original report

West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer

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abstract

PURPOSE The West German Study Group PlanB trial evaluated an anthracycline-free chemotherapy standard (six cycles of docetaxel and cyclophosphamide [TC]) in the routine treatment of human epidermal growth factor receptor 2–negative early breast cancer (EBC).

PATIENTS AND METHODS Patients with pT1 to pT4c, all pN+, and pN0/high-risk EBC were eligible. High-risk pN0 was defined by one or more of the following: pT greater than 2, grade 2 to 3, high urokinase-type plasminogen activator/plasminogen activator inhibitor-1, hormone receptor (HR) negativity, and less than 35 years of age. After an early amendment, all HR-positive tumors underwent recurrence score (RS) testing, with chemotherapy omission recommended in RS less than or equal to 11 pN0 to pN1 disease. Patients were randomly assigned to four cycles of epirubicin $(E)_{90}$/cyclophoshamide $(C)_{600}$ followed by four cycles of docetaxel $(T)_{100}$ or six cycles of $T_{75}C_{600}$ (administered once every 3 weeks). The primary end point was disease-free survival (DFS); secondary end points were overall survival (OS) and safety. The protocol specified $P = .05$ for a noninferiority margin of 4.4% for all patients combined.

RESULTS Of the 3,198 registered patients, 348 (RS ≤ 11) omitted chemotherapy, and 401 were not randomly assigned. The intention-to-treat population included 2,449 patients (1,227 EC-T *v* 1,222 TC: postmenopausal, 62.2% *v* 60.8%; pN0, 58.2% *v* 59.5%; pT1, 57.6% *v* 52.3%; HR positive, 81.4% *v* 82.2%; RS greater than 25 [in HR-positive patients], 26.2% *v* 27.5%). Within the safety population (1,167 *v* 1,178 patients), 87.5% *v* 93.0% completed therapy. After a 60-month median follow-up, 5-year outcomes were similar in the EC-T and TC arms (DFS, 89.6% [95% CI, 87.9% to 91.5%] *v* 89.9% [95% CI, 88.1% to 91.8%]; OS, 94.5% [95% CI, 93.1% to 95.9%] *v* 94.7% [95% CI, 93.3% to 96.1%]). The DFS difference was within the noninferiority margin of the original trial design. Five treatment-related deaths were reported for TC (one for EC-T), despite a trend toward more-severe adverse events in the latter. Interaction analysis revealed no predictive trends with respect to key factors, including triple-negative, luminal A/B-like, pN, age, and RS status.

CONCLUSION In the West German Study Group PlanB trial, 5-year outcomes for TC and EC-T were equally excellent. Six cycles of TC is an effective/safe option in human epidermal growth factor receptor 2–negative EBC with pN0 high genomic risk or pN1 EBC with genomically intermediate- to high-risk disease.

J Clin Oncol 37:799-808. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT
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Data Supplements
Author affiliations and support information (if applicable) appear at the end of this article.
Accepted on January 2, 2019 and published at jco.org on February 20, 2019: DOI https://doi.org/10.1200/JCO.18.00028
Clinical trials information: NCT01049425.

INTRODUCTION

The role of anthracyclines in chemotherapy regimens in early breast cancer (EBC) still is being debated. Meta-analysis of long-term outcomes in early randomized EBC trials demonstrated that first-generation chemotherapy regimens (cyclophosphamide, methotrexate, and fluorouracil) are less effective than anthracycline-based polychemotherapy regimens, such as fluorouracil, doxorubicin, and cyclophosphamide or fluorouracil, epirubicin, and cyclophosphamide.[1] A subsequent meta-analysis demonstrated that the addition of taxanes to anthracycline-based regimens further reduces recurrence and breast cancer mortality.[2] Relative risk reductions were not

substantially affected by traditional clinicopathologic characteristics, such as age, nodal status, tumor size, tumor differentiation, estrogen receptor status, and tamoxifen use.[2] Of note, anthracycline-based regimens were shown to be associated with a nonsignificant excess mortality of 0.2% as a result of cardiac disease, leukemia, or lymphoma.[2] As the number of long-term survivors, elderly patients, and patients with pre-existing cardiac risk factors increases, the toxicity profile becomes a more important discriminator in adjuvant treatment selection. This explains the widespread use (47.8%) of an anthracycline-free regimen like docetaxel and cyclophosphamide (TC) in older patients (ages 67 to 94 years), as reported in an analysis of the SEER-Medicare database in 2010.[3] The increased use of TC versus doxorubicin and cyclophosphamide (AC) was based on evidence from a single phase III trial that compared four cycles of TC and four cycles of AC in 1,016 patients with EBC (71% hormone receptor [HR] positive; approximately one half node negative).[4] After a median follow-up of 5.5 years, the 5-year disease-free survival (DFS) rate significantly favored TC (86% *v* 80%); differences in overall survival (OS; 90% *v* 87%) were not significant.[4] Because four cycles of AC was considered a weak comparator,[5] second-generation phase III trials evaluated the role of anthracycline-free regimens compared with six cycles of TC (6 × TC) versus 20 to 24 weeks of a taxane plus AC (TaxAC) standard regimen.[6,7] Such trials were conducted in human epidermal growth factor receptor 2 (HER2)–negative disease because HER2-positive disease is investigated separately with regimens that contain HER2-targeted therapies.

This article presents the final analysis of the prospective, randomized, multicenter phase III West German Study Group (WSG) PlanB trial in clinically intermediate- to high-risk EBC. WSG PlanB combined a classic phase III chemotherapy trial design, which compared 6 × TC with an anthracycline/taxane-containing standard (epirubicin and cyclophosphamide followed by docetaxel [EC-T]) with next-generation patient selection, using both pathology/immunohistochemistry and genomic testing with the recurrence score (RS) assay.

PATIENTS AND METHODS

Study Participants

As previously described,[8,9] the trial included female patients (ages 18 to 75 years) with histologically confirmed, unilateral primary invasive breast cancer, adequate surgical treatment, and no evidence of metastatic disease. Key inclusion criteria were HER2 negativity, pT1 to pT4c, known HR status, pN+ or pN0 with one or more risk factors (≥ pT2, grade 2/3, high urokinase-type plasminogen activator/plasminogen activator inhibitor-1, < 35 years of age, or HR negativity), Eastern Cooperative Oncology Group performance status of less than 2 or Karnofsky status of greater than or equal to 80%, and signed informed consent and for patients with HR-positive EBC with four or more positive lymph nodes or RS greater than 11, and a willingness to participate in the adjuvant chemotherapy WSG PlanB trial.

Study Design

WSG PlanB (Fig 1) was approved by German ethics boards and conducted in accordance with the Declaration of Helsinki. It was initiated as a chemotherapy trial in 2009 to test noninferiority of an anthracycline-free regimen (6 × $T_{75}C_{600}$ [TC] once every 3 weeks) compared with an anthracycline-containing regimen (four cycles of $E_{90}C_{600}$ once every 3 weeks followed by four cycles of docetaxel$_{100}$ once every 3 weeks [EC-T]). According to the protocol, randomization to the chemotherapy arms was stratified according to center, pN status (in three categories: pN0, pN1, and pN2 to pN3), (local) HR status, and age (< 50 *v* ≥ 50 years). Block randomization was used. After including 264 patients, the trial was amended to recommend endocrine therapy alone (omitting chemotherapy) in patients with locally HR-positive pN0 to pN1 tumors and RS less than or equal to 11. Other treatments followed national guidelines at the time. Follow-up, RS analysis, immunohistochemistry, fluorescence in situ hybridization, and protein encoded by the *MKI67* gene (Ki-67) analyses were performed as previously described.[8,9]

End Points

The primary end point of WSG PlanB was DFS; an event that was defined as any invasive cancer event or death (with or without recurrence). Secondary end points were distant recurrence-free interval (dRFI), OS, and safety. End points of the WSG-PlanB translational program were described previously.[8,9]

Statistical Considerations

The chemotherapy trial was designed and powered to test noninferiority of the TC versus EC-T arms. The protocol specified a one-sided test of the DFS hazard ratio at $\alpha = .05$, with the limiting hazard ratio defined implicitly in terms of a nominal 4.4% margin in 5-year DFS. The trial power analysis assumed a 5-year follow-up for all surviving patients, with 90% completing the protocol treatment and, in view of the trial population, a 5-year DFS of 71.1% for EC-T as in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial.[10] Under these assumptions, with a chemotherapy random assignment target of 2,203 evaluable patients (recruiting target, 2,448 patients), the planned test had 80% power.

The 95% and 90% CIs of the DFS hazard ratio for TC versus ET-C were estimated using univariable Cox proportional hazards regression analysis. For the primary, one-sided, noninferiority test, the 90% upper confidence limit was compared with the limiting hazard ratio that corresponded to a 4.4% 5-year DFS margin at the observed 5-year DFS level in the ET-C arm. Comparison with the corresponding hazard ratio for an assumed 5-year DFS in ET-C also is

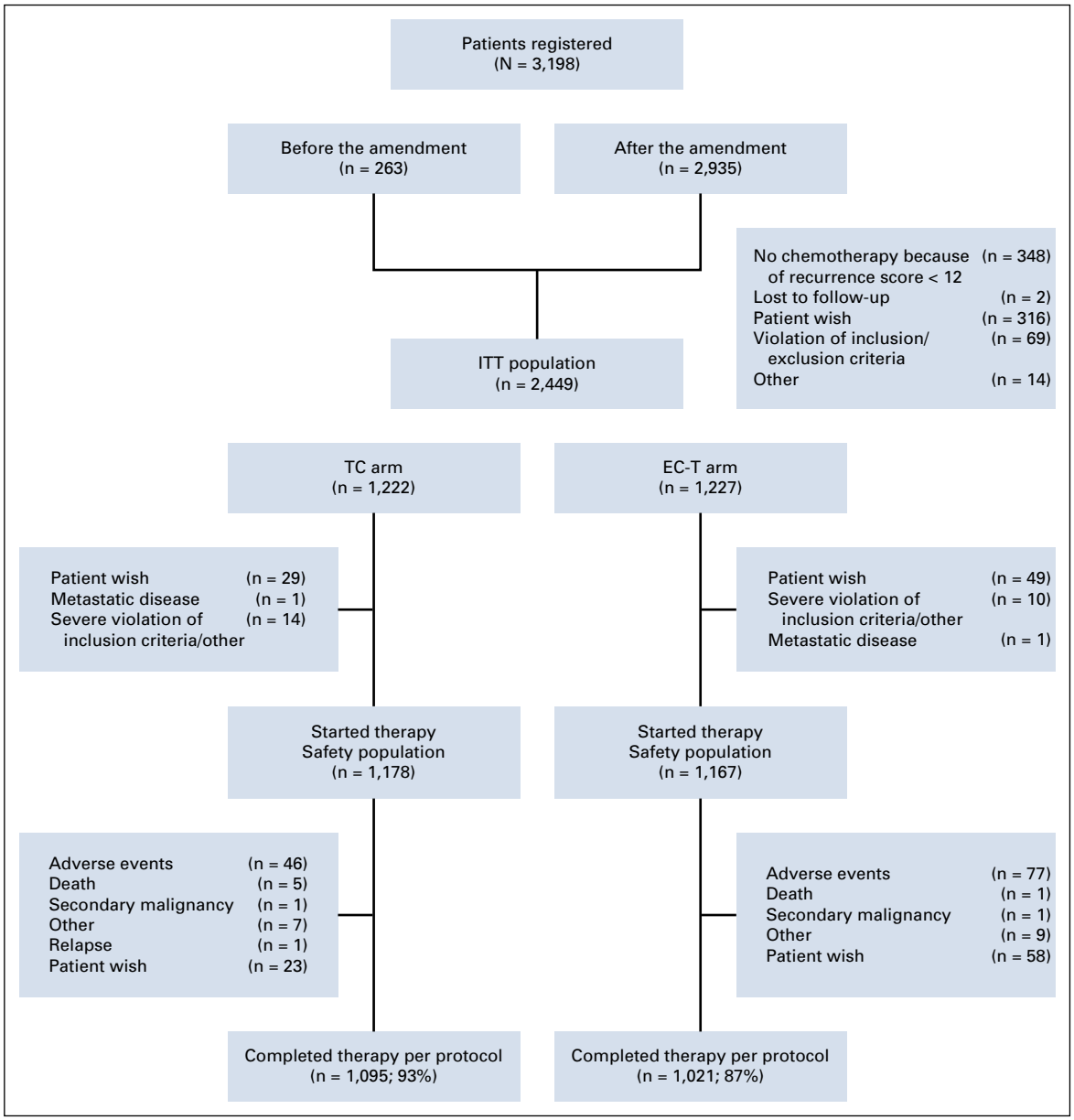

FIG 1. West German Study Group PlanB trial CONSORT diagram. EC-T, epirubicin and cyclophosphamide followed by docetaxel; ITT, intention to treat; TC, docetaxel and cyclophosphamide.

reported. Hazard ratios for TC versus ET-C and CIs were computed in clinically relevant subgroups.

Estimates of 5-year DFS, dRFI, or OS with approximate 95% CIs were obtained by the Kaplan-Meier method. Adjusted hazard ratios of explanatory factors, therapy, and interactions were estimated by multivariable Cox proportional hazards regression models (forward stepwise). In this analysis, some explanatory factors were coded as continuous variables using population percentile scores (fractional ranks). The hazard ratio of 75th to 25th percentile is reported for these variables. The ordinal variables pN, pT, and local and central grade were recoded using dummy binary variables (eg, for the four-level ordinal variable pN, there are three binary variables pN3 *v* pN0 to pN2, pN2 to pN3 *v* pN0 to pN1, and pN1 to pN3 *v* pN0).[11] Fisher's exact test and χ^2 test (including Mantel-Haenszel test of linear association) were used to compare proportions. Statistical analysis was performed using SPSS version 23 software (IBM Corporation, Chicago, IL).

RESULTS

Patient Characteristics

Between February 2009 and December 2011, 3,198 patients were registered, and 2,449 were randomly assigned to 6 × TC (n = 1,222) and four cycles of EC-T (n = 1,227;

TABLE 1. Baseline Characteristics

Characteristic	Arm: TC (n = 1,222) No.	%	Arm: EC-T (n = 1,227) No.	%	*P*
Menopausal status					
Pre	439	35.9	429	35.0	.52
Post	682	55.8	706	57.5	
NA	101	8.3	92	7.5	
Surgery					
BCS	995	81.4	990	80.7	.64
Mastectomy	224	18.3	235	19.2	
NA	3	0.2	2	0.2	
pN status					
pN0	727	59.5	714	58.2	.65
pN1	404	33.1	428	34.9	
pN2	72	5.9	63	5.1	
pN3	19	1.6	22	1.8	
pT status					
pT1	637	52.1	705	57.5	.058
pT2	532	43.5	471	38.4	
pT3	41	3.4	42	3.4	
pT4	9	0.7	7	0.6	
NA	3	0.2	2	0.2	
HR status (local)					
Negative	217	17.8	228	18.6	.6
Positive	1,005	82.2	999	81.4	
TN (central)					
No	917	75.0	916	74.7	.91
Yes	214	17.5	211	17.2	
NA	91	7.4	100	8.1	
Ki-67 (central, semiquantitative)					
0-10	364	29.8	384	31.3	.49
15-35	567	46.4	560	45.6	
≥ 40	157	12.8	141	11.5	
NA	134	11.0	142	11.6	
Central grade					
1-2	659	53.9	664	54.1	.9
3	518	42.4	516	42.1	
NA	45	3.7	47	3.8	
Local grade					
1-2	782	64.0	787	64.1	.97
3	437	35.8	438	35.7	
NA	3	0.2	2	0.2	
RS (HR positive)					
≤ 25	703	57.5	710	57.9	.48
> 25	266	21.8	252	20.5	
NA	253	20.7	265	21.6	
pN0/RS 12-25	363	29.7	366	29.8	.68
pN0/RS > 25	159	13.0	151	12.3	
pN+/RS 12-25	280	22.9	294	24.0	.518
pN+/RS > 25	107	8.8	101	8.2	

Abbreviations: BCS, breast-conserving surgery; EC-T, epirubicin and cyclophosphamide followed by docetaxel; HR, hormone receptor; NA, not available; RS, recurrence score; TC, docetaxel and cyclophosphamide.

Fig 1). Of these 2,449 randomly assigned patients, 264 were "randomized" to the chemotherapy trial before the early amendment, which implemented RS testing for HR-positive patients (2,186 subsequently). Endocrine therapy (but not chemotherapy) was administered to 348 patients with pN0 to pN1 disease on the basis of RS less than or equal to 11; 401 patients were not allocated to chemotherapy for other reasons, including 316 who refused further study participation, particularly in the node-negative group with RS of 12 to 18 (approximately one third of patients).

Patient characteristics were well balanced between the study arms (Table 1). Median age of chemotherapy-treated patients was 55 years (range, 25 to 77 years); approximately 40% had node-positive disease, and approximately 44% had poorly differentiated tumors (by central assessment).

Efficacy Analysis

After a median follow-up of 60 months (in patients alive at time of follow-up), no significant differences in DFS, dRFI, or OS were observed between the study arms (Fig 2A to C). In TC versus EC-T, respectively, estimated 5-year DFS was 89.6% (95% CI, 87.8% to 91.5%) *v* 89.8% (95% CI, 87.9% to 91.6%), with a hazard ratio of 1.004 (95% CI, 0.776 to 1.299); estimated 5-year dRFI was 94.1% (95% CI, 92.7% to 95.5%) *v* 93.4% (95% CI, 91.9% to 94.9%), with a hazard ratio of 0.875 (95% CI, 0.625 to 1.225); and estimated 5-year OS was 94.7% (95% CI, 93.3% to 96.1%) *v* 94.5% (95% CI, 93.1% to 95.9%), with a hazard ratio of 0.937 (95% CI, 0.654 to 1.342). The trial criterion for noninferiority was achieved because the 90% upper confidence limit for the DFS hazard ratio (appropriate for the planned one-sided noninferiority test at $\alpha = .05$) of 1.246 did not exceed the limiting noninferiority hazard ratio of 1.467, which corresponded to the permitted 4.4%

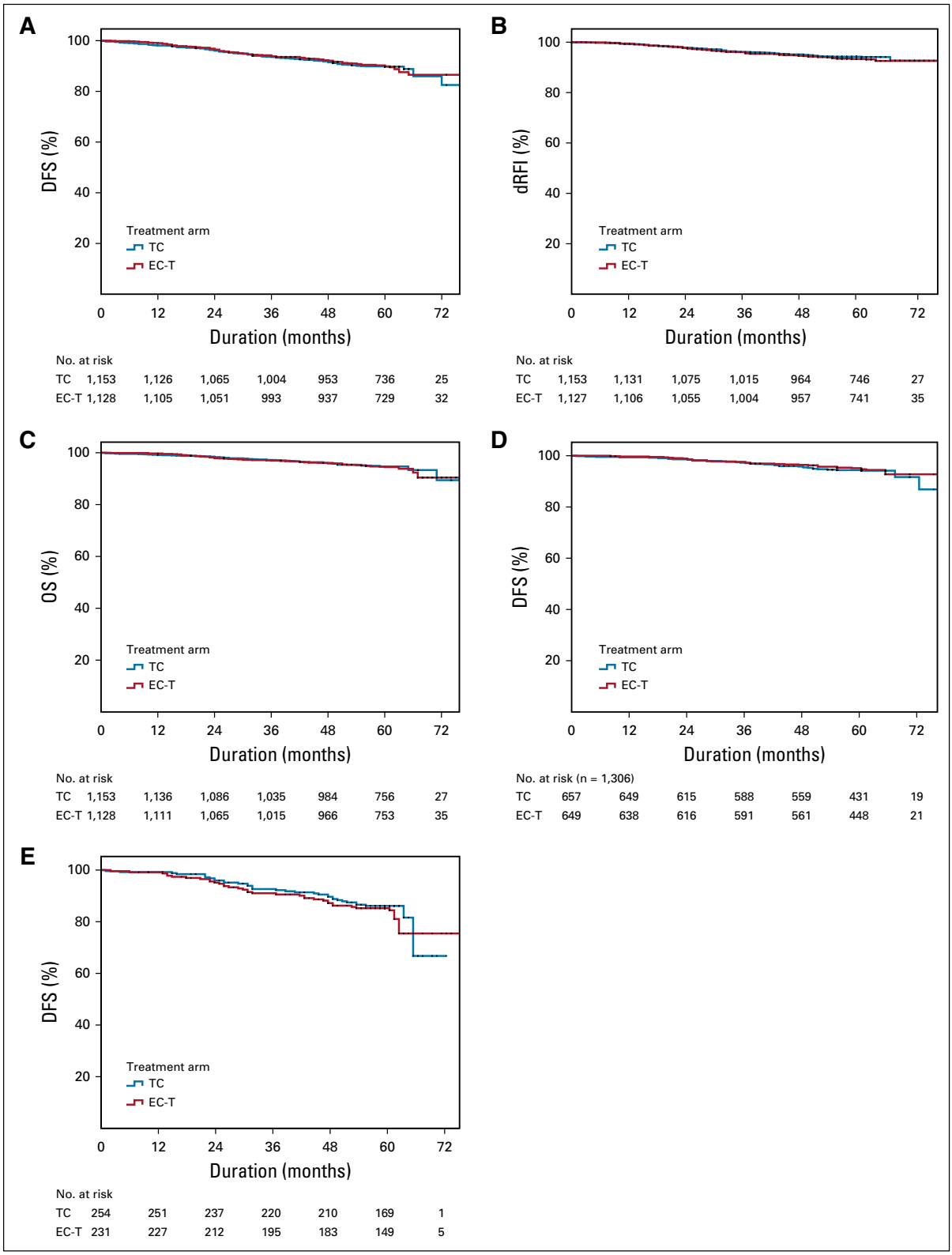

FIG 2. (A) Disease-free survival (DFS), (B) distant recurrence-free interval (dRFI), and (C) overall survival (OS) by treatment arm. (D) DFS by treatment arm and recurrence score (RS) of 25 or less and (E) DFS by treatment arm and RS greater than 25; the intention-to-treat population includes patients with RS measured (after early amendment). For the docetaxel and cyclophosphamide (TC) versus epirubicin and cyclophosphamide followed by docetaxel (EC-T) arms, respectively, numbers at risk were as follows: DFS and OS, n = 1,153 *v* 1,128; dRFI, n = 1,153 *v* 1,127; DFS/RS of 25 or less, n = 657 *v* 649; and DFS/RS greater than 25, n = 254 *v* 231. Patients in the intention-to-treat population with missing follow-up data (n = 69 *v* 99 for TC *v* EC-T, respectively) are omitted (one extra missing for dRFI).

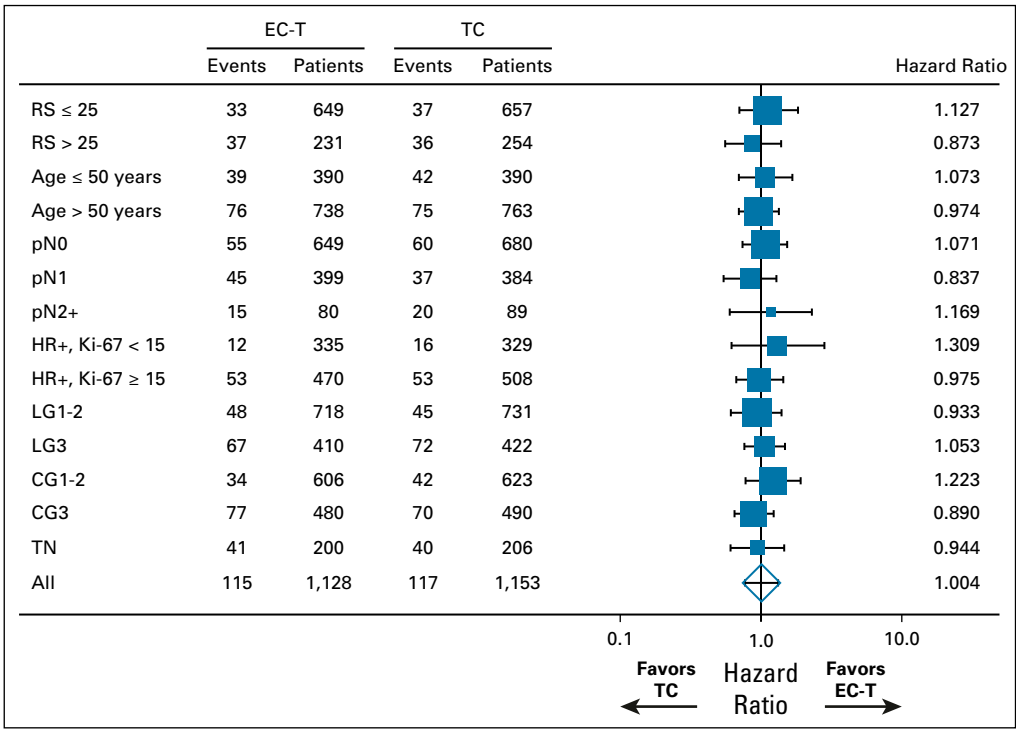

FIG 3. Forest plot of disease-free survival chemotherapy arm hazard ratios in subgroups (95% CIs, no corrections for multiple testing). CG, central grade; EC-T, epirubicin and cyclophosphamide followed by docetaxel; HR+, hormone receptor positive; Ki-67, protein encoded by the *MKI67* gene; LG, local grade; RS, recurrence score; TC, docetaxel and cyclophosphamide; TN, triple negative.

margin at the observed 5-year DFS of 89.8% in EC-T. (However, this 90% upper confidence limit of 1.246 exceeded the limit of 1.187 derived from the originally assumed 5-year DFS of 71.1% in EC-T.)

Figure 3 shows a forest plot of the efficacy of TC versus EC-T (hazard ratio < 1 would favor TC) according to several key prognostic factors, RS, nodal status, luminal A-like (Ki-67 < 15%) versus luminal B-like (Ki-67 ≥ 15%), local and central grade, and triple-negative (TN) status. Anthracycline-free chemotherapy (TC) was comparable to anthracycline-containing chemotherapy (EC-T) in all evaluated subgroups. Although, as previously reported,[8,9] RS had a substantial prognostic impact in this trial, the 5-year DFS, dRFI, and interaction analyses revealed no predictive trends with respect to key factors, including TN, luminal A/B-like, pN, RS, and age (> 50 *v* ≤ 50 years). In addition, the 5-year DFS rate (94.6%; 95% CI, 92.0% to 97.2%) and the dRFI rate (97.8%; 95% CI, 96.0% to 99.6%) were excellent in patients not treated with adjuvant chemotherapy, regardless of nodal status (DFS and dRFI rates, 94.5% and 97.7% in node-negative and 94.9% and 97.9% in pN1 disease, respectively).

In univariable analysis for DFS, nodal status, tumor size, surgery, local and central grade, continuous RS, progesterone receptor, and Ki-67 were prognostic factors. In a multivariable analysis (Data Supplement), only RS and Ki-67 as continuous variables, nodal status, histologic grade, and surgery type were significant and entered into the model, whereas study arm, tumor size, estrogen receptor, and progesterone receptor were not.

Safety

Six treatment-related deaths were observed within the study: five (0.4%) in the TC arm (one urosepsis, one *Streptococcus* septicemia, one peritonitis/diverticulitis, one *Staphylococcus* epidermidis septicemia, and one pulmonary embolism) and one (0.1%) in the EC-T arm (septicemia; $P = .2$). Three of the six treatment-related deaths occurred in the 65 years and older age-group, and two occurred in patients who received primary granulocyte colony–stimulating factor (G-CSF) prophylaxis. According to an interim safety analysis, febrile neutropenia rate was 6.1% (TC) *v* 3.9% (EC-T); therefore, generous primary G-CSF prophylaxis was recommended as well as ciprofloxacine prophylaxis in patients with a history of diverticulitis or chronic infectious GI disease or expected duration of neutropenia greater than 1 week. The EC-T arm versus the TC arm was characterized by significantly more dose reductions (230 [19.7%] *v* 78 [6.6%], respectively; $P < .001$) and dose delays (> 7 days; 78 [6.7%] *v* 47 [4.0%], respectively; $P = .004$). Overall, 87% and 93% of patients in these respective arms completed therapy by protocol.

Grade 3 to 4 leukopenia, neutropenia, nausea, vomiting, (peripheral) polyneuropathy, hand-foot syndrome, mucositis/stomatitis, arthralgia, myalgia, and fatigue were observed in significantly more patients treated with EC-T than with TC (Table 2). Only a nonsignificant trend toward higher frequency of grade 3 to 4 infections and febrile neutropenia was seen within the TC arm. Use of primary G-CSF prophylaxis during the first cycle of therapy was documented in 14.9% and 4.9% of patients in the TC and

EC-T arms, respectively ($P < .001$). Febrile neutropenia rates were significantly lower in patients with primary prophylaxis during the first cycle of therapy in the TC arm (primary prophylaxis *v* not, 1.7% *v* 6.0%; $P = .02$). In additional follow-up, four deaths (two in both arms) were observed as a result of heart failure and one as a result of acute myeloid leukemia (EC-T arm).

DISCUSSION

WSG PlanB is one of four international large randomized trial programs (Table 3) that evaluated an anthracycline-free regimen (TC) versus a conventional TaxAC in HER2-negative EBC. WSG PlanB is unique in that only clinically high-risk (TN, pN2 to pN3) or genomically intermediate- to high-risk HR-positive/pN0 to pN1 patients were eligible. DFS, dRFI, and OS were excellent and virtually identical in patients who received the anthracycline-containing or the anthracycline-free regimen. Subgroups that benefited from the anthracycline-containing regimen were not identified by interaction analysis, although a potentially clinically relevant benefit in particular (eg, high-risk) subgroups cannot be ruled out.

Our findings are in seeming contrast to the Anthracyclines in Early Breast Cancer (ABC) trials,[6] which reported inferiority of 6 × TC compared with TaxAC-based standards with regard to DFS but not OS (Table 3).

Of note, the TaxAC regimen in WSG PlanB was slightly different from that in the ABC trials; however, this difference is unlikely to account for outcome differences because the Breast Cancer International Research Group BCIRG-005 trial reported equal efficacy for sequential TaxAC and 6 × docetaxel with doxorubicin and cyclophosphamide.[13] Patients recruited to the ABC trials had more node-positive disease (59% *v* 41%) and fewer HR-positive tumors (69% *v* 81.8%; Table 3), and those with only genomically high-risk tumors, if available (4% testing), were randomly assigned, which resulted in a higher-risk baseline prognosis than that of WSG PlanB.[6] Conclusions with regard to optimal clinical utility of 6 × TC are complicated by differing statistical designs and assumptions in the ABC and WSG PlanB trials. The ABC joint analysis was planned on the basis of two trials with a superiority design, which both were closed prematurely as a result of futility.[6] The subsequent NSABP B-49 trial was initiated to allow a meta-analysis from these three trials with a sufficiently high sample size to test for noninferiority of TC versus TaxAC. The presented results were based on a preplanned interim analysis after 334 events, with reporting contingent on the hazard ratio exceeding 1.18 after 3.3 years of median follow-up. Indeed, the observed interim hazard ratio was 1.23 (95% CI, 1.01 to 1.50). WSG PlanB was designed a priori as a noninferiority trial comparing TC with EC-T in HER2-negative EBC. The observed 5-year DFS difference was within the noninferiority margin of the original trial design. However, because of a much higher DFS in both WSG PlanB arms than expected (5-year DFS of approximately 90% compared with the assumed 71.1%)—as in the Danish trial[7]—the 95% CI for the DFS hazard ratio was rather broad (0.77 to 1.29); thus, our study is underpowered to exclude small differences in 5-year DFS. Several key points should be noted. The DFS hazard ratio CIs in the ABC meta-analysis and WSG PlanB overlap substantially, particularly in patients with pN0 to pN1 disease, despite differences in the hazard ratio point estimates. Furthermore, the ABC analysis had a median follow-up of 3.3 years[6] (compared with 5 years in WSG PlanB) so that more mature ABC data could still modify the hazard ratio. Studies with a longer follow-up, such as WSG PlanB and the Danish Breast Cancer Cooperative Group 07-READ[7] in topoisomerase II–normal tumors (90% HER2 negative), have not seen survival differences in favor of anthracycline-containing chemotherapy. For an HER2-positive population as well, the early positive prognostic effect of anthracycline-containing chemotherapy (combined with trastuzumab *v* docetaxel and carboplatin) does not translate into a survival benefit.[14] In ABC, the hazard ratio that favored TaxAC may have been partly attributable to a preponderance of events in pN2 to pN3 patients, whereas in WSG PlanB, only limited conclusions can be drawn about pN2 to pN3 patients because of relatively wide CIs in these subgroups.

WSG PlanB has limited power to quantify subtype-specific effects. With this limitation in mind, the positive effect of anthracycline-containing chemotherapy in TN disease in the ABC analysis has not been confirmed by WSG PlanB and all other trials with longer follow-up.[7] Use of a sequential docetaxel regimen as control in WSG PlanB, which may be suboptimal in TN breast cancer,[15] also could be a possible explanation for these conflicting results. In luminal tumors, several retrospective analyses have shown that chemotherapy rendered little or no benefit in patients with genomically favorable (luminal A-like) EBC. We and others have shown that luminal B-like tumors benefit from the addition of taxanes.[16,17] In WSG PlanB, neither centrally measured Ki-67 nor RS were predictive for anthracycline efficacy. Both regimens showed similar efficacy in luminal A-like versus luminal B-like or RS low/high tumors, thus making 6 × TC an appropriate choice, even for pN0 to pN1 tumors at higher biologic risk (by RS testing or by Ki-67).

In terms of acute toxicity, both the pivotal phase III study (four cycles of AC *v* four cycles of TC)[4] and WSG PlanB slightly favor TC. Patients treated with an anthracycline-containing regimen had more nausea and vomiting, whereas those treated with TC had more neutropenia[4] or slightly more febrile neutropenia in WSG PlanB. Early on, a numerical excess of infection-related deaths was observed in the WSG PlanB TC arm, but after release of recommendations for particular caution in patients with pre-existing GI disease (eg, known diverticulosis), no additional deaths occurred. Jones et al[4] reported a single incident of congestive heart failure for AC (0.2%) and none

for TC. In WSG PlanB, cardiac failure was reported in 0.3% of patients in both arms, consistent with data that showed clinically meaningful cardiac long-term toxicity of third-generation regimens that contain TaxAC.[6] Overall, WSG PlanB safety results are consistent with those of the ABC trials (specifically, the safety analysis of NSABP B-49) that showed no clinically relevant differences in frequencies of severe adverse events in TaxAC versus TC.[6] In summary, both regimens are well tolerated, but adverse effect profiles differ.

With regard to genomic testing, WSG PlanB previously demonstrated that 17% of clinically high-risk pN0 to pN1 patients with low RS who were spared chemotherapy had an excellent 5-year DFS rate of 94% and dRFI rate of 98%.8.[18] WSG PlanB renders clinically valuable results, particularly in view of the recent results of the TAILORx trial (Hormone Therapy With or Without Combination Chemotherapy in Treating Women Who Have Undergone Surgery for Node-Negative Breast Cancer; ClinicalTrials.gov identifier: NCT02050750),[18] because it is the only trial to address the TaxAC versus TC question with a stringent Oncotype DX preselection. Even after excluding those 45% of patients in WSG PlanB who, on the basis of TAILORx,[18] would not have received adjuvant chemotherapy, the 5-year DFS is similar in the two chemotherapy arms (approximately 88%).

In conclusion, on the basis of existing evidence, 6 × TC can be considered an effective and safe chemotherapy option in HER2-negative, intermediate- to high-risk patients with EBC with zero to three positive lymph nodes as well as in those with known cardiac disease or pre-existing risk factors for cardiac toxicity. Differences in toxicity profiles and an individualized approach to treatment selection need to be discussed with patients. Whether six or four cycles of the same chemotherapy regimen are needed remains unclear[19]; however, the main body of recent evidence has been generated for 6 × TC.

The evidence provided by WSG PlanB is strongest for patients with pN0 to pN1 disease and does not address dose-dense regimens in high-risk EBC. WSG PlanB and recent TAILORx results[18] indicate overtreatment of most, but not all patients with intermediate RS. Thus, results from the randomized arms of RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer; ClinicalTrials.gov identifier: NCT01272037) and the WSG PlanB follow-up trial ADAPT (Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial; ClinicalTrials.gov identifier: NCT01817452) are eagerly awaited because they will provide clinically useful prospective evidence with regard to chemotherapy benefit in clinically intermediate- to high-risk EBC.

TABLE 2. Grade 3 to 5 Adverse Events During Study Treatment

	TC		EC-T		
Adverse Event	**No.**	**%**	**No.**	**%**	***P***
Leukopenia	598	50.8	671	57.5	.001
Neutropenia	598	50.8	676	57.9	.001
Anemia	4	0.3	9	0.8	.18
Febrile neutropenia	63	5.3	45	3.9	.09
Infection	82	7.0	62	5.3	.1
Nausea	20	1.7	44	3.8	.002
Vomiting	5	0.4	23	2.0	< .001
(Peripheral) polyneuropathy	10	0.8	26	2.2	.007
Hand-foot syndrome/palmar syndrome	9	0.8	33	2.8	< .001
Diarrhea	37	3.1	39	3.3	.8
Mucositis/stomatitis	20	1.7	43	3.7	.003
Arthralgia/myalgia	18	1.5	35	3.0	.02
Pain	37	3.1	61	5.2	.01
Cardiac failure	3	0.3	3	0.3	> .999
Fatigue	35	3.0	68	5.8	.001
Thrombosis	19	1.6	24	2.1	.48
Therapy-related death	5	0.4	1	0.08	.2
Cardiac-related death*	2	0.1	2	0.1	>.999
Acute myeloid leukemia*	0	0	1	0.08	.3

*During follow-up.

TABLE 3. Summary of Large Trials in HER2-Negative EBC That Evaluated an Anthracycline-Free Regimen (TC) Versus a Conventional Anthracycline-Taxane Regimen

Trial	No. of Patients	Median Follow-Up	Experimental Regimen	Control Regimen	Inclusion Criteria	DFS	OS
USOR 9735[12]	1,016	7 years	4 × $T_{75}C_{600}$ once every 3 weeks	4 × $A_{60}C_{600}$	Stage I-III HER2 negative BC	7 year: 81% (TC) *v* 75%; *P* = .033	7 year: 87% (TC) *v* 82%; *P* = .032
ABC pooled analysis[6]	4,242	40 months	6 × $T_{75}C_{600}$ once every 3 weeks	USOR 06-090/NSABP B-46: 6 × $T_{75}A_{50}C_{500}$ once every 3 weeks NSABP B-49: 4 × $A_{60}C_{600}$ once every 3 weeks → 12 × Pac_{80} once every week 4 × $A_{60}C_{600}$ once every 2 weeks → 12 × Pac_{80} once every week 4 × $A_{60}C_{600}$ every 2 weeks → 4 × Pac_{175} once every 2 weeks	HER2 negative: pN+ or pN0 with one or more of the following criteria: HR negative, grade 3, RS ≥ 25 (NSABP B-46/B-49), or RS ≥ 31 (USOR 06-090)	4-year invasive DFS: 88.2% (TC) *v* 90.7%, *P* = .04	4 year: 94.7% (TC) *v* 95.0%; *P* = .6
DBCG 07-READ[7]	2,012	65 months	6 × $T_{75}C_{600}$ once every 3 weeks	3 × FE_{90}/C_{600} once every 3 weeks → 3 × T_{100} once every 3 weeks	Topoisomerase II-normal: pN+ and pN0 high-risk (< 39 years, tumor size > 2 cm, grade 2/3, ER negative, or HER2 positive)	5 year: 88.3% (TC) *v* 87.9%; *P* = 1	5 year: 93.3% *v* 94.8%; *P* = .41
WSG PlanB	2,449	61 months	6 × $T_{75}C_{600}$ once every 3 weeks	4 × $E_{90}C_{600}$ once every 3 weeks → 4 × T_{100} every 3 weeks	HER2 negative, pN+, or pN0 with one or more of the following risk factors: ≥ pT2, grade 2/3, high uPA/PAI-1, < 35 years, or ER/PR negative)	5 year: 89.9% (TC) *v* 89.6%	5 year: 95.9% (TC) *v* 94.5%

NOTE. Subscripts indicate dose in mg per square meter.

Abbreviations: ABC, Anthracyclines in Early Breast Cancer; AC, doxorubicin and cyclophosphamide; DBCG, Danish Breast Cancer Group; DFS, disease-free survival; EBC, early breast cancer; EC-T, epirubicin and cyclophosphamide followed by docetaxel; ER, estrogen receptor; FEC, fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; Pac, paclitaxel; PR, progesterone receptor; TAC, docetaxel with doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide; uPA/PAI-1, urokinase-type plasminogen activator/plasminogen activator inhibitor-1; USOR, US Oncology Research; WSG, West German Study Group.

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Presented at the 34th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 6-10, 2011; American Society of Oncology 2012 Annual Meeting, Chicago, IL, June 1-5, 2012; 37th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 9-13, 2014; 10th European Breast Cancer Conference, Amsterdam, the Netherlands, March 9-11, 2016; and American Society of Clinical Oncology 2017 Annual Meeting, Chicago, IL, June 2-6, 2017.

SUPPORT

Supported by Genomic Health, Sanofi, and Amgen.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.00028.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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No other potential conflicts of interest were reported.

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