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ORIGINAL REPORT

Concurrent Doxorubicin Plus Docetaxel Is Not More Effective Than Concurrent Doxorubicin Plus Cyclophosphamide in Operable Breast Cancer With 0 to 3 Positive Axillary Nodes: North American Breast Cancer Intergroup Trial E 2197

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ABSTRACT

Purpose
The combination of doxorubicin and cyclophosphamide (AC) is a standard adjuvant regimen. Doxorubicin and docetaxel (AT) is one of the most active cytotoxic regimens for metastatic breast cancer. The purpose of this trial was to determine whether adjuvant AT improved disease-free survival compared with AC in operable breast cancer.

Patients and Methods
Women with invasive breast cancer were eligible if there were one to three positive lymph nodes or if the node-negative tumor was greater than 1 cm. Patients were randomly assigned after surgery to receive doxorubicin (60 mg/m^2) plus either cyclophosphamide (600 mg/m^2; AC) or docetaxel (60 mg/m^2; AT) given every 3 weeks for four cycles, followed by hormone therapy for patients with estrogen receptor (ER) and/or progesterone receptor (PR)–positive tumors.

Results
There were 2,882 eligible patients enrolled. After a median follow-up of 79.5 months, there was no significant difference in disease-free survival (DFS; 85% in both arms) or overall survival (91% *v* 92%) at 5 years. The hazard ratio for AC versus AT was 1.02 (95% CI for DFS, 0.86 to 1.22; $P = .78$). In an exploratory analysis of prespecified stratification factors by ER and PR expression there were trends toward improved DFS for AT in ER/PR-negative disease. Grade 3 neutropenia associated with fever or infection occurred more often with AT (26% *v* 10%; $P < .05$).

Conclusion
AT did not improve DFS or overall survival in this population, and was associated with more toxicity.

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INTRODUCTION

The combination of doxorubicin (adriamycin) and cyclophosphamide (AC) has been a standard adjuvant breast cancer regimen.[1] Taxanes have become part of the mainstay of the treatment of advanced breast cancer for the past 15 years.[2-6] Given their single-agent activity, relative noncrossresistance, partially nonoverlapping toxicities, and different mechanisms of action, there was clear rationale for combining the taxanes with doxorubicin.

The combination of anthracyclines plus either paclitaxel or docetaxel were reported to have high response rates exceeding 50% or more in advanced breast cancer in multiple phase II trials.[6-9] The high level of activity was confirmed in two sequentially performed phase II trials performed by the Eastern Cooperative Oncology Group (ECOG) that evaluated the doxorubicin and paclitaxel combination (E4195) and doxorubicin and docetaxel combination (E1196), which were associated with responses rates of 52% and 57%, respectively.[7,10] The superior efficacy of the combination was also confirmed in a phase III ECOG trial (E1193) that compared single-agent doxorubicin, single-agent paclitaxel, and the doxorubicin and paclitaxel combination in patients with metastatic disease, although the improvement in objective response for the combination (46%) compared with each single agent (33% to 34%) was not as impressive as in the phase II trials.[6] There

appeared to be a higher risk of cardiac toxicity associated with doxorubicin and paclitaxel but not docetaxel which was attributed to sequence dependent alteration of doxorubicin pharmacokinetics by paclitaxel that was not observed with docetaxel.[11]

At the time that this trial was developed, there was no evidence indicating that adjuvant taxane therapy was effective. Soon after the trial was activated, the sequential use of four courses of paclitaxel after four courses of AC was shown to be associated with improved disease-free survival, a finding that was subsequently confirmed in other trials.[12-16] The purpose of E2197 was to determine whether a short course of four courses of adjuvant chemotherapy, using concurrent rather than sequential treatment strategy, might also be more effective than standard AC chemotherapy.

PATIENTS AND METHODS

Study Design

E2197 included women with operable, histologically confirmed adenocarcinoma of the breast with histologically involved lymph nodes (one to three) or if lymph node negative, tumor that was greater than 1.0 cm.

Patients were enrolled within 84 days of complete surgical excision of the primary tumor (lumpectomy or mastectomy) and an axillary dissection (with at least six nodes removed), or a sentinel node biopsy alone (if the sentinel node was negative). Patients with T4 or N2-3 were not eligible. Patients were required to have adequate hematologic, hepatic, cardiac, and renal function (neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000, normal left ventricular ejection fraction (LVEF) $\geq$ 50%, and total bilirubin $\leq$ upper limit of normal) $\leq$ 8 weeks before random assignment. Patients must have been disease free of prior invasive malignancies for $\geq$ 5 years with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix. No prior chemotherapy or radiation therapy was allowed. Patients who received radiation to the breast for ductal carcinoma in situ were eligible. Patients may have received tamoxifen for chemoprevention or up to 4 weeks of tamoxifen for this malignancy, but were required to discontinue its use before enrollment. All subjects were required to sign an institutional review board–approved informed consent before being enrolled on this study.

After stratification for nodal status (positive, negative); menopausal status (premenopausal, postmenopausal); and ER/PR status (ER/PR unknown, ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−) patients were randomly assigned to arm A or B. Arm A consisted of AT (doxorubicin 60 mg/m^2 intravenously [IV], docetaxel 60 mg/m^2 IV over 1 hour infusion with ciprofloxacin 500 mg twice per day starting days 8 to17 and decadron 8 mg orally twice per day beginning 1 day before treatment with docetaxel and continued for 2 additional days). Arm B consisted of AC (doxorubicin 60 mg/m^2 IV, cyclophosphamide 600 mg/m^2 IV with ciprofloxacin given at physician's discretion). Treatments were assigned using permuted blocks within strata with dynamic balancing within main institutions and their affiliate networks. Both treatments were given every 3 weeks for four cycles unless tumor recurred, toxicity was excessive, or the patient withdrew consent. Patients with febrile neutropenia were to be placed on granulocyte colony-stimulating factor (G-CSF) according to American Society of Clinical Oncology guidelines of the time, but primary prophylaxis with G-CSF was not used.[17] Patients with continuing neutropenia after a subsequent dose of chemotherapy despite G-CSF or who had grade 3 to 4 toxicity, had the chemotherapy dose reduced by 25%. Postoperative irradiation was given at the completion of all chemotherapy for all patients treated with breast conservation and in selected high-risk patients after mastectomy at the discretion of the treating physician. Patients with tumors classified as ER+ and/or PR+ were to receive tamoxifen 20 mg orally daily for 5 years after chemotherapy. In June 2005, the protocol was modified to permit switching from tamoxifen to an aromatase inhibitor (AI) before completing 5 years of tamoxifen or to initiate an AI after completing a course of tamoxifen in postmenopausal women.

Patients were seen before each course of chemotherapy for physical and hematologic evaluations. After chemotherapy ended, mammography and hematologic exams were performed annually and patients were seen for a history

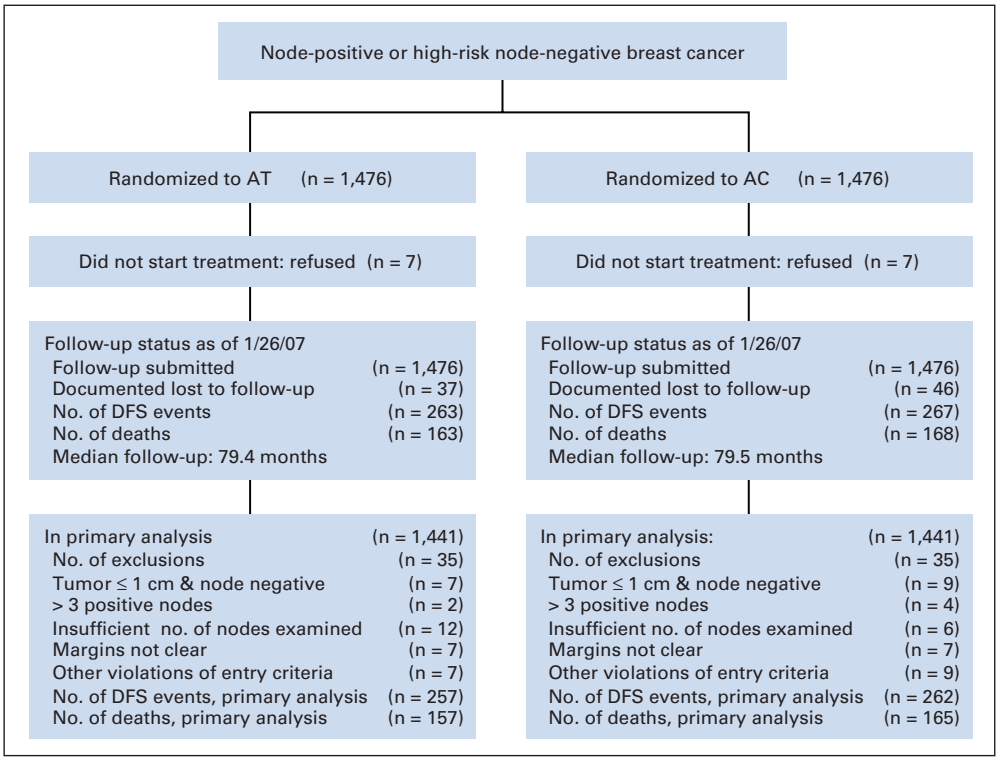

Fig 1. CONSORT diagram. AT, doxorubicin and docetaxel; AC, doxorubicin and cyclophosphamide; DFS, disease-free survival.

Table 1. Patient Characteristics Among Patients Classified as Eligible (n = 2,882)

Characteristic	Arm				Total	
	A (AT)		B (AC)			
	No.	%	No.	%	No.	%
No. of patients	1,441		1,441		2,882	
Race*						
White	1,256	87	1,259	88	2,515	87
Other	182	13	179	12	361	13
Bilateral breast cancer†						
Yes	13	0.9	7	0.5	20	0.7
Age						
Minimum	24		25		24	
25th percentile	44		44		44	
Median	51		51		51	
75th percentile	58		58		58	
Maximum	85		80		85	
Age group						
< 40	165	11	157	11	322	11
≥ 40	1,276	89	1,284	89	2,560	89
Menopausal status						
Pre/peri	692	48	683	47	1,375	48
Post	749	52	758	53	1,507	52
Surgery						
Less than mastectomy	769	53	775	54	1,544	54
Total mastectomy	67	5	84	6	151	5
Modified radical mastectomy	605	42	582	40	1,187	41
SNB/axillary dissection	376	26	401	28	777	27
SNB/no axillary dissection	86	6	91	6	177	6
No SNB/axillary dissection	979	68	949	66	1,928	67
ER/PR status‡						
ER−PR−	453	32	465	32	918	32
ER−PR+	52	4	38	3	90	3
ER+PR−	162	11	163	11	325	11
ER+PR+	765	53	769	54	1,534	54
Nodal status						
Negative	955	66	938	65	1,893	66
Positive§	486	34	503	35	989	34
No. of positive nodes						
0	955	66	938	65	1,893	66
1	288	20	289	20	577	20
2	137	9	131	9	268	9
3	57	4	77	5	134	4
At least 1‖	4	1	6	1	10	1
Tumor size¶						
Minimum	0.1		0.2		0.1	
25th percentile	1.5		1.5		1.5	
Median	2.0		2.0		2.0	
75th percentile	3.0		2.8		2.8	
Maximum	8.5		12.5		12.5	
Tumor size group, cm						
< 2	608	42	637	44	1,245	43
≥ 2	832	58	800	56	1,632	57
Tumor grade#						
Low	152	11	145	11	297	11
Intermediate	552	41	548	40	1,100	40
High	659	48	672	49	1,331	49

Abbreviations: AT, doxorubicin and docetaxel; AC, doxorubicin and cyclophosphamide; SNB, sentinel node biopsy; ER, estrogen receptor; PR, progesterone receptor.
*Data on race not available for three patients within each arm.
†For patients with bilateral breast cancer, the worst (ie, highest tumor size and/or highest grade) is reported in this Table.
‡Based on results from local institution review. ER and/or PR status not available for nine patients on the AT arm and six patients on the AC arm.
§Defined as positive if sentinel node positive by standard exam (hematoxylin and eosin) or number of positive nodes from axillary dissection greater than zero.
‖Result of test available but number of positive nodes from SNB and/or axillary dissection unknown.
¶Tumor size not available for one patient on the AT arm and four patients on the AC arm.
#Tumor grade not available for 78 patients on the AT arm and 76 patients on the AC arm.

Table 2. Summary of Outcome Information (n = 2,882)

Parameter	Arm A (AT)	Arm B (AC)	No.
Breast recurrence			
Ipsilateral	22	24	46
Locoregional	39	38	77
Distant	125	128	253
Contralateral invasive breast cancer			
Isolated	26	27	53
And other site	4	3	7
Total*	216	220	436
Deaths	116	123	239
Without recurrence	41	42	83
Total	157	165	322
Nonbreast second primaries			
Isolated	57	39	96
And recurrence	14	13	27
Total	71	52	123†
Contralateral in situ breast cancer			
Isolated	6	6	12‡
And other site (melanoma)	1	0	1‡

Abbreviations: AT, doxorubicin and docetaxel; AC, doxorubicin and cyclophosphamide; DFS, disease-free survival.
*Only first recurrence events were collected.
†Among 114 patients.
‡One of these 13 died and was counted as an event in the DFS analysis. The other 12 were censored in the DFS analysis at date last known to be alive.

Table 3. Univariate and Adjusted Hazard Ratios

Patients	AC *v* AT HR*	95% CI	*P*
Eligible (n = 2,882)			
DFS	1.02	0.86 to 1.22	.78
DFS adjusted†	1.03	0.87 to 1.22	.74
OS	1.06	0.85 to 1.31	.62
OS adjusted†	1.06	0.85 to 1.31	.63
All (N = 2,952)			
DFS	1.02	0.86 to 1.21	.83
DFS adjusted†	1.03	0.87 to 1.22	.76
OS	1.03	0.83 to 1.28	.76
OS adjusted†	1.04	0.84 to 1.30	.73

Abbreviations: AC, doxorubicin and cyclophosphamide; AT, doxorubicin and docetaxel; HR, hazard ratio; DFS, disease-free survival; OS, overall survival.
*HR > 1 indicates improved outcome for AT.
†Adjusted for age, menopausal status, primary surgery, estrogen receptor/progesterone receptor status, nodal status, tumor size, and tumor grade.

and physical every 3 months for the first 2 years from study entry, every 6 months for the next 3 years, and annually thereafter.

Statistical Considerations

The primary end point was disease-free survival (DFS), defined as the time from date of random assignment to date of invasive breast cancer recurrence, invasive contralateral breast cancer, or death from any cause, whichever occurred first. Patients with incomplete follow-up or, without documented DFS event (including those who developed in situ contralateral breast cancer or a nonbreast second primary cancer), were censored at the date last known to be alive. Overall survival (OS) was defined as time from date of random assignment to death from any cause.

The trial was designed to detect a 25% reduction in the failure hazard rate, and assumed a 78% 5-year DFS for the AC arm (based on data from E1180 and E5188).[18,19] Assuming 1,000 eligible patients enrolled per year for 2.5 years with an additional 3 years of follow-up, 2,500 eligible patients provided 83% power to detect this difference using a two-sided .05 level log-rank test.

Full information corresponded to 420 DFS failures among the eligible patients who began protocol treatment. O'Brien-Fleming boundaries were used at interim analyses to monitor for early stopping.[20] The ECOG Data Monitoring Committee (DMC) reviewed safety and outcome (when prespecified) data twice per year. Two prespecified analyses of outcome data were reviewed by the ECOG DMC in September 2001 and April 2003. Study continuation was recommended after both meetings.

In May and October 1999, the ECOG DMC reviewed pre- and postchemotherapy LVEF data. No significant differences were found between the two arms with respect to percentage of patients with a drop in LVEF. At the time of those analyses, two cases of congestive heart failure (CHF) had been reported.

The primary analysis of outcome was an intent-to-treat analysis among patients classified as eligible. All reported *P* values were two sided. The Kruskal-Wallis test for ordered data was used to compare maximum toxicity grade between treatment groups.[21] The Kaplan-Meier method[22] was used to estimate distributions for DFS and OS and the log-rank test[23] was used to assess differences between these distributions with respect to treatment. Cox proportional hazards models were used to estimate the effect of treatment alone, effect of treatment after adjustment for baseline covariates, and to test for interactions between prognostic factors and treatment.[24] The Wald test was used to test for significant covariates in the proportional hazards models.[25] Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

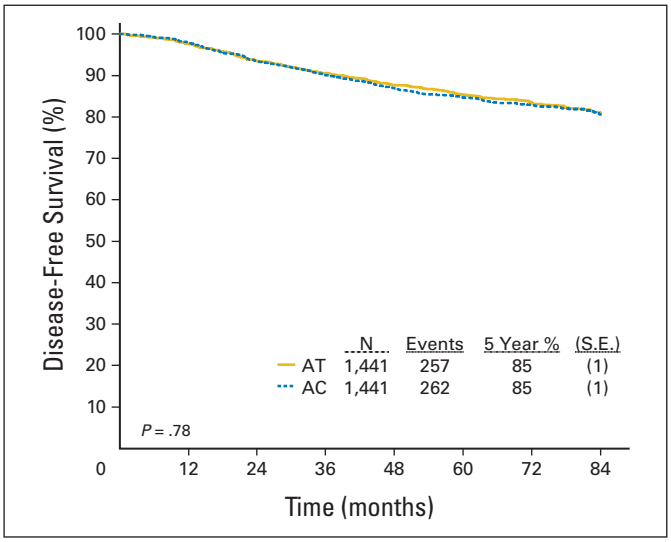

Fig 2. Kaplan-Meier curve for disease-free survival. Solid yellow curve indicates doxorubicin and docetaxel (AT); dotted blue curve indicates doxorubicin and cyclophosphamide (AC).

RESULTS

Patient Eligibility and Characteristics

Between July 30, 1998, and January 21, 2000, 2,952 patients were enrolled by ECOG (44%), Cancer and Leukemia Group B (15%), Southwest Oncology Group (29%), North Central Cancer Treatment Group (9%), and the Expanded Participation Project (3%). Seventy patients (2.4%) were classified as ineligible, leaving 2,882 patients eligible (Fig 1).

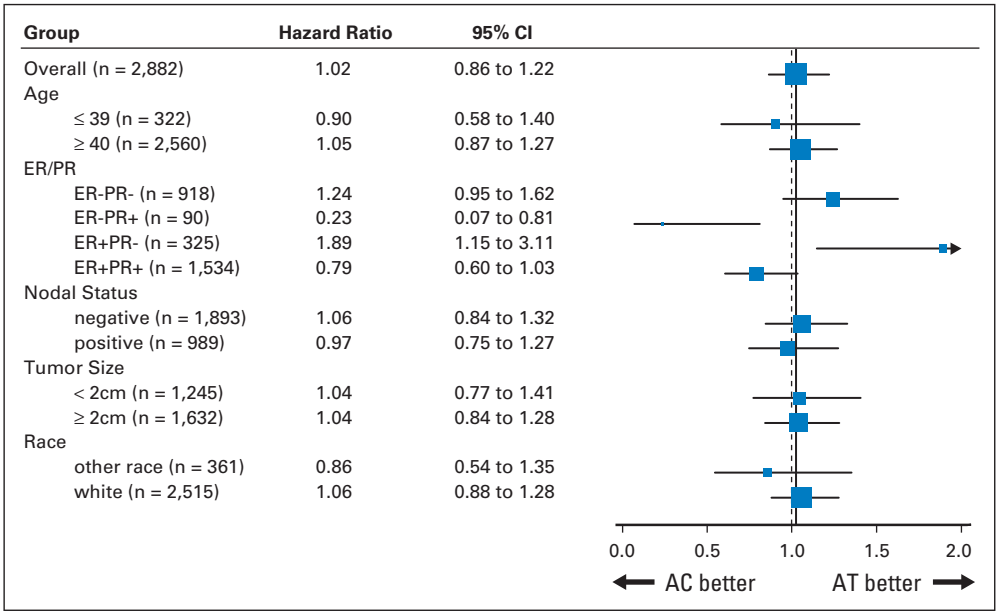

Fig 3. Forest plot: disease-free survival by subgroups. ER, estrogen receptor; PR, progesterone receptor; AC, doxorubicin and cyclophosphamide; AT, doxorubicin and docetaxel.

Patient characteristics were well balanced between treatment groups (Table 1). Assigned therapy was started in 99.5% of patients and was completed in 94% of the patients in the AT arm and 97% in the AC arm. Among the eligible patients, 11.5% and 4.6% of patients on the AT and AC arms, respectively, received lower than 90% of the planned cumulative dose. Three percent of patients who received a breast sparing procedure did not receive radiation therapy. One thousand eight hundred eighty-six patients began tamoxifen. For patients where both a start and end date for tamoxifen was available (n = 1,521), median time on tamoxifen was 59 months (range, < 1 to 84) for patients receiving AT and 58 months (range, < 1 to 74) for patients receiving AC. Limited data for AI use were available for 374 patients, 168 and 206 on the AT and AC arms, respectively. Of these patients, 34% and 38% on the AT and AC arms respectively completed at least 5 years of tamoxifen.

DFS and OS

Table 2 summarizes sites of recurrence, deaths, and other clinically significant events that were not included in the DFS end point. In the current analysis (January 2007), there were 257 DFS events in the AT arm, including 216 recurrences and 41 deaths without recurrence. There were 262 DFS events in the AC arm, including 220 recurrences and 42 deaths without recurrence. Figure 2 shows DFS Kaplan-Meier curves for each treatment arm which demonstrates an 85% DFS rate at 5 years with no significant difference in DFS between the two treatments (hazard ratio [HR] for AC *v* AT 1.02; 95% CI, 0.86 to 1.22; $P = .78$; Table 3). When adjusting for baseline characteristics including age, menopausal status, primary surgery, ER/PR status, nodal status, tumor size, and tumor grade, the effect of treatment on DFS is similar to the result when accounting for treatment alone (HR for AC *v* AT 1.03; 95% CI, 0.87 to 1.22; $P = .74$; Table 3). If all patients (N = 2,952) were analyzed (including ineligible patients), there were 530 DFS events. Results were similar to the results for patients classified as eligible (HR for AC *v* AT 1.02; 95% CI, 0.86 to 1.21; $P = .83$; Table 3).

Figure 3 shows the effect of treatment on DFS within subgroups of baseline characteristics. There was a statistically significant interaction between ER/PR status and treatment where patients with tumors classified as ER- and PR-negative and ER positive PR negative experienced more favorable outcome with use of AT (P values for interactions terms .02 and < .01, respectively). Figure 4 shows the DFS curves within the ER/PR subgroups. No other interactions between the baseline characteristics and treatment were statistically significant.

With 79.5 months median follow-up, 322 patients among the eligible population had died. Appendix Figure A1, online only, shows OS Kaplan and Meier curves for each treatment arm which demonstrates 92% survival rate at 5 years for the AT arm and 91% for the AC arm. There was no significant difference in survival between the two treatments (HR for AC *v* AT 1.06; 95% CI, 0.85 to 1.31; $P = .62$; Table 3). When adjusting for baseline characteristics, the effect of treatment on OS is similar to the result when accounting for the effect of treatment alone (HR for AC *v* AT 1.06; 95% CI. 0.85 to 1.31; $P = .63$; Table 3). No interactions between the baseline characteristics and treatment with respect to survival were statistically significant.

When all patients, eligible and ineligible were analyzed (n = 2952), there were 331 deaths. Results for this analysis were similar to the results for patients classified as eligible and again there was no difference in OS between AT and AC (HR AC *v* AT 1.03; 95% CI, 0.83 to 1.28; $P = .76$; Table 3).

Toxicity

There was a higher incidence of grade 3 neutropenia associated with fever or infection in the AT arm compared with the AC arm (26% *v* 10%; $P < .05$); primary G-CSF prophylaxis was not used, which was the standard of care at the time by ASCO guidelines.[17] Other most frequently clinically important grade 3/4 adverse events included neutropenia (54% with AT *v* 38% with AC; $P < .05$) and leucopenia (22% with AT *v* 8% with AC; $P < .05$; Appendix Tables A1 and A2, online only). There were six deaths classified as related to treatment including four in the AT arm (visceral arterial ischemia, infection with grade 3/4 neutropenia, cardiac arrest, acute respiratory distress syndrome) and two deaths in the AC arm (myocardial infarction and acute myeloid leukemia). There were seven cases of myelodysplastic syndromes/acute

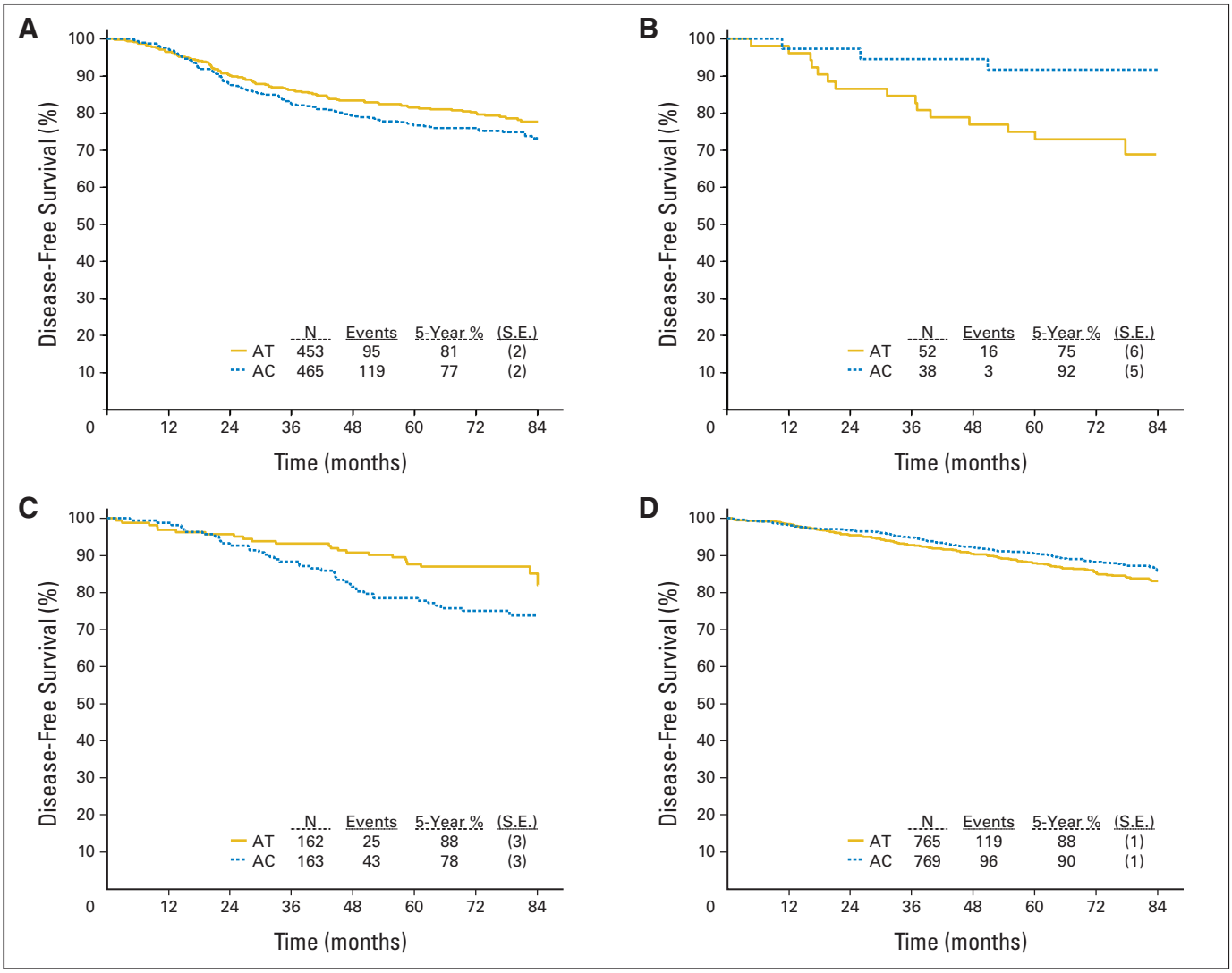

Fig 4. Kaplan-Meier disease-free survival curves by estrogen receptor (ER)/progesterone receptor (PR) subgroups: solid yellow curves indicates doxorubicin and docetaxel (AT); dotted blue curves indicates doxorubicin and cyclophosphamide (AC). (A) ER negative, PR negative. (B): ER negative, PR positive (C) ER positive, PR negative. (D) ER positive, PR positive.

myeloid leukemia on each arm. Twelve patients developed CHF during chemotherapy—eight on AT (six grade 3, one grade 4, one grade 5), four on AC (all grade 3), and 19 patients developed CHF more than 30 days postchemotherapy—12 on AT (11 grade 3, one grade 4), seven on AC (all grade 3). There was no significant difference in changes in LVEF from baseline between the two arms (Appendix Table A3, online only).

DISCUSSION

The purpose of this trial was to determine if concurrent administration of adjuvant AT every 3 weeks for four cycles was more effective than the standard concurrent doxorubicin and cyclophosphamide regimen in patients with operable breast cancer and 0 to three positive axillary lymph nodes. We believed that there was a reasonable likelihood that this would be the case based on data from phase II and phase III trials available at the time, and subsequently by a phase III trial confirming a significantly higher objective response rate for the doxorubicin and docetaxel combination compared with the doxorubicin and cyclophosphamide combination in patients with metastatic breast cancer.[26-28] However, the DFS and OS rates were essentially identical between the two arms in our trial, although the 5-year DFS survival rates observed in both treatment arms (85%), was substantially better than had been predicted based on historical data (78%). In an exploratory analysis, the AT arm was associated with a strong trend toward improved DFS in patients with ER- and PR-negative disease. Although the AT arm was not associated with more cardiac toxicity, it was associated with significantly higher rates of severe neutropenia, febrile neutropenia, and other severe nonhematologic toxicities.

Several other trials have demonstrated a clear benefit for adjuvant docetaxel or paclitaxel, whether used concurrently with doxorubicin-containing therapy, or sequentially after anthracycline-based therapy. Martin et al reported that concurrent administration of

docetaxel with doxorubicin and cyclophosphamide (TAC) significantly improved DFS and OS when compared with fluorouracil, doxorubicin, and cyclophsophamide.[15] Several studies also demonstrated that sequential administration of paclitaxel or docetaxel after anthracycline-based therapy was more effective than the same regimen without taxane therapy.[12,13,29] Moreover, meta-analyses that included studies incorporating adjuvant taxanes also demonstrated a benefit for taxane therapy.[30,31] It appears that the concurrent administration of a short course of doxorubicin and docetaxel, as used in our trial, is not an effective way of intergrating taxanes into adjuvant therapy.

Most recently, Jones at al reported the results of a US Oncology (USO) trial comparing AC to docetaxel and cyclophosphamide (TC).[32] TC resulted in a superior DFS compared with AC in this trial (5-year DFS 86% for TC *v* 80% AC; $P = .015$; HR, 0.67) without a significant difference in OS (TC 90% *v* AC 87%; $P = .13$; HR, 0.76) although 7-year follow-up has now demonstrated an improvement in OS for TC (TC 87% *v* AC 82%; $P = .032$; HR, 0.69).[32,33] All of these data would have led the unbiased investigator to expect that AT would be superior to AC in E2197. While one cannot do cross trial comparisons, the TC arm of this trial is similar to the overall outcome on E2197. There are some specific differences between the trials that may account for the divergence. First, the dose of docetaxel in E2197 was 60 mg/m^2 to maintain the dose of adriamycin constant in both arms where as the docetaxel dose in the USO study was 75 mg/m^2. This may be important since it has been shown that there is a docetaxel dose response effect.[34] In addition, the patient population was of slightly higher risk in the USO study with 53% of patients having positive lymph nodes compared with 34% in E2197. The National Surgical Adjuvant Breast and Bowel Project B30 is designed to compare AC for four cycles followed by docetaxel for four cycles versus AT for four cycles versus TAC for four cycles. This study has completed accrual but the results have not yet been reported.

The ER/PR subgroups were prespecified stratification groups at randomization designed to balance the treatment arms and are not powered to detect differences between arms within the subgroups. In an exploratory subset analysis, we found that AT tended to be more effective in patients ER- and PR-negative disease. Although we did not perform central ER, PR, and HER2/*neu* testing for all patients enrolled in our trial, a subset of 776 patients who had central testing performed demonstrated 90% concordance with local ER/PR testing and 79% concordance with local HER2/*neu* testing; concordance was higher for HER2/*neu* testing when cases were determined to be HER2/*neu* negative locally.[35] These data support the hypothesis presented by Berry et al, that in the ER positive tumors the large benefit provided by tamoxifen, overwhelms the potential benefit of chemotherapy, or that the prognosis of these tumors is so good it is difficult to detect a difference between the two chemotherapy arms.[36] Others have also demonstrated greater treatment benefit for adjuvant taxanes in ER/PR-negative disease, although this has not been consistently demonstrated in other studies.[15,36]

Of great interest is the biologic hypothesis generated by E2197 from the ER/PR prespecified subset analysis and supports the importance of collecting clinical specimens for future prospective laboratory analysis on archival samples from controlled randomized clinical trials. These data also support the premise of the Trial Assigning IndividuaLized Options for Treatment, which uses Oncotype DX (Genomic Health Inc, Redwood City, CA), using molecular characteristics, to stratify tumors based on genomic profiling to determine prognosis and potential benefit to specific therapy. Studies aimed at the biologic tumor characteristics as determinants of outcome from E2197 will include central review of ER/PR and HER2, Oncotype DX, and genomic profiling to determine if individual genes may predict outcome of specific sensitivity or resistance to a specific therapy.

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.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

