4	15	2	17	2
Thrombocytopenia	15	2	17	2	8	2	10	1
Dehydration	15	0	15	2	9	0	9	1
Dysmenorrhea	15	1	16	2	5	1	6	0.7
Amenorrhea	15	0	15	2	19	0	19	2
Stomatitis	5	0	5	0.6	8	3	11	1
Constipation	12	0	12	1	6	0	6	0.7
Headache	8	1	9	1	7	0	7	0.8
Hyperglycemia	9	1	10	1	9	0	9	1
Allergic reaction	11	0	11	1	6	1	7	0.8

NOTE. All other differences between groups were not significant.
*$P < .01$ between groups.
†Includes paresthesia.
‡$P = .03$ between groups.

have shown similar results if a third arm had been constructed using four cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel.

While accruing patients to our trial, information denoting the success of extended antiestrogen therapy with aromatase inhibitors fostered an amendment to allow postmenopausal patients receiving tamoxifen to crossover to an aromatase inhibitor after 2 to 3 years of tamoxifen.[26] Since the initiation of this trial, the taxonomy of breast

Table 6. Comparison of Overall Survival by Treatment Arm

Treatment Arm	Deaths	Percent Surviving (months)					
		12	24	36	48	60	72
Arm 1, AC → P	104	98.7	95.5	92.6	89.8	87.7	81.7
Arm 2, AP → wP	88	99.7	96.9	94.5	92.0	89.9	87.0

NOTE. Median overall survival was not applicable (NA; range, < 1 to 79.2 months [arm 1] and < 1 to 85.0 months [arm 2]). Median 95% CI was NA. Arm 2 was used as the reference arm for HR. $P = .12$; HR, 1.26; 95% CI, 0.94 to 1.68.
Abbreviations: AC, doxorubicin and cyclophosphamide; P, paclitaxel; AP, doxorubicin and paclitaxel; wP, weekly paclitaxel; HR, hazard ratio.

Table 7. Comparison of Disease-Free Survival by Treatment Arm

Treatment Arm	Deaths	Percent Alive or Relapse Free (months)					
		12	24	36	48	60	72
Arm 1, AC → P	160	96.3	90.1	85.7	83.2	81.0	79.6
Arm 2, AP → wP	147	98.0	92.8	89.0	85.5	81.7	78.9

NOTE. Median disease-free survival was not applicable (NA; range, < 1 to 79.2 months [arm 1] and < 1 to 84.3 months [arm 2]). Median 95% CI was NA. Arm 2 was used as the reference arm for HR. $P = .37$; HR, 1.11; 95% CI, 0.89 to 1.39.
Abbreviations: AC, doxorubicin and cyclophosphamide; P, paclitaxel; AP, doxorubicin and paclitaxel; wP, weekly paclitaxel; HR, hazard ratio.

cancer and its therapeutics have changed. Through the seminal work of Perou et al,[27] breast cancer is no longer thought of as a single disease entity; rather, it has evolved into five clinical disease subtypes that each possess a unique genetic signature by microarray analysis.

With breast cancer taxonomy now organized by genomics and biology, a subsequent presentation of over 15 years of Cancer and Leukemia Group B trials demonstrated minimal benefit for many patients receiving aggressive adjuvant therapy.[28] This challenged the old adage that more drugs with greater toxicity would be an equitable trade-off for better outcomes in the adjuvant setting.[15]

A recent Eastern Cooperative Oncology Group cytotoxic trial reported by Goldstein et al[29] was retrospectively analyzed utilizing this new genomic and clinical taxonomy, and some benefits of specific cytotoxics were demonstrated in unique subgroups. At the San Antonio Breast Cancer Symposium 2005, Jones et al[30] successfully challenged a 25-year-old clinical standard of doxorubicin plus cyclophosphamide by demonstrating superior efficacy for docetaxel plus cyclophosphamide in early-stage breast cancer. Both of these trials espouse the newer understanding and limitation of breast cancer cytotoxic therapeutics, which is to say that not all patients need six to eight cycles of adjuvant cytotoxic chemotherapy.

Adjuvant antiestrogen–only therapy has now become a common standard with the use of gene array testing by Paik et al[31] and Vant Veer et al[32] by categorizing patients into a good-performance subgroup of patients who had previously achieved minimal benefit from cytotoxic therapy.[15]

Though this trial did not achieve its intended end point, in the unplanned subset analysis, *HER2*-positive and triple-negative subgroups did benefit from therapy in arm 2. The patients with triple-negative disease are a heterogeneous group that potentially benefits from alkylating agents; however, most of this evidence is preclinical.[33] Our data is similar to that published by Goldstein et al[29] in which early-stage triple-negative patients respond better to doxorubicin plus a taxane than with doxorubicin plus cyclophosphamide.

Per the results of this trial, a dose-dense paclitaxel regimen is as efficacious as doxorubicin plus cyclophosphamide followed by paclitaxel; however, the substitution comes at a price of increased peripheral neuropathy. Despite the reversibility of the peripheral neuropathy, the weekly paclitaxel arm of this trial was more neurotoxic than the weekly arm in the trial by Sparano[25] (14% *v* 8%, respectively). Neurotoxicity was expected, as 18% of patients in CALGB 9344 reported neurotoxicity (15%, moderate paresthesias and 3%, sensory neurotoxicity that interfered with normal functioning),[34] and peripheral neuropathy is a common adverse effect of chemotherapy, especially in taxane-based therapy.[35]

Since the completion of this trial, many patients with early-stage, hormone receptor–positive disease are best treated with anti–hormone therapy alone. As a case in point for the patients with hormone receptor–positive disease in this trial, there was no difference in time to progression or overall survival between these two arms. Therefore, any increased neuropathy seems unwarranted for this subgroup. In that same light, though, patient demographics for CALGB 9344 demonstrated a greater extent of node-positive disease when compared with this trial. Outcomes from adjuvant therapy remain poor for patients with triple-negative disease, and arm 2 did achieve near statistical significance in the treatment of patients with triple-negative disease. One may choose to utilize this therapy in patients with triple-negative breast cancer, who have no peripheral neuropathy, or in patients for whom the benefits outweigh the risks of potential toxicity. However, for patients with hormone receptor–positive disease and with limited extent of disease, and for those with substantial peripheral neuropathy, the weekly paclitaxel regimen appears to be too problematic, because fewer neurotoxic alternatives are available.

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: David Loesch, Caris Molecular Profiling Institute (C) **Consultant or Advisory Role:** F. Anthony Greco, Bristol-Myers Squibb (C); Frankie Holmes, Novartis (C), Genentech (C), Bristol-Myers Squibb (C), Abraxis (C), Eisai (C); Nicholas Robert, Bristol-Myers Squibb (C) **Stock Ownership:** None **Honoraria:** Frankie Holmes, Genentech, Novartis, Bristol-Myers Squibb, Abraxis, Eisai **Research Funding:** John D. Hainsworth, Bristol-Myers Squibb **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

We thank the study participants who shared their experiences with US Oncology physicians (Appendix, online only); the site coordinators in the field; project managers Kristi Hargraves, Kat Torkzadesh, Charles Taylor; and data reviewer Tracy Locke, who assured the accuracy and integrity of the data.

Appendix

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