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ORIGINAL REPORT

Pathologic Complete Response With Six Compared With Three Cycles of Neoadjuvant Epirubicin Plus Docetaxel and Granulocyte Colony-Stimulating Factor in Operable Breast Cancer: Results of ABCSG-14

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ABSTRACT

Purpose

Preoperative (neoadjuvant) chemotherapy for operable breast cancer downstages tumors initially not suitable for breast-conserving surgery. A pathologic complete response (pCR) to neoadjuvant chemotherapy may be a surrogate for longer overall survival, but this beneficial effect remains to be established. This phase III trial evaluated whether doubling the number of cycles of neoadjuvant treatment increased the pCR rate.

Patients and Methods

Patients with biopsy-proven breast cancer (T1-4a-c, N±, M0; stage I to III) were eligible and randomly assigned to either three or six cycles of epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 on day 1 and granulocyte colony-stimulating factor on days 3 through 10 (ED+G), every 21 days. The primary end point was the pCR rate of the breast tumor. Secondary end points were pathologic nodal status after surgery and the rate of breast-conserving surgery.

Results

A total of 292 patients were accrued, and 288 patients were assessable for efficacy and safety. Groups were well balanced for known prognostic factors. Six cycles of ED+G, compared with three cycles, resulted in a significantly higher pCR rate (18.6% *v* 7.7%, respectively; $P = .0045$), a higher percentage of patients with negative axillary status (56.6% *v* 42.8%, respectively; $P = .02$), and a trend towards more breast-conserving surgery (75.9% *v* 66.9%, respectively; $P = .10$). Rates of adverse events were similar, and no patients died on treatment.

Conclusion

Doubling the number of neoadjuvant ED+G cycles from three to six results in higher rates of pCR and negative axillary nodal status with no excess of adverse effects. Thus, six cycles of ED+G should be the standard neoadjuvant treatment for operable breast cancer if this combination is chosen.

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INTRODUCTION

Compared with adjuvant systemic therapy, neoadjuvant chemotherapy of primary breast cancer downstages the primary tumor as well as axillary lymph node involvement, leading to a higher rate of breast-conserving surgery in approximately 50% to 70% of patients with tumors primarily not suited for limited surgery.[1-4] Thus, the neoadjuvant approach has become the treatment of choice for this purpose in many institutions worldwide. However, the positive influence of preoperative chemotherapy on survival, which is the ultimate goal of any therapeutic intervention in oncology, remains unproven.[5-7]

In two large studies by the National Surgical Adjuvant Breast and Bowel Project, B-18 and B-27, subgroup analysis of patients experiencing a pathologic complete response (pCR) of the invasive tumor (T0 or ductal carcinoma in situ after preoperative chemotherapy with four cycles of doxorubicin and cyclophosphamide either alone or followed by docetaxel) showed a significantly prolonged overall survival time.[5,8] These results lead to the conclusion that pCR of the primary tumor is a surrogate

for pCR of systemic micrometastases responsible for clinically overt metastatic relapse.

Published data show pCR rates of 10% to 15% with anthracycline-containing regimens[5,8-10] and 15% to 25% if a taxane is used.[8,10-13] Preliminary results of a closed clinical trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-7), in which three cycles of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and fluorouracil (600 mg/m^2 intravenously [IV]) were administered preoperatively on days 1 and 8 every 28 days to 215 patients, demonstrated a pCR rate of only 3.7%.[14] A pilot phase II trial in 53 patients with primary breast cancer and no distant disease conducted at one of the ABCSG institutions (University of Vienna, Vienna, Austria) demonstrated that the combination of epirubicin and docetaxel plus granulocyte colony-stimulating factor (ED+G) is feasible and effective (pCR rate, 14% after a median of five cycles; range, three to eight cycles).[15] The argument for prolonging preoperative treatment is that many patients may be undergoing surgery during an ongoing partial response and that these partial responses might be converted into pCRs if more chemotherapy is administered. Therefore, the ABCSG has designed a prospectively randomized, multicenter clinical trial to study the outcome in terms of the pCR rate in patients treated with three cycles of chemotherapy compared with six cycles of the identical chemotherapy regimen in the preoperative setting.

PATIENTS AND METHODS

This prospective randomized clinical investigation followed Good Clinical Practice guidelines, and the protocol was approved by the ethics committee at each participating center. The trial was monitored by an independent body of the ABCSG according to a predefined schedule. All patients provided written informed consent.

The primary aim of this study was to compare the pCR rate of the breast tumors at the time of final surgery after preoperative treatment with either three cycles of ED+G, which was the standard of care at the time in Austria, or six cycles of the same chemotherapy regimen. Secondary end points were pathologic nodal status after surgery, rate of breast-conserving surgery, and toxicity.

Patients

Eligible patients had histologic proof of invasive breast cancer of any clinical tumor stage (except inflammatory breast cancer) with or without palpable axillary lymph nodes and were scheduled for neoadjuvant therapy. Distant disease had to be ruled out by chest x-ray, liver sonography, and bone scan. Patients must have had adequate hematologic findings (neutrophils $\geq 4.0 \times 10^9$/L, platelets $\geq 150 \times 10^9$/L, and hemoglobin $\geq$ 13 g/dL) and adequate hepatic and renal function (total bilirubin $< 1\times$ the institutional upper normal limit [UNL], AST/ALT $< 1\times$ UNL, alkaline phosphatases $< 1\times$ UNL, and serum creatinine $\leq 1\times$ UNL). Normal cardiac function must have been confirmed by a left ventricular ejection fraction of more than 50% as judged by radionuclide ventriculography or echocardiography. All procedures except biochemistry and hematology (within 3 days) must have been completed within the 2 weeks before study entry. Patients with preoperative local treatment for breast cancer (ie, incomplete surgery, radiotherapy), prior or concurrent systemic antitumor therapy, past or current history of other neoplasm (except for cured nonmelanoma skin cancer or in situ carcinoma of the cervix), pre-existing motor or sensory neurotoxicity of a severity $\geq$ grade 2 by WHO criteria, or a medically uncontrollable heart condition or any other serious illness or medical condition were excluded. Pregnant or lactating women were also excluded, and patients of childbearing potential were required to implement adequate nonhormonal contraceptive measures at study entry and during study participation.

Treatment

Patients were stratified according to clinical tumor stage (T1, T2, T3, or T4a-c), clinical lymph node status (positive or negative), menopausal status (premenopausal: hormone profile in serum or $<$ 12 months after last menstrual bleeding; or postmenopausal: hormone profile in serum or $>$ 12 months after last menstrual bleeding), hormone receptor status (negative: estrogen receptor [ER] and progesterone receptor [PgR] negative by immunohistochemistry [IHC]; positive: ER and/or PgR positive by IHC; or not determinable), human epidermal growth factor receptor 2 (HER2) status (positive: IHC 3+ or fluorescent in situ hybridization [FISH] positive; negative: IHC negative, 1+, or 2+ or FISH negative; or not determinable), grade (grade 3; grades 1, 2, or X; or not determinable), and participating center. These parameters were prospectively defined to be correlated with the pCR rate for each treatment arm and also with the entire trial population.

Patients were randomly assigned to treatment groups according to the method of Pocock and Simon[16] using a computer program.[17] Patients received either three cycles or six cycles of epirubicin 75 mg/m^2 IV followed by docetaxel 75 mg/m^2 (1-hour IV infusion) on day 1 and granulocyte colony-stimulating factor (G-CSF) 5 μg/kg/d subcutaneously on days 3 to 10 (filgrastim, Neupogen; Amgen, Thousand Oaks, CA). Dexamethasone (8 mg) administration twice daily (orally or IV) from days 0 to 2 to prevent docetaxel-induced hypersensitivity reactions was mandatory. Serotonin antagonists were to be administered to prevent or mitigate nausea and vomiting, with the drug, dosing, and schedule at the investigators' discretion. Toxicity and adverse effects were monitored by documenting any serious adverse event (SAE) while on study (day of random assignment until day 30 after final surgery). An SAE was defined as any event leading to hospitalization of the patient or prolonging a scheduled hospital stay.

Tumor and axillary nodal status was checked clinically on day 1 of each treatment cycle. Mammography and sonography of the tumor-bearing breast were scheduled after three cycles in all patients and after six cycles in patients in the experimental group to monitor tumor response and to control for progressive disease. At these time points, measurements of the left ventricular ejection fraction were also performed.

Final local surgery was performed within 2 to 4 weeks after day 1 of the last scheduled chemotherapy cycle. In case of clinically and/or radiologically confirmed progression of the tumor or axillary disease at any time during the preoperative treatment, chemotherapy was to be discontinued and the patient was to undergo salvage surgery. No second-line, preoperative chemotherapy was allowed.

Adequate local surgery was defined as modified radical mastectomy with axillary lymph node clearance or as a breast-conserving procedure with axillary lymph node dissection according to the institutions' guidelines and following the consensus guidelines of the Austrian Working Group for Oncologic Surgery. A minimum of eight lymph nodes was to be removed and described in the pathology report. Pathologically clear margins must have been achieved. Endoscopic techniques for axillary clearing were not allowed, whereas a sentinel node biopsy was possible according to a subprotocol of ABCSG-14 as long as a conventional axillary lymph node dissection to control for false-negative results of the sentinel technique was also performed. The results of this substudy to ABCSG-14 will be published later.

A pCR was defined as the absence of invasive tumor in the final surgical breast sample (stage yT0 or yDCIS) as judged by the local pathologist. Specimens judged as pCR were reviewed by a single pathologist at the Department of Pathology at the University of Vienna. Pathologists were blinded to the patients' treatment arm. After completion of the safety follow-up (ie, 28 days after surgery), the decision about systemic adjuvant chemotherapy was at the discretion of the treating physician.

Statistics

The primary end point for this analysis was pCR of the breast tumor. Patients were randomly assigned[16,17] and balanced for the following prognostic factors: tumor stage, HER2 status, lymph node status, menopausal status, hormone receptor status, grading, and participating centers grouped into federal states of Austria. A total of 282 patients would be required to detect a

difference in pCR rate of 7% (control group) versus 18% (experimental group) for the final analysis with a power of 82% ($\alpha = .05$, one-sided Fisher's exact test). A recruiting period of 3 years was assumed (94 patients per year), and the dropout rate was estimated not to exceed 5%. Differences between demographic data and outcome variables are described with frequencies and percentages and tested with the Fisher's exact test or χ^2 test when appropriate. *P* values are two sided unless otherwise stated and significant at $P < .05$. For univariate and multivariate comparisons, a logistic regression model was used, and estimated effects were quantified with odds ratios. All analyses were carried out using the SAS statistical software package (version 8.02; SAS Institute, Cary, NC).

RESULTS

Between June 1999 and December 2002, 292 patients were recruited onto the trial, and 288 patients were eligible for response evaluation (one patient developed metastasis, one patient was lost to follow-up, and two patients withdrew consent; Fig 1). Both treatment groups were well balanced for known prognostic factors (Table 1).

Efficacy

The pCR rate of the primary tumor was significantly higher in patients receiving six cycles of ED+G than in patients receiving three cycles (18.6% *v* 7.7%, respectively; $P = .0045$; Table 2). A pCR of the primary tumor and negative axillary nodes were documented in 23 patients (15.9%) after six cycles of ED+G and in seven patients (4.9%) after three cycles of ED+G ($P = .0121$). Significantly more patients had a negative axillary status after six cycles of ED+G than after three cycles (56.6% *v* 42.8%, patients; $P = .02$), and there was a trend towards more breast-conserving surgery after six cycles of ED+G (Table 2). The rate of primary progression was 2.8% in patients receiving three cycles of ED+G and 5.5% in patients receiving six cycles.

Table 1. Patients Characteristics

Characteristic	Three Cycles of ED+G (n = 143) No. of Patients	%	Six Cycles of ED+G (n = 145) No. of Patients	%
Age, years				
Median	50		49	
Range	30-70		27-70	
Menopausal status				
Premenopausal	84	58.7	83	57.2
Postmenopausal	59	41.3	62	42.8
Tumor stage				
T1	36	25.2	40	27.6
T2	90	62.9	92	63.5
T3	12	8.4	7	4.8
T4	5	3.5	6	4.1
Clinical nodal stage				
Negative	86	60.1	81	55.9
Positive	57	39.9	64	44.1
Hormone receptor status				
Positive	96	67.1	97	66.9
Negative	47	32.9	48	33.1
HER2 status				
Negative	109	76.2	110	75.8
Positive	29	20.3	31	21.4
Not determinable	5	3.5	4	2.8
Grade				
1-2	80	56.0	84	57.9
3	56	39.1	56	38.6
Not determinable	7	4.9	5	3.5

Abbreviations: ED+G, epirubicin and docetaxel plus granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2.

Adverse Effects and Toxicity

The treatment regimens were generally well tolerated, and the rates of SAEs were similar (Table 3). In particular, no significant differences in the incidence of SAEs as a result of hematologic, cardiac, neurologic, or other toxicity were observed. No patients died while on treatment.

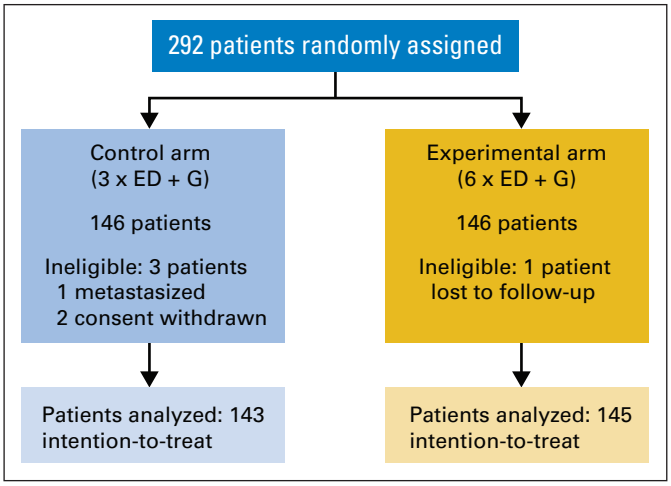

Fig 1. Trial plan. ED+G, epirubicin and docetaxel plus granulocyte colony-stimulating factor.

Prognostic Factors

Patients in this study were stratified for known prognostic factors. These strata and the allocated treatment group were prospectively defined as possible predictors for a pCR.

Univariate analysis for predictive markers for pCR in all 288 assessable patients showed a significant result for a negative hormone receptor status, a poor tumor differentiation, clinically negative axillary lymph nodes at diagnosis, and six cycles of ED+G (Table 4). The multiple logistic regression model affirmed that negative hormone receptor status, negative axillary status, and six cycles of ED+G are independent predictors for pCR, whereas the tumor grade is not.

When analyzing only the 145 patients who received six cycles of ED+G, negative hormone receptor status, negative axillary status, and positive HER2 status were significantly associated with the possibility of a pCR in the univariate analysis, whereas a negative hormone receptor status and a positive HER2 status remained significant in the Cox model (Table 5). In addition, when looking at the ER and the PgR status separately, it seems that only the ER is associated with this result (ER negative *v* positive: odds ratio = 1.68; 95% CI, 1.02 to 2.77; $P = .04$; PgR negative *v* positive: odds ratio = 1.19; 95% CI, 0.63 to 2.25; $P = .59$).

Table 2. Response to Three or Six Cycles of ED+G

Response	Three Cycles of ED+G (n = 143)		Six Cycles of ED+G (n = 145)		*P*
	No. of Patients	%	No. of Patients	%	
Pathologic complete response	11	7.7	27	18.6	.0045
ypT0	9	6.3	17	11.7	
ypDCIS	2	1.4	10	6.9	
Partial response + stable disease	128	89.5	110	75.9	
Progressive disease	4	2.8	8	5.6	
After three cycles	4	2.8	3	2.1	
After six cycles	—	—	5	3.5	
Axillary nodal status	138		136		
Negative	59	42.8	77	56.6	.02
Positive	79	57.2	59	43.4	
Data missing	5	3.5	9	6.2	
Surgical procedure	139		137		
BCS	93	66.9	104	75.9	.1
MRM	46	33.1	33	24.1	
Data missing	4	2.8	8	5.5	

Abbreviations: ED+G, epirubicin and docetaxel plus granulocyte colony-stimulating factor; ypT0, no tumor after neoadjuvant therapy; ypDCIS, ductal carcinoma in situ only after neoadjuvant therapy; BCS, breast-conserving surgery; MRM, modified radical mastectomy.

DISCUSSION

The combination of ED+G resulted in a significantly higher pCR rate of 18.6% after six cycles compared with a rate of 7.7% after three cycles. Multivariate analyses demonstrated an almost three-fold increase in the chance of achieving a pCR with six cycles of ED+G. Consequently, the receipt of six cycles of ED+G seems to be an independent positive predictive factor for achieving a pCR. Although no data from randomized trials directly comparable to ABCSG-14 have been published, recent data suggest that a longer period of chemotherapy compares favorably with a shorter treatment.[18,19]

The percentage of patients with a pathologically negative axillary status at the time of surgery was significantly higher after six cycles of ED+G compared with three cycles. This might also reflect the higher systemic efficacy of six cycles of ED+G and shows that, by prescheduling and limiting the number of treatment cycles arbitrarily, significantly fewer patients with a good clinical response or partial tumor response will experience a complete eradication of invasive tumor cells in the breast and possibly also of systemic microscopic disease. In addition, 76% of patients were able to undergo breast-conserving surgery after six cycles of ED+G compared with 67% of patients after three cycles, resulting in a more favorable functional and cosmetic outcome in a higher proportion of treated women. The rates of primary resistance to ED+G treatment (2.8% with three cycles and 5.5% with six cycles) were acceptable and comparable with all neoadjuvant studies.

These positive and encouraging results were not hampered by increases in relevant toxicities as shown by an equal total number of SAEs in both treatment arms and no differences in the incidences of hematologic, GI, neurologic, cardiac, or other SAEs. The relatively low incidence of hospitalizations caused by severe neutropenia, febrile neutropenia, or infection is certainly attributable to G-CSF primary

Table 3. Serious Adverse Events After ED+G

Adverse Event	All (n = 288)		Three Cycles of ED+G (n = 143)		Six Cycles of ED+G (n = 145)		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Hematologic	22	7.6	14	4.9	8	2.8	.1898
Gastrointestinal	6	2.1	3	1.0	3	1.0	.99
Neurologic	2	0.7	1	0.4	1	0.4	.99
Hypersensitivity reaction	1	0.4	1	0.4	0	0	.4965
Infection	12	4.2	5	1.7	7	2.4	.7696
Edema	1	0.4	0	0	1	0.4	.4965
Infusion site reaction	2	0.7	0	0	2	0.7	.4983
Cardiac	1	0.4	1	0.4	0	0	.4965
Various	15	5.2	6	2.1	9	3.1	.5975
All serious adverse events	62	21.5	31	10.8	31	10.8	.99

Abbreviation: ED+G, epirubicin and docetaxel plus granulocyte colony-stimulating factor.

Table 4. Odds Ratio for Reaching a Pathologic Complete Response in All Patients (N = 288): Logistic Regression Model

Variable	Univariate Analysis			Multivariate Analysis		
	Odds Ratio Estimate	95% CI	*P**	Odds Ratio Estimate	95% CI	*P**
Hormone receptor status: negative *v* positive	4.5	2.2 to 9.3	.0001	3.1	1.3 to 7.3	.009
Grading: grade 3 *v* grade 1, 2, X	3.5	1.7 to 7.4	.0008	2.3	0.9 to 5.5	.0673
Nodal stage, clinical: negative *v* positive at baseline	3.1	1.5 to 6.3	.0023	2.7	1.2 to 6.0	.0167
Therapy: 6 *v* 3 cycles of ED+G	2.9	1.4 to 6.0	.0058	2.9	1.3 to 6.7	.0104
HER2 status: positive *v* negative	2.1	1.0 to 4.5	.0503	1.7	0.8 to 3.9	.1988
Tumor stage, clinical: T2 *v* T1, T3 *v* T2, T4 *v* T3 at baseline	1.0	0.6 to 1.7	.9426	0.8	0.4 to 1.6	.5749
Menopausal status: postmenopausal *v* premenopausal	1.0	0.5 to 2.0	.9918	0.7	0.3 to 1.6	.4655

Abbreviations: ED+G, epirubicin and docetaxel plus granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2.
*$P < .05$ indicates statistical significance.

prophylaxis. There were no treatment-related deaths during the study, and therefore, six cycles of ED+G can be considered a safe and tolerable outpatient treatment regimen.

In an effort to identify possible predictors for a pCR, we prospectively planned to correlate known risk factors with the rates of pCR in the entire trial population as well as in each of the two treatment arms. Using a multivariate logistic regression model including the 288 eligible patients, a negative hormone receptor status and a negative axillary status at the time of diagnosis were independent factors for a 3.1-fold and 2.7-fold increase, respectively, in the chance of reaching a pCR with neoadjuvant ED+G.

Hormone receptor negativity predicts for achieving a pCR after ED+G, but this effect is only driven by the ER and not by PgR. Although a negative ER is obviously important for predicting sensitivity to cytotoxic therapy, the PgR might be of more importance for predicting sensitivity to hormonal manipulation. This has already been shown by ABCSG-5, in which a regimen of goserelin plus tamoxifen was compared with cyclophosphamide, methotrexate, and fluorouracil in the adjuvant treatment of premenopausal patients with hormone-dependent tumors.[20] Taking these results together, we speculate that the two steroid receptors may be even more sophisticated predictive factors for sensitivity/resistance for both hormonal manipulation and cytotoxic treatment. Further prospective evaluation seems warranted.

Undifferentiated tumors (grade 3) showed only a strong trend towards a higher rate of pCR. Moreover, six cycles of ED+G was also an independent positive risk factor, increasing the chance of reaching a pCR by 2.9-fold. A separate analysis of the 145 patients who received six cycles of ED+G showed that, within this group, the rate of pCR was triple that of the three-cycle group and that a negative hormone receptor status and a positive HER2 status were significantly associated with a three-fold chance for reaching a pCR. Axillary nodal status was not a significant factor for a pCR within this patient group. Tumor size, age, menopausal status, and grade of tumor differentiation were not associated with the chance of experiencing a pCR.

Although it is well established that hormone-independent tumors respond better to cytotoxic treatment than hormone receptor–positive tumors, most retrospective clinical data about HER2 being a predictive factor for the efficacy of anthracyclines and taxanes are not unequivocal. In vitro data[21] with single agents do not support our results, which can be interpreted as HER2-positive tumors (IHC 3+/FISH positive) responding well, particularly when exposed repeatedly (for six cycles) in vivo. Because our study prospectively evaluated a possible correlation between HER2 status and a complete response after exposure to epirubicin-docetaxel combination treatment and the identical result was obtained in a phase II pilot trial for ABCSG-14,[15] it seems that this result is valid. In this phase II pilot trial, 65 patients with comparable characteristics to patients treated in ABCSG-14 received a

Table 5. Odds Ratio for Reaching a Pathologic Complete Response in Patients Receiving Six Cycles of ED+G (n = 145): Logistic Regression Model

Variable	Univariate Analysis			Multivariate Analysis		
	Odds Ratio Estimate	95% CI	*P**	Odds Ratio Estimate	95% CI	*P**
Hormone receptor status: negative *v* positive	3.3	1.4 to 7.9	.0065	3.0	1.0 to 8.9	.0485
Nodal stage: negative *v* positive	2.6	1.1 to 6.1	.0337	2.5	0.9 to 6.5	.0710
HER2 status: positive *v* negative	2.6	1.0 to 6.4	.0460	2.9	1.0 to 8.1	.0432
Grading: grade 3 *v* grade 1, 2, X	2.4	1.0 to 5.7	.0533	1.5	0.5 to 4.4	.4364
Tumor stage: T2 *v* T1, T3 *v* T2, T4 *v* T3	1.0	0.5 to 1.9	.9477	0.9	0.4 to 2.0	.7969
Menopausal status: postmenopausal *v* premenopausal	0.7	0.3 to 1.7	.4812	0.5	0.2 to 1.3	.1419

Abbreviations: ED+G, epirubicin and docetaxel plus granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2.
*A P value < 0.05 indicates statistical significance.

median of five cycles of the ED+G regimen used in ABCSG-14, and 57% of the patients (eight of 14 patients) with HER2-positive tumors experienced a pCR compared with only 4% of the patients (two of 51 patients) with HER2-negative tumors. This significant difference has now been confirmed by the outcome of ABCSG-14. This high sensitivity of HER2-positive tumors to anthracycline- and taxane-containing regimens may also give way to more individualized treatment regimens, especially when HER2 is also used as a target of therapy in the neoadjuvant setting and anti-HER2 monoclonal antibodies are added. Recently, an extraordinarily high complete response rate of 67% was achieved after neoadjuvant treatment with sequential paclitaxel, fluorouracil, epirubicin, and cyclophosphamide plus trastuzumab in HER2-positive tumors, whereas the same regimen without trastuzumab resulted in a pCR rate of only 25%, leading to an early discontinuation of the trial.[22]

The role of pCR on survival was underscored by the final results of National Surgical Adjuvant Breast and Bowel Project B-27.[8] Although overall survival and disease-free survival were independent of the treatment regimen (four cycles of doxorubicin + cyclophosphamide ± four cycles of docetaxel), the pCR rate increased from 12.8% to 26.1% with the sequential anthracycline-taxane approach. This trial also demonstrated a significant survival benefit of 92% *v* 80% at 5 years for patients experiencing a pCR versus patients who did not experience a pCR.

In conclusion, prospectively designed clinical trials are emerging showing that a pCR after neoadjuvant systemic treatment is associated with a higher chance for surviving breast cancer. As a result of ABCSG-14, we conclude that six cycles of ED+G improve the chances of reaching a pCR almost three-fold compared with only three cycles. This is true for hormone receptor–negative tumors and for HER2-positive tumors in particular. Therefore, if epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks are used as neoadjuvant treatment alone or within a treatment sequence for primary breast cancer, six cycles rather than three cycles should be applied to optimize treatment outcome. Primary prophylactic use of G-CSF is recommended to keep the rate of adverse effects caused by neutropenia and infection low.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest.

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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®).